Isoniazid Preventive Therapy (IPT)

Josefina Cadorna-Carlos, M.D.

Professor of Pediatrics

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Objectives

1. Define IPT.

2. Discuss the indications for IPT.

3. Present RCT's for IPT (6H vs 9H).

Classification of Childhood TB (Am. Thoracic Society/CDC 1990)

Class I: TB exposure [TT (-), S/S (-), CXR (-)]

Class II: TB infection [exposure (+), TT (+), S/S (-), CXR (-)]

Class III: TB Disease

Class IV: TB Inactve

Classification of Childhood TB (Am. Thoracic Society/CDC 1990)

Class III: TB Disease

A child who has active TB has 3 or more of the following criteria

1. (+) Exposure
2. (+) Mantoux test
3. (+) S/S suggestive of TB
4. (+) CXR
5. