TUBERCOLOSI
una emergenza

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TBC
(ieri, oggi, domani)

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Dipartimento di Pediatria
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La tubercolosi in pediatria

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Tuberculosis: an old story

PCR amplification of *M. Tuberculosis* complex DNA (IS6110) in ancient tissues

1: 50-bp standard ladder
2-4: amplification products of tissue samples
5-6: blank controls
The “recent” history of tuberculosis

Mortality rate
-1850: 400/100.000
-1900: 200/100.000
-1950: 25/100.000
-1995: 10/100.000

1930 - Pastorization of milk
1940 - Antituberculous drugs

Diagnostic tools
-1882: Identification of *Mycobacterium tuberculosis* by Koch
-1898: First radiography in children by Escherich
-1910: Tuberculin testing by von Pirquet and Mantoux
-1991: Nucleic acid amplification test
-2005: Immunologic test
Tuberculosis is re-emerging disease....

Lancet, August 23, 2007
Tuberculosis in children

- Epidemiology
- Transmission
- Immune response to infection
- Classification
- Clinical manifestations
- Diagnosis
- Treatment
Tuberculosis: the dimension of the problem

✓ Every second of every day, *M. Tuberculosis* infects another human being somewhere in the world.

✓ More than 10% of new cases and about 5% of deaths occur in children under 15 yrs.

✓ The global incidence of 9 million cases of active TB per year is a thin fraction of the estimated 2 billion people infected (1/3 of the world population).

✓ 13 countries account for nearly 75% of the world TB cases. However, the low incidence of TB in developed countries is illusory.
Tuberculosis: still a health problem

WHO, 2006

Millennium Development Goals: Global Plan to Stop TB
Aim: to reduce TB prevalence and deaths to half of 1990 levels by 2015

TB is a social disease: it has always occurred disproportionately among disadvantaged populations

WHO, 2006
The new world plague: why?

- Co-epidemic of HIV-infection
- Immigration
- Increased transmission in congregate settings
- Decline in the public health infrastructure
- Multi-Drug-Resistant TB (MDR-TB)
TB in Italy

Tuberculosis notification rates by age group, 1995-2005

Cases / 100 000

- >64
- 45-64
- 15-44
- 0-14

TB in Italy

Tuberculosis notification rates by sex, 1995-2005

Cases / 100,000

- Male
- Female
- Total

Year:
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
TB in Italy

Tuberculosis cases by geographic origin, 1995-2005

No. of cases


Native
Foreign born
Unknown
Tuberculosis in children

✓ Epidemiology
✓ Transmission
✓ Immune response to infection
✓ Classification
✓ Clinical manifestations
✓ Diagnosis
✓ Treatment
Mycobacterium tuberculosis

M. tuberculosis complex groups 5 closely related mycobacteria: M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti

Mycobacterium tuberculosis is an aerobic, intracellular pathogen, which has a predilection for the lung tissue rich in oxygen supply.
Transmission of TB

- The infection is transmitted from one person to another through invisible droplet nuclei (1-5 µ), generated when someone with active TB of the lungs coughs, sneezes, spits, or talks (the droplets dry and remain suspended in air for hours).

- The infection occasionally occurs by direct contact with infected discharges (abscess, urine, saliva, etc) and by means of heavily contaminated means (shoes, endoscopes).

- Transmission is relatively inefficient and depends on the infectivity of the source case, on the amount of time the exposed person breaths the contaminated airs, and the environment in which contact occurs.
Peculiarity of TB in children

- High risk of progression from infection to disease (according to age, poor cellular immune response)
- High risk of dissemination of the disease
- High incidence of extrapulmonary manifestations
- Low bacterial load
- Low incidence of cavitation (except post-primary TB)
- Low disease transmission (except adolescents)
- Low bacterial isolation (obtaining sputum is difficult)
- Aspecific / atypical radiology
- High incidence of cutaneous anergy
The role of children in TB transmission

- Children are usually infected by an adult or adolescent in the immediate household. Extra-familial infection is rare.

- Children with TB rarely infect other children.

- Children play an extremely important role in the potential transmission of TB, because they may harbour a partially healed infection that lies dormant, but may reactivate many years later (adolescence, pregnancy, old age) under the effect of particular stress conditions (“reservoir for the future”).

- Children are of crucial importance in any control program. A diagnosis of TB in a child is a sentinel event!
“From a tuberculosis control point of view, the treatment of children is not considered a priority, as they rarely transmit the disease and contribute little to the maintenance of the tuberculosis epidemic. However, children do contribute a substantial proportion of the global tuberculosis disease burden, with considerable morbidity and mortality”
The paradox of *Mycobacterium TB*

- *MTB* has a relatively low infectivity
- It is immotile and replicate very slowly
- It does not produce a toxin
- It lacks an efficient animal vector

However...

