USE OF IGRAS FOR LBTI DIAGNOSIS IN YOUNG CHILDREN

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Tuberculosis Control Branch
OVERVIEW

- Epidemiology of TB in young children
- Deciding who to test for LTBI
- Current guidelines and clinical practice
- Studies on use of IGRAs in children <2 years old
- Summary of my conclusions
Epidemiology
Pediatric Tuberculosis Cases (Age <18 years): California, 2006-2016

The graph shows the number of pediatric tuberculosis cases in California from 2006 to 2016, categorized by age groups: 0-4, 5-14, and 15-17 years. The data indicates a general decline in the number of cases over the years. The highest numbers were observed in 2008 for all age groups, with significant variations observed in subsequent years.
SITE OF DISEASE, PEDIATRIC CASES 2010-2016
FOREIGN BORN, PEDIATRIC CASES 2010-2015 (N=711)
# TB Risk Among Infected Children

<table>
<thead>
<tr>
<th>Age at primary infection</th>
<th>Any TB disease</th>
<th>Pulmonary disease</th>
<th>TB meningitis or miliary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>50%</td>
<td>30-40%</td>
<td>10-20%</td>
</tr>
<tr>
<td>1-2 years</td>
<td>20-30%</td>
<td>10-20%</td>
<td>2-5%</td>
</tr>
<tr>
<td>2-5 years</td>
<td>5%</td>
<td>5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>5-10 years</td>
<td>2%</td>
<td>2%</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>10-20%</td>
<td>10-20%</td>
<td>&lt;0.5%</td>
</tr>
</tbody>
</table>

WHO TO TEST FOR LTBI
**Pediatric TB Risk Assessment**

Check appropriate risk factor boxes below.

**LTBI testing** is recommended if any of the 4 boxes below are checked.

If LTBI test result is positive and active TB disease is ruled out, LTBI treatment is recommended.

- **Foreign-born** person from a country with an elevated TB rate
  - Includes any country other than the United States, Canada, Australia, New Zealand, or a country in western or northern Europe
  - Interferon Gamma Release Assay is preferred over Tuberculin Skin Test for foreign-born persons ≥2 years old

- **Immunosuppression**, current or planned
  - HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥2 mg/kg/day, or ≥15 mg/day for ≥2 weeks) or other immunosuppressive medication

- **Close contact** to someone with infectious TB disease at any time

- **Foreign travel or residence** of ≥1 month consecutively in a country with an elevated TB rate
  - Any country other than the United States, Canada, Australia, New Zealand, or a country in Western or Northern Europe
WHY TARGETED TB TESTING?

- Low prevalence of TB
- No gold standard for LTBI diagnosis
- Goal 1: is to treat those infected (need good sensitivity)
- Goal 2: don’t treat those uninfected (need good specificity)
- Sensitivity even MORE important in children at higher risk of TB disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>84%</td>
<td>88%</td>
</tr>
<tr>
<td>QFT</td>
<td>83%</td>
<td>91%</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>84%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Avoid testing low risk people, because a positive test is more likely to be a false positive than a true positive

Chapter 6: Diagnosis of TB infection in Children (Mandalakas, DiNardo) from the Handbook of Child & Adolescent Tuberculosis (Starke & Donald)
CURRENT GUIDELINES
CLINICAL PRACTICE
## Preferred Testing by Age and Guideline

<table>
<thead>
<tr>
<th>Guideline</th>
<th>&lt;2 years</th>
<th>2-&lt;5 years</th>
<th>5+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC/ATS/IDSA 2016</td>
<td>TST</td>
<td>TST</td>
<td>IGRA</td>
</tr>
<tr>
<td>AAP 2015</td>
<td>TST</td>
<td><strong>TST</strong></td>
<td>IGRA</td>
</tr>
<tr>
<td>UpToDate 2016</td>
<td>TST</td>
<td><strong>TST</strong></td>
<td>IGRA</td>
</tr>
<tr>
<td>CDPH 2017</td>
<td>TST</td>
<td>IGRA</td>
<td>IGRA</td>
</tr>
<tr>
<td>Experts 2017</td>
<td>TST</td>
<td>IGRA</td>
<td>IGRA</td>
</tr>
</tbody>
</table>
WHY THE CONCERN IN USING IGRAS FOR KIDS <5?

