Network di Microbiologia e Virologia del Nord Est

Incontro di Aggiornamento
INTERFERON GAMMA RELEASE ASSAYS (IGRAs) NELLA DIAGNOSI E MONITORAGGIO DELLE MALATTIE INFETTIVE
Trento, 19 aprile 2013

IGRAs TEST NELLA DIAGNOSI DELL’INFEZIONE TUBERCOLARE

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EPIDEMIOLOGICAL CLASSIFICATION OF INFECTIOUS DISEASES

Decreasing

- Polio
- Meningococcus C (UK)
- Pneumococcus (US)
- Infected people
- HIV (US)
- HCV (US)
- Diphtheria
- Cholera

Emerging

- Avian influenza
- SARS
- West Nile virus (US)
- Ebola
- vCJD
- BSE
- CJD
- Antibiotic resistance (MRSA) (UK)
- Anthrax

 Persisting

- Tuberculosis
- HIV (WW)
- Malaria

Nat Med 2004; 10: 1177
Alveolar macrophage kill MTB: **no infection**

**Infection:** MTB released in extra-cellular space, recruitment of mononuclear cells

**LATENT INFECTION**
- Strong effective cellular response
- Containment of MTB proliferation

**REACTIVATION**
- HIV
- Drugs
- Senescence
- Co-morbidities

**ACTIVE DISEASE**
- Poor ineffective immune response
- Progressive disease

Granuloma formation
- Spread to lymph nodes, blood and other organs

*Nat Med 2000; 6: 1327-9 modified*
Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

Laith J. Abu-Raddad\textsuperscript{a,1}, Lorenzo Sabatelli\textsuperscript{a}, Jerusha T. Achterberg\textsuperscript{a,b,c}, Jonathan D. Sugimoto\textsuperscript{a,b}, Ira M. Longini, Jr.\textsuperscript{a,d}, Christopher Dye\textsuperscript{e}, and M. Elizabeth Halloran\textsuperscript{a,d,2}

\textsuperscript{a}Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; Departments of \textsuperscript{b}Epidemiology, \textsuperscript{c}Anthropology, and \textsuperscript{d}Biostatistics, University of Washington, Seattle, WA 98195; and \textsuperscript{e}Office of HIV/AIDS, Tuberculosis, Malaria, and Neglected Tropical Diseases, World Health Organization, CH-1211 Geneva 27, Switzerland

- Using an age-structured mathematical model of TB, analysis of the potential benefits of novel interventions under development and those not yet in the portfolio.
**TREATMENT OF LTBI IS ONE OF THE MOST COST-EFFECTIVE HEALTH INTERVENTIONS**

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Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

for the TB Trials Consortium PREVENT TB Study Team*
3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) vs 9 months of self-administered daily isoniazid (300 mg)

Active TB in 7 of 3986 (cumulative rate 0.19%) vs 15 of 3745 subjects (cumulative rate 0.43%)

THE TUBERCULIN SKIN TEST

THE USE OF CHEMOTHERAPY AS A PROPHYLACTIC MEASURE IN TUBERCULOSIS

Shirley H. Ferebee, Frank W. Mount, George W. Comstock
Operational Research Section, Tuberculosis Program, Public Health Service, Department of Health, Education and Welfare, Washington, D.C.
RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

TOTAL POPULATION RECEIVING PLACEBO

Rate per 1,000: **8.5**
RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

TST < 5 MM RECEIVING PLACEBO

Rate per 1,000: 4.9
RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

TST > 5 < 9 MM RECEIVING PLACEBO

Rate per 1,000: 8.3
RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

TST > 10 < 14 MM RECEIVING PLACEBO

Rate per 1,000: 10.3
RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

TST > 15 < 19 MM RECEIVING PLACEBO

Rate per 1,000: **12.5**
RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

TST > 20 MM RECEIVING PLACEBO

Rate per 1,000: 20.0
RISK OF TB AMONG HOUSEHOLD CONTACTS DURING FIRST YEAR

POPULATION RECEIVING PLACEBO

S Ferebee et al Am Rev Respir Dis 1962
Predictive Value of a Whole Blood IFN-γ Assay for the Development of Active Tuberculosis Disease after Recent Infection with *Mycobacterium tuberculosis*

Roland Diel¹, Robert Loddenkemper², Karen Meywald-Walter³, Stefan Niemann⁴, and Albert Nienhaus⁵

- **601 close contacts** (28% foreign-born, 46% BCG-vaccinated) of TB patients tested with both **TST** and **QFT**.
- **40%** TST-positive (5 mm) vs **11%** QFT-positive
- QFT-positives only associated with **exposure time**.
- INH offered to QFT-positive; only **38%** accepted.
- 2 years of follow-up
- **6** (untreated) contacts progressed to **active TB**.