*TB is the most lethal bacterial disease of all time*

Because it is “leaving death” in a “safe haven”
Tuberculosis in children

- Epidemiology
- Transmission
  - Immune response to infection
- Classification
- Clinical manifestations
- Diagnosis
- Treatment
Innate immunity to TB infection

The inhaled bacteria reach the alveoli of the lung, where they enter into the resident macrophages, resist to phagocytosis due to inhibition of phago-lysosomal activity (*internalization*), and replicate.
Innate immunity to TB infection

- In response to infection, the resident alveolar macrophages produce inflammatory cytokines and chemokines.

- These serve as signals of infection and induce the migration of monocyte-derived macrophages and resident dendritic cells to the focal site of infection.
Adaptive immune response to TB infection

- Recruited DC engulf bacteria which have been able to replicate within the AM and migrate to the regional lymph nodes where they prime local CD4+ and CD8+ T-cells against mycobacterial antigens.

- Primed T cells expand and migrate back to the lungs to the focus of infection where, together with AM, DC, B-cells, endothelial cells and fibroblasts, form the granuloma.
Granuloma, the “final result” of the host response

- In the central part of the cluster, adjacent macrophages fuse to form multinucleate giants cells (Langherans cells), which contain ingested bacilli in the cytoplasm.

- Granuloma includes bacilli which survive within macrophages and serves to wall off the bacteria from the rest of the lung (*hybernation*), limiting spread.

- The central part of the granuloma is often necrotic.
Spread of TB infection from a primary pulmonary focus

During this early phase, before cell-mediated immune system is fully active, the infection may spread either along the lymphatic chains to involve more distant nodes or through blood (occult lympho-hematogenous dissemination) and can cause later extrapulmonary infection.
The dynamic relationship between *M. Tuberculosis* and the human host

Most disease occur in the first 2 years after infection:
- Pulmonary (60-80%)
- Extrapulmonary (20-40%)
Sites of TB disease in childhood in an epidemiological survey

Approximately 80% of reported TB cases are limited to the lungs. This disproportional distribution is substantially different between persons with HIV infection.

Balasegaram, Arch Dis Child 2003;88:772
Risk of developing the disease for an “infected” patient

- An immunocompetent adult with TB infection has a *lifetime* risk of 5-10% of developing the disease. Half of the risk is in the first 2-3 yrs.

- Adults with HIV infection who become infected with TB have a *annual* risk of 5-10% of developing the disease.

- The risk of developing the disease in childhood is *age-related*, and is very high in infants and young children.

- Immunocompromised children are the highest risk group of developing TB.
The risk of progression of TB infection to disease in children

<table>
<thead>
<tr>
<th>Age at Primary Infection (yr)</th>
<th>Risk to Progress to Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>No disease, 50%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease, 30–40%</td>
</tr>
<tr>
<td></td>
<td>Disseminated (miliary) disease or TBM, 10–20%</td>
</tr>
<tr>
<td>1–2</td>
<td>No disease, 75–80%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease, 10–20%</td>
</tr>
<tr>
<td></td>
<td>Disseminated (miliary) disease or TBM, 2–5%</td>
</tr>
<tr>
<td>2–5</td>
<td>No disease, 95%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease, 5%</td>
</tr>
<tr>
<td></td>
<td>Disseminated (miliary) disease or TBM, 0.5%</td>
</tr>
<tr>
<td>5–10</td>
<td>No disease, 98%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease, 2%</td>
</tr>
<tr>
<td></td>
<td>Disseminated (miliary) disease or TBM, &lt; 0.5%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>No disease, 80–90%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease, 10–20%</td>
</tr>
<tr>
<td></td>
<td>Disseminated (miliary) disease or TBM, &lt; 0.5%</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: TBM = tuberculous meningitis.*

*Marais, AJRCCM 2006;173:1078*
Tuberculosis in children

- Epidemiology
- Transmission
- Immune response to infection
- Classification
- Clinical manifestations
- Diagnosis
- Treatment
International classification system for TB

ATS Statement – AJRCCM 2000;161:1376

0  - No TB exposure, no infection

I   - TB exposure, no evidence of infection
      History of exposure, negative TB skin test

II  - TB infection, no disease (latent TB infection)
      Positive TB skin test, no clinical or radiographic evidence of disease

III - TB clinically active (current TB disease)
      MTB cultured, or positive TB skin test and clinical or radiographic evidence of disease

IV  - TB not clinically active (previous TB disease)
      History of prior TB episode, positive TB skin test, negative culture, no clinical evidence of disease, healed TB at chest radiograph

V   - TB suspected (diagnosis pending)
      Suspected on the basis of clinical or radiological signs, but negative TB skin test and negative or unknown result of culture
Tuberculosis in children

- Epidemiology
- Transmission
- Immune response to infection
- Classification
- Clinical manifestations
  - Primary TB
  - Postprimary TB
- Diagnosis
- Treatment
The primary complex (Ghon complex) is composed by:

- a) the parenchymal focus
- b) the involved regional lymph nodes
- c) the lymphatics between them

In children, inflammatory reactions are more intense in the lymph nodes than in the lung and cause most of the radiological manifestations of pediatric TB.