- Limited evidence of use in younger kids
  - Limitations of TST “well-known”
  - Concern sensitivity of IGRA is not good enough

- Harder to obtain IGRA
  - Blood draws can be more difficult in young kids

- Higher risk for indeterminate results

- Concern for decreased ability of young child’s immune system to respond effectively
  - Possibly lower values for positive control and MTB antigen test
SO WHY NOT JUST LEAVE IT AT TST?

- Recognized adult benefits
  - Avoid overlap with NTM & BCG vaccine
  - Only requires 1 visit
  - Fewer reader errors
  - Reduces over-treatment due to false +TSTs

- These concerns increased in pediatric population
  - More BCG false+
    - BCG given at birth in many countries
    - Highest influence on TST test result for children <3-5 years old [1,2]
  - As use of TST decreases, institutional knowledge will decrease leading to improperly placed and read TSTs in children
STUDIES ON IGRAs
<2 YEARS
# San Francisco TB Study*

<table>
<thead>
<tr>
<th></th>
<th>&lt; 2 years of age</th>
<th>2-&lt;5 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>56 (5%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (20%) indeterminate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1 (TST-) treated for active TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 9 not treated (1TST+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (2%) QFT+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Treated for LTBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44 (78%) QFT-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1 treated for active disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 37 not treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No TB cases over 5.8 years of follow-up for 46 untreated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>236 (22%)</td>
</tr>
<tr>
<td>17 (7%) indeterminate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 12 not treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (4%) QFT+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 3 treated for active disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1 not treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>210 (89%) QFT-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 199 not treated (47 TST+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No TB cases over 5.5 years of follow-up for 212 untreated</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cdc Tb Epidemiology Studies Consortium*

- Prospective cohort study

- All participants had QFT, T-SPOT, and TST and TB exposure risk

- TST cut-off used 10mm for kids <5 yrs of age

- 463 kids <5 years old, about 100 <2 years

LTBI Test Characteristics by LCA in Foreign-Born Children <5 Years (n=463)

For LCA we used ≥5 spots as a positive T-SPOT result. Ho, TBESC. 2016.
WHAT THIS MEANS FOR THE CLINICIAN:
POPULATION < 5 YEARS AT HIGH RISK FOR LTBI

Hypothetical cohort of 1000 foreign-born children < 5 yrs (4% LTBI prevalence)

<table>
<thead>
<tr>
<th></th>
<th>LTBI</th>
<th>No LTBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST+</td>
<td>30</td>
<td>284</td>
</tr>
<tr>
<td>TST-</td>
<td>10</td>
<td>676</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>960</td>
</tr>
</tbody>
</table>

**TST**
- Sensitivity of 74.8%
- Specificity of 74.0%

Of 1000 people—
- **90% (284/314) with TST+ don’t have LTBI**
- Positive predictive value (PPV) is ~10% (30/314)
- **25% (10/40) LTBI missed**

**QFT**
- Sensitivity of 70.4%
- Specificity of 98.9%

Of 1000 people—
- **26% (10/38) with positive QFT don’t have LTBI**
- PPV is 74% (28/38)
- **30% (12/40) LTBI missed**

**T-SPOT**
- Sensitivity of 58.9%
- Specificity of 99.0%

Of 1000 people—
- **29% (10/34) with positive T-SPOT don’t have LTBI**
- PPV is 71% (24/34)
- **40% (16/40) LTBI missed**

Ho, TBESC. 2016.
SOUTH AFRICA STUDY*

- N = 2772 children
- QFT at 4-6mo., then again about a year later
- Evaluated for disease every 3 months
- TB disease
  - Culture/Xpert +
  - Symptoms, abnormal CXR, and +TST
- Indeterminates
  - 0.4% overall