Diel R et al, *AJRCCM* 2008; 177: 1164-70
Progression rates (2 years):
QFT=14.6%   TST=2.3%

Diel R et al, AJRCCM 2008; 177: 1164-70
Diel R et al, *AJRCCM* 2008; 177: 1164-70

2-year progression rates
TST 2.3%  QFT 14.6%

Diel R et al, *AJRCCM* 2008; 177: 1164-70
Negative and positive predictive value of a whole-blood interferon-γ release assay for developing active tuberculosis
An Update

Diel R et al, Am J Respir Crit Care Med 2011; 83; 88-95

N=954

3.1%

TST >5 mm: 604 (63.3%)

TST+/QFT+: 191 (31.6% of TST+)

TB: 89.5% household contacts

QFT+/TST-: 7 (3.5% of QFT+)

QFT-IT >0.35: 198 (20.8%)

12.9%
Progression rates
TST 3.1% QFT 12.9%

Diel R et al, AJRCCM 2011; 183: 88-95
‘Regardless of the test used to identify latent tuberculosis infection, testing should be primarily targeted at diagnosing infected patients who will benefit from treatment.’

Mazurek & Villarino MMWR 2002
Persons at increased risk* for progression of infection to active tuberculosis include

- persons with human immunodeficiency virus (HIV) infection;†
- infants and children aged <5 years;‡
- persons who are receiving immunosuppressive therapy such as tumor necrosis factor–alpha (TNF-α) antagonists, systemic corticosteroids equivalent to ≥15 mg of prednisone per day, or immune suppressive drug therapy following organ transplantation;‡
- persons who were recently infected with *M. tuberculosis* (within the past 2 years);
- persons with a history of untreated or inadequately treated active tuberculosis, including persons with fibrotic changes on chest radiograph consistent with prior active tuberculosis;
- persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, or cancer of the head, neck, or lung;
- persons who have had a gastrectomy or jejunoileal bypass;
- persons who weigh <90% of their ideal body weight;
- cigarette smokers and persons who abuse drugs or alcohol; and
- populations defined locally as having an increased incidence of active tuberculosis, possibly including medically underserved or low-income populations.
An IGRA may be used in place of (but not in addition to) a TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection, with preferences and special considerations noted below. Despite the indication of a preference in these instances, use of the alternative test (FDA-approved IGRA or TST) is acceptable medical and public health practice.
Keep in mind ...

Asses individual risk for both MTB infection and progression and use the most reliable test(s) in the individuals with the highest TB risk.

Avoid testing those which you wouldn’t treat

A DECISION TO TEST IS A DECISION TO TREAT
Inclusion of latent tuberculosis infection as a separate entity into the international classification of diseases

Marc Tebruegge¹,²,³, Eeva Salo⁴, Nicole Ritz⁵,⁶, Beate Kampmann⁶,⁷, On behalf of the Paediatric Tuberculosis Network European Trialsgroup (ptbnet)

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Abstract
The 11th revision of the International Classification of Diseases (ICD-11) proposed by the WHO is currently in the consultation phase. In common with previous versions of the ICD this revised version does not contain a code for latent tuberculosis infection (LTBI), contrasting with the inclusion of a large number of codes for various manifestations of active tuberculosis (TB). Inclusion of a separate code for LTBI into ICD-11 is critically important for epidemiological, clinical and research purposes. On behalf of the Paediatric Tuberculosis Network European Trialsgroup, we encourage colleagues worldwide who are caring for TB patients or are involved in TB research to join us in supporting the case for a long overdue ICD code for LTBI.
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