Lymphatic drainage in primary pulmonary TB

Because of the lymphatic drainage:

a) a primary focus in the left lung, parenchyma may be associated with enlarged lymph nodes in both left and right mediastinum

b) a primary focus in the right lung, is associated with enlarged lymph nodes only in the right side
The favourable evolution of primary pulmonary TB

- The primary complex may progress for 1 to 2 months, diminish in size after 3 to 4 months, and may remain visible for 6 to 12 months or longer.

- When disease heals, calcific deposits will often be observed in the site of caseation of the lung and lymph nodes.

- Currently, extensive calcification occurs uncommonly in the west world (early treatment ?)
The unfavourable evolution of primary pulmonary TB

- Pleural effusion
- Bronchial obstruction
- Progressive pulmonary TB
- Acute miliary TB
Complications of primary TB

Pleural effusion

- Tuberculous pleural effusion is a relatively common early manifestation of primary pulmonary TB.
- It originates in the discharge of bacilli into the pleural cavity from an adjacent lesion (subpleural focus).
- It is more frequent in older children.
Complication of primary TB

Pleural effusion
Complications of primary pulmonary TB

Bronchial obstruction

Enlarged infected lymph nodes adjacent to bronchus may cause partial bronchial obstruction through:

- diffuse inflammation of the mucosa
- external compression
- endobronchial granuloma tissue

Lung hyperinflation
Primary pulmonary TB

Bronchial obstruction by enlarged lymph nodes
Primary pulmonary TB

Bronchial obstruction by enlarged lymph nodes

Salesi Children’s Hospital, Ancona
Complication of primary TB

Bronchial obstruction: Lung hyperinflation

6/6/2006
29/6/2006
17/11/2006

Salesi Children’s Hospital, Ancona
Tuberculosis

Salesi Children’s Hospital, Ancona
Enlarged infected lymph nodes adjacent to bronchus may cause total bronchial obstruction through:

- diffuse inflammation of the mucosa
- external compression
- endobronchial granuloma tissue
- perforation of bronchus and development of plugs of a toothpaste-like caseum

Segmental lesion
Complication of primary TB

Bronchial obstruction: Segmental lesion

Salesi Children’s Hospital, Ancona
Caso ....

Novembre 2006 - Kevin, 3 anni, Marche

**Wheezeing** ricorrente e **tosse** catarrale da circa 1 anno

Dopo alcuni episodi, Rx torace “addensamento parenchimale campo medio dx” → antibiotici → ripetizione Rx torace “....quadro Rx sostanzialmente non modificato” → esami vari (immunoglobuline, test sudore, etc.): normali → antibiotici e farmaci AR “a giro” per mesi

Inviato a visita specialistica per “polmonite persistente”
- PA 115/70 mm/Hg
- Cortisolo h 8,00: 0,1 mcg/dl (vn 5-23)
- Cortisoluria 24/h: 2 mg (vn 7-150)

Malattia?
Right middle lobe syndrome
(atelectasis, infection, parenchymal infiltration, bronchiectasis)

Predisposing factors:
- Anatomical position of the lobe
- Bronchus intermedius (narrow diameter, acute take-off angle)
- Adjacent lymph nodes
- No collateral ventilation

Associated conditions:
- Extra or intrabronchial obstruction
- Asthma
- CF
- Primary ciliary dyskinesia
- Infection (TB, immunodeficiency)

Salesi Children’s Hospital, Ancona
The role of timely intervention in middle lobe syndrome in children

*Priftis, Chest 2005;128:2504*

55 children with MLS, median age 5.5 yrs
Duration of symptoms: 14.5 months – HRCT, Bronchoscopy – Follow-up for 24 months

In half of the population, MLS were unnoticed, although symptoms persisted for many months.

Any postponement in obtaining a chest X-ray in patients with non-specific persistent respiratory symptoms may result in failure to diagnose MLS.