**SOUTH AFRICA STUDY**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Cases</th>
<th>Incidence (95% CI)</th>
<th>IRR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Revised case definition 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.35 IU/mL</td>
<td>2232</td>
<td>16</td>
<td>0.7 (0.4-1.1)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>0.35–4.00 IU/mL</td>
<td>79</td>
<td>2</td>
<td>2.5 (0.4–9.4)</td>
<td>3.7 (0.4–15.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>&gt;4.00 IU/mL</td>
<td>63</td>
<td>10</td>
<td>28.0 (14.9–45.7)</td>
<td>42.5 (17.2–99.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Culture or Xpert positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.35 IU/mL</td>
<td>2232</td>
<td>11</td>
<td>0.5 (0.2–0.8)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>0.35–4.00 IU/mL</td>
<td>79</td>
<td>2</td>
<td>2.5 (0.4–9.4)</td>
<td>5.4 (0.6–24.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>&gt;4.00 IU/mL</td>
<td>63</td>
<td>7</td>
<td>19.6 (8.9–36.8)</td>
<td>43.3 (14.2–122.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Incidence reported in cases per 100 person-years. IRR=incidence rate ratio. Ref=reference. *IRR of higher than 4.00 vs 0.35–4.00 for revised case definition 1: 11.4 (95% CI 2.4–107.2), p<0.000047. †IRR of higher than 4.00 vs 0.35–4.00 for culture or Xpert positive: 8.0 (95% CI 1.5–78.8); p=0.0094.

*Table 1: Incidence of tuberculosis (cases per 100 person-years) according to day 336 QuantiFERON interferon-γ value by case definition*

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Sensitivity of IGRAs for LTBI (<2)

- **TSPOT**
  - Higher sensitivity than TST
  - Positive result associated with greater risk of developing active disease compared to TST

- **QFT**
  - Among kids <5, QFT better marker of household exposure to TB than TST
  - Trended towards better performance than TST, especially among BCG vaccinated
  - Higher values associated with greater risk of TB disease
IFN GAMMA RESPONSES

- IFN-γ response to TB antigen
  - Unrelated to age (4 papers)
  - Infants with greater values (1 paper)
  - Infants <1 with lower values (1 paper)

- IFN-γ response to positive control
  - Unrelated to age (3 papers)
Indeterminate QFTs

- Wide range from 0-40%

- Combined studies for kids <2
  - 7% indeterminate (76/1090)
  - 1% including SA study (109/6399)

- Combined studies for kids <1
  - 9% indeterminate (25/269)
  - 1% including SA study (45/3066)
MY SUMMARY: USE OF IGRAs <2 yrs

- Probably as good as (if not better) than TST, BUT not enough data

- Concern for active TB or moderate to high risk exposure
  - Always do physical exam, symptom review
  - BOTH TST and IGRA
  - If exam, symptom review, or TST/IGRA concerning for possible active disease
    - Get CXR
    - Collect samples to test for TB
    - Treat for active disease
  - Even if both tests are NEG, does not completely exclude TB disease – need clinical correlation
<2 YRS WITH NO KNOWN OR LOW RISK TB EXPOSURE... OPTIONS

- **TST only**
  - Current practice

- **IGRA only**
  - Consider for BCG-vaccinated, only risk as birth in high-incidence country, parents IGRA neg

- **Both tests**
  - Would have to decide apriori which to follow
  - Example: Kaiser Northern California Plan
    - TST as 1st line
    - For kids with BCG, >3 months, and TST <15mm, QFT to determine need for tx
    - Repeat QFT at age 2yrs
CONCLUSIONS

- IGRA is a better test for BCG-vaccinated children 2 years and older

- Preliminary data suggests IGRA is at least as good as TST in kids <2

- As adult testing moves towards predominately IGRA-based, TST knowledge will decline
  - If you use TST in kids, make sure ongoing training occurs
  - Increase capacity to do IGRAs in public health

- Feel free to contact me with specific cases or questions!

- If you do use IGRAs in the <2 population, please document and follow children -> we need more data to inform our practices!
REFERENCES