**Main Symptoms**

- Cough: 65%
- Sputum production: 71%
- Wheezing: 7%
- Recurrent fever: 7%
- Chest pain: 29%

**Bronchiectasis**

- Without (n. 40)
- With (n. 15)
Complication of primary TB

Progressive pulmonary TB
Cavitary disease in children

Lung cavitation may result from 3 distinct pathologic processes:

1. Poor containment at the site of organism deposition (very young and/or immune-compromised children)

2. Aspiration of living bacilli when a disease lymph node erupts into the airway, with destructive caseating pneumonia (children less than 5 yr of age)

3. Adult-type disease (children greater than 10 yr of age)
Postprimary pulmonary TB

- It is rare in children

- It develops late in the course of the infection, more frequently in adolescents

- It may result *exogenously* by a superinfection, or more frequently *endogenously* by reactivation of a quiescent infection

- The lesions usually appear in the *apical or subapical* portion of the lung, frequently ulcerate and liquefied material disseminates through the bronchi with disease dissemination
Postprimary TB
Postprimary pulmonary TB
Symptoms of TB are usually scanty. Children may manifest:

- 90% respiratory symptoms (cough, wheezing, etc.)
  + failure to thrive
  weight loss
  night sweats

- 10% other symptoms (neurologic, abdominal, osteoarticular)

Try to avoid a disaster by giving “acritically” steroids in “undistressed” wheezy children !!!!
Tuberculosis in children

- Epidemiology
- Transmission
- Immune response to infection
- Classification
- Clinical manifestations
- Diagnosis
- Treatment
The diagnosis of childhood tuberculosis presents a major challenge, as the “gold standard” - that is confirmation of infection by demonstration of *M. Tuberculosis* - is commonly not achieved and is often not attempted.
Criteria for the diagnosis of pulmonary TB

Two or more of the following:

- History of close contact with known or suspected case of TB (frequently within the household)
- Positive tuberculin skin test
- Radiographic findings compatible with TB
- Positive TB stain of sputum or gastric lavage
- Response to anti-TB therapy
  (decrease symptoms, increase weight of 10%)
Recognizing TB in children

In TB, the personal history should always be interpreted in conjunction with the family history.

Symptoms of TB are usually scanty. Children may manifest:

- 90% respiratory symptoms (cough, wheezing, etc.)
  + failure to thrive
  weight loss
  night sweats

- 10% other symptoms (neurologic, abdominal, osteoarticular)
“There is a sense of scepticism regarding the potential value of symptom-based diagnostic approaches for TB. However, the natural history of childhood TB demonstrates that symptoms may offer good diagnostic value if they are well-defined and if appropriate risk stratification is applied”
A symptom-based approach to diagnose pulmonary tuberculosis in children

*Marais, Pediatrics 2006;118:e1350*

1- Persistent non-remitting cough > 2 week duration
2- Failure to thrive in the preceding 3 months
3- Reported fatigue

Pulmonary tuberculosis can be diagnosed with a reasonable degree of accuracy in HIV-uninfected children using a simple symptoms-based approach.

<table>
<thead>
<tr>
<th>Combined Variables at Presentationa</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Low-risk children</td>
<td></td>
</tr>
<tr>
<td>≥3 years and HIV uninfected</td>
<td>82.3</td>
</tr>
<tr>
<td>High-risk children</td>
<td></td>
</tr>
<tr>
<td>&lt;3 years and HIV uninfected</td>
<td>51.8</td>
</tr>
<tr>
<td>HIV infected (irrespective of age)</td>
<td>56.2</td>
</tr>
</tbody>
</table>
Tuberculosis during infancy

Tertiary care Greek hospital
from 1982 to 1998

33 children (mean age 10 month) with endo thoracic TB

The presence of cough and wheezing in unwell infants should always induce to suspect TB
Microbiologic diagnosis

- Microscopy (Ziehl-Nielsen, Auramine)  
  (low sensitivity; specific; short time, min.  
  no distinction between MTB and NMTB)

- Culture (Lowenstein, radiometric, liquid culture)  
  (low-medium sensitivity; high specificity; time, wks;  
  distinction between MTB and NMTB)

- Nucleic acid amplification test (PCR technique - IS6110)  
  (medium sensitivity; high specificity; short time: hours;)

Negative PCR never eliminates TB as diagnostic possibility,  
and a positive result does not confirm it!
The diagnostic value of different bacteriologic specimens in pulmonary TB

- Induced sputum
  *(mean rate of isolation = 25-30%)*

- Gastric aspirates
  *(mean rate of isolation = 25-40%)*

- Bronchoalveolar lavage
  *(mean rate of isolation = 40-50%)*

Unrespective of the method used, the bacteriologic yield mainly depends on the specific intrathoracic disease manifestations.
What a microbiology laboratory should do after cultivation of mycobacteria?

- Identification of *M.* from culture
- Testing drug susceptibility
- Genotyping of *M. tuberculosis*
Mantoux testing & readings

- The use of Mantoux testing to identify TB infection has been based on the size of skin induration present in a single reading (after 48-72 hrs)

- The recommendation is that Mantoux tests be read in a single axis, perpendicular to the long axis of the forearm; this ensures consistency with other international TB control agencies
Problems with tuberculin skin test

- Reading is observer-dependent

\[ \text{Intrinsic variability} \]

- The antigens for testing are not specific for MTB
- Possible interference of BCG vaccination

\[ \text{Low specificity (false positive)} \]

- Cutaneous delayed-type hypersensitivity to MTB may take up to 12 weeks to develop
- False negative reactions (“anergy”) may occur

\[ \text{Low sensitivity (false negative)} \]
Factors causing false negative tuberculin skin tests

Factors related to the person being tested
- infections (viral, bacterial, fungal)
- live virus vaccination
- diseases affecting lymphoid organs (leukemia, etc.)
- drugs (steroids, immunosuppressors)
- age (newborns, elderly patients)
- stress (surgery, burns, etc.)

Factors related to the tuberculin used
- improper storage
- improper dilutions
- contamination

Factors related to the method of administration
- injection of too little antigen
- subcutaneous injection

Factors related to reading test and recording results
Interpretation of tuberculin skin test

“positive” or “negative”?

Cut-off points are different and mainly depend on the objective (i.e. cut-off used in population prevalence studies are not applicable to the evaluation of individual patients).

The predictive value of the test is not only a function of the test by itself, but also of the circumstances under which it is done (clinical, geographic, epidemiologic and socioeconomic context).
<table>
<thead>
<tr>
<th>Interpretation as “positive” Mantoux reaction in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>• Close contacts with known or suspected infectious TB</td>
</tr>
<tr>
<td>• Suspected of having TB</td>
</tr>
<tr>
<td>- chest x-ray</td>
</tr>
<tr>
<td>- clinical signs or symptoms</td>
</tr>
<tr>
<td>• Immunocompromised children (HIV, transplant, drugs, etc.)</td>
</tr>
<tr>
<td>≥ 10 mm</td>
</tr>
<tr>
<td>• Children at increased risk of dissemination</td>
</tr>
<tr>
<td>- age ≤4 yrs</td>
</tr>
<tr>
<td>- specific health conditions (diabetes, lymphoma, etc.)</td>
</tr>
<tr>
<td>• Children at increased risk of exposition to TB</td>
</tr>
<tr>
<td>- born in, or with parents from endemic areas</td>
</tr>
<tr>
<td>- contact with adults with HIV, drug added, etc.</td>
</tr>
<tr>
<td>- travel to endemic area</td>
</tr>
<tr>
<td>≥ 15 mm</td>
</tr>
<tr>
<td>• Any child &gt;4 yrs without risk factors</td>
</tr>
</tbody>
</table>
The ability of two highly antigenic proteins (ESAT-6 and CFP-10), which are restricted to *M. Tuberculosis*, to stimulate T cells forms the basis for novel assays that assess the presence of tuberculosis infection by detection of release of interferon-gamma by T cells in response to these antigens *in vitro*.

These antigenic proteins are present in a genome fraction of *M. Tuberculosis* which is attenuated (RD1: Region of Difference 1) in BCG vaccine.
The immunological basis for TST and interferon-gamma tests
The Interferon-Gamma Release Assays (IGRA)

- Enzyme-Linked ImmunoSpot (T-Spot.TB)
- QuantiFERON TB Gold (QFG)
  QuantiFERON TB Gold in tube (QFGIT)
The Interferon-Gamma Release Assays (IGRA)

Whole blood (diluted or undiluted/peripheral blood mononuclear cells) → Incubation (overnight or 5–6 days) → Sensitised T cells released IFN-γ → IFN-γ production measured using ELISA (e.g., QuantiFERON-TB) or ELISPOT (e.g., T SPOT-TB) → Results expressed as IFN-γ (pg·mL⁻¹ or IU·mL⁻¹) or number of IFN-γ secreting T cells (spot-forming cells)
The Interferon-Gamma Release Assays (IGRA)

- less compromised than TST by HIV-infection
- more specific than TST in BCG vaccinated individuals
- cannot differentiate between latent and active TB
- not sufficiently accurate to predict the risk of TB
IGRA do not identify more children with active tuberculosis than the tuberculin skin test

*Kampmann, ERJ 2009;33:1374*

209 children investigated for active (n. 91) or latent TB (n. 118) with:
TST, QFG-IT, T-SPOT.TB

A negative IGRA should not dissuade pediatricians from diagnosing and treating active TB
IGRA do not identify more children with active tuberculosis than the tuberculin skin test

*Kampmann, ERJ 2009;33:1374*

209 children investigated for active (n. 91) or latent TB (n. 118) with: TST, QFG-IT, T-SPOT.TB

If used for diagnosis of latent TB, IGRA could significantly reduce the number of children receiving chemoprophylaxis
Tuberculosis in children

- Epidemiology
- Transmission
- Immune response to infection
- Classification
- Clinical manifestations
- Diagnosis
- Treatment
Aims of antituberculosis treatment

Antituberculosis treatment aims to cure the patient and to prevent the emergence of drug-resistant organisms within the community by adhering to the following 3 principles:

1- Inducing rapid reduction of the organism load (to improve clinical symptoms, limit disease progression, terminate transmission, prevent the emergence of drug resistance)

2- Ensuring effective eradication of dormant and intermittently metabolizing (persistent) bacilli (to prevent disease relapse)

3- Achieving this with the minimal adverse effects for the child
Phases of antituberculosis treatment

Period 1 (last 2-3 days)
Fast-growing extracellular bacilli are killed, mainly by the excellent bactericidal activity of INH

Period 2 (last 2-8 weeks)
Slower growing extracellular bacilli are killed. The rate of killing is determined more by the physiological state of bacilli and less by the bactericidal activity of the drugs

Period 3 (last 4-6 months)
Persistent intracellular bacilli are eradicated mainly by RMP, although INH will continue to offer protection against the development of resistance. Host immunity plays an important role to effect organism eradication and to prevent disease relapse
The problem of drug resistance

• The number of drug-resistant, naturally occurring mutants is proportional to the size of mycobacterial population.

• Random resistance to multiple drugs is extremely rare, and therefore the use of multiple drugs in combination during the intensive phase of treatment drastically reduces the risk of treatment failure.

• The risk of random drug resistance is virtually eliminated once the intensive phase of treatment is successfully completed and the bulk of the organism load has been eliminated.
Because of the paucibacillary nature of their disease, children rarely contribute to the emergence of drug resistance, however they are greatly affected by it.

Multidrug resistant tuberculosis is defined as resistance to rifampicin and isoniazid, with or without other drug resistance.

Isoniazid resistance can occur when preventive therapy with this drug is inadvertently given to patients with subclinical or unrecognized tuberculosis.
Resistance of M.T. in Italy

Combined multidrug resistance, by origin, 2001-2005
Data representativeness unknown

% resistance

- 6%
- 4%
- 2%
- 0%

2001 2002 2003 2004 2005

Native
Foreign born
Management of TB: practical key points

- The most common cause of treatment failure and acquired drug resistance is non-adherence.
- Directly observed therapy (DOT) is the most effective means of combating non-adherence.
- Intermittent regimens may facilitate therapy.
- Testing the susceptibility of *M. tuberculosis* to drugs is essential for tailoring treatment.
Drug therapy for TB: useful concepts

- Acetylator status for Isoniazid

- Bactericidal activity
  - Early bactericidal activity
  - Sterilizing activity

- Drug resistance
  - Primary resistance
  - Acquired resistance

- Post-antibiotic effect
Management of “exposed children”

Class I

1- Determine the source of the infection and the susceptibility to drugs.

2- Begin treatment (*primary prophylaxis*) with INH alone (*) in:
   - children younger than 4 years of age
   - children with risk factors for disease

3- Repeat Mantoux after 12 weeks (***)
   a) if negative (and no longer exposed): stop treatment
   b) if positive: consider the patient as “infected” and treat consequently

(*) If the child is infected with INH-resistant strain, use RFP
(**) In immunocompromised children, the TST is not sufficiently reliable test to exclude TB infection and exposed children should be treated as “infected”
Management of “latent TB infection”
Class II

Daily treatment (secondary prophylaxis) with INH alone (or RFP if there is resistance to INH) (*) for 6-9 months

(*) The mycobacterial load is small in this case and the probability of a resistant organism to even a single drug is very low
Management of latent TB infection

Class II

The following groups should be treated:

- All children and adolescents with “positive” TB test
- All close contacts of any age with Mantoux >5 mm
- People with HIV infection with Mantoux >5 mm
- People with positive TB reaction and special clinical conditions (diabetes, etc.)
- New infected people regardless of age who have had Mantoux conversion in the past 2 yrs
- People with past TB who received inadequate treatment
# Treatment of current disease
## Class III

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>INH, RFP, PZA</td>
<td>INH, RFP</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>daily x 2 months</td>
<td>daily (or 2-3/week) x 4 months</td>
</tr>
<tr>
<td>Meningitis</td>
<td>INH, RFP, PZA, STM (or ETN) daily for 2 wks</td>
<td>INH and RFP daily (or 2-3/week) x 6-9 mths</td>
</tr>
</tbody>
</table>

- *The daily regimen is used when patients self administer their drugs*
- *The intermittent regimens are intended for directly observed therapy*
Drug resistance for *MTB*

- *MTB* becomes resistant to single drugs through random, *spontaneous mutations* at a fixed rate (RIF $1/10^8$, ISH $1/10^6$, ETH $1/10^4$).

- Adults with cavitary pulmonary TB have bacillary load of the order of $10^9$ organisms.

- The probability of spontaneous resistance to multiple drugs is remote (RIF + ISH: $Rif 1/10^8 \times ISH 1/10^6 = 1/10^{14}$).

- MDR can develop only with the assistance of inadequate antibiotic therapy (*acquired resistance*).
# Antituberculosis drugs

## Dosages and adverse effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Daily</th>
<th>Dosage Twice –Thrice weekly</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>10-15 mg/kg oral</td>
<td>20-40 mg/Kg/dose</td>
<td>Hepatitis, peripheral neuritis, lupus, seizures, hypersensitivity with rash and fever. Drug interactions with dilantin</td>
</tr>
<tr>
<td></td>
<td>(max 300 mg)</td>
<td>(max 900 mg/dose)</td>
<td></td>
</tr>
<tr>
<td><strong>Rifampicin</strong></td>
<td>10-20 mg/kg oral</td>
<td>10-20 mg/kg/dose</td>
<td>Orange body secretions, flu-like syndrome, hepatitis, thrombocytopenia, leukopenia, nausea, multiple drug interactions</td>
</tr>
<tr>
<td></td>
<td>(max 600 mg)</td>
<td>(max 600 mg/dose)</td>
<td></td>
</tr>
<tr>
<td><strong>Pyrazinamide</strong></td>
<td>15-30 mg/kg oral</td>
<td>50-70 mg/kg/dose</td>
<td>Hyperuricemia, hepatitis, rash, anorexia</td>
</tr>
<tr>
<td></td>
<td>(max 2 g)</td>
<td>(max 4 g)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethambutol</strong></td>
<td>15-25 mg/kg oral</td>
<td>50 mg/kg/dose</td>
<td>Optic neuritis, gastrointestinal discomfort</td>
</tr>
<tr>
<td></td>
<td>(max 2,5 g)</td>
<td>(max 2,5 g)</td>
<td></td>
</tr>
<tr>
<td><strong>Streptomycin</strong></td>
<td>20-40 mg/kg iv or im</td>
<td>25-40 mg/dose</td>
<td>Ototoxicity, vestibular dysfunction, nephrotoxicity, rash, hypersensitivity reactions</td>
</tr>
<tr>
<td></td>
<td>(max 1.5 g)</td>
<td>(max 1.5 g)</td>
<td></td>
</tr>
</tbody>
</table>
Management of previous TB disease

Class IV

Consider single cases
Management of suspected TB disease
Class V

Consider single cases
Nonadherence has a differential diagnosis

(psychologic, sociologic, religious, economic and practical reasons)
Poor treatment multiplies the number of surviving, infectious cases in the community and, thus, actually deteriorates the epidemiological situation.

Stephen Grybowski, 1991
La TB esiste anche in Italia....
Caso 4

Sundas, 10 anni, pakistan

Dolori addominali da diversi mesi, calo ponderale 3 kg

Ad aprile, esami di routine: VES e indici di fogosi elevati

A giugno ricovero in ospedale 2° livello: indici di flogosi elevati, anemia sideropenica, disprotidemia, etc.

Tel eco-addome “ispessimento parietale del ceco e parte del colon ascendente”; sangue occulto positivo

Tutto confermato + Mantoux 20 mm
Abdominal TB: MRI findings

21/7/2006

Salesi Children’s Hospital, Ancona
Abdominal TB: endoscopy

de Benedictis, Gastroenterology, 2008

Salesi Children's Hospital, Ancona
Abdominal TB: endoscopy

de Benedictis, Gastroenterology, 2008

Salesi Children’s Hospital, Ancona
Caso 5

Azzurra, italiana, 24 mesi

Febbre isolata 38,5° ➔ antibiotici

Ricovero Ospedale 2° livello per il persistere della febbre ➔ VES elevata; Rx-torace: negativo

Dopo alcuni giorni, inappetenza, irritabilità, astenia, vomito, strabismo, compromissione dello stato di coscienza ➔ TC cranio: “idrocefalo iperteso triventricolare”

Trasferimento Rianimazione Salesi ➔ RMN: “idrocefalo non comunicante e segni di meningite basale”; liquor indicativo di meningite tubercolare; Mantoux: negativa

Genitori OK – Badante della nonna: Cr mammella + TB
TB meningitis: CT scan

15/7/2006

Salesi Children's Hospital, Ancona

12/12/2006
Caso 6

Mihaela, rumena, 15 anni (in Italia da x anni)

2006: Trattamento con INH (x 18 mesi) per contatto con padre affetto da TB polmonare attiva. Mantoux 23 mm; ripetuti Rx-torace: negativi

Da ottobre 2008 tosse catarrale e calo ponderale di 6 kg
Dicembre 2008: Rx torace....
Caso 7

Rebecca, italiana, 3 anni

Storia di **mal di schiena** da alcuni mesi → antinfiammatori

Dolore acuto alla schiena per sobbalzo su slittino →
Rx-colonna: lesione osteolitica di L4 e L5 →
TC colonna: .... mai visto prima !
Mantoux: 20 mm

Genitori OK – Insegnante con TB cavitaria
Pott disease
la tubercolosi interessa tutti gli organi: valorizzate i sintomi

se il trattamento di una malattia presunta non è efficace, metti in dubbio la diagnosi ....

la tubercolosi (purtroppo) c’è
Tuberculosis in children

- Epidemiology
- Transmission
- Immune response to infection
- Classification
- Primary pulmonary TB and complications
- Chronic pulmonary TB
- Treatment
- Open questions
Open questions

- Indications for Mantoux test
- Role of BCG vaccination
- Distinguishing Mantoux reactions caused by BCG from those caused by natural infection
- Positive Mantoux test cut off
Indications for Mantoux testing

- Screening of high-risk groups
- Recent contact with a case of infectious TB
- Chest X-ray changes consistent with past inactive TB
- The presence (or in anticipation) of high risk medical conditions
- As a baseline, in employees whose work may involve an increased risk of TB exposure
- Prior to prolonged travel or employment in high TB prevalence countries/communities
- Prior to administering the BCG vaccine
- Prior to donation in potential live organ donors
BCG vaccination

- BCG is a suspension of live attenuated *M. bovis* and remains the only vaccine available for TB.

- The aim of BCG vaccination is not to prevent transmission of MTB but rather to prevent progression of infection to disease. (Its main role is in preventing meningeal and disseminated TB in young children for whom its efficacy is > 80%)

- It is not recommended for routine vaccination of adults, but may have benefits over a Mantoux screening policy in health workers expected to be exposed to multi-drug resistant TB.
La vaccinazione antitubercolare con BCG è obbligatoria per:

- soggetti cutinegativi a rischio di contagio di età compresa tra zero e 5 anni

- tutti coloro che operano in ambienti ad alto rischio di TB multi-farmacoresistente

- tutti coloro che operano in ambienti ad alto rischio di TB e presentano controindicazioni cliniche all’uso della terapia preventiva (che non possono essere sottoposti a chemioprofilassi in caso di cuticonversione)
E’ abolita:

- la vaccinazione generalizzata di tutti gli studenti iscritti alla Facoltà di Medicina e Chirurgia

- la vaccinazione generalizzata (e la rivaccinazione) nei Corsi Professionali Sanitari
Contraindications for BCG vaccination

- Mantoux reactions ≥ 5 mm
- Immunosuppression (HIV infection, drugs, etc.)
- High risk of HIV infection (includes neonates of HIV-positive mothers)
- Generalized skin disease
- Pregnancy
- A past history of BCG vaccination
- A past history of TB
Effect of BCG vaccination on Mantoux testing

- Most people vaccinated with BCG will develop a Mantoux reaction $\geq 10$ mm within 8-12 wks of vaccination.
- Reaction does not correlate with effectiveness of the vaccine.
- The likelihood and degree of persistence of this response is most strongly influenced by the age at vaccination:
  - If BCG is given in the 1st yr of life, it is unlikely to cause Mantoux reactions of $\geq 10$ mm after the age of 2 or 3 yrs.
  - Those vaccinated later in childhood are more likely to have persistent responses, but the majority of these will be $< 10$ mm within 10 years of vaccination.
How to interpret Mantoux reactions caused by BCG from those caused by natural infection?

- The most important factor influencing the probability that a tuberculin reaction represents true infection with MTB rather than the effect of BCG is the prevalence of LTBI in the population sub-group being tested.

- Some authorities recommend that BCG vaccination status be ignored when performing the Mantoux test if the patient is in a high risk group for TB infection or if the vaccine was given in infancy.

- In these instances the likelihood of true infection with MTB relative to a false-positive reaction is increased.
Disseminated (miliary) disease in children

This form of TB occurs predominantly in very young (immune-immature) and/or immune-compromised children (HIV-infected or severely malnourished).

These children have suboptimal cellular immune responses and demonstrate poor containment of the organism, both within the regional lymph nodes and at multiple sites of occult dissemination.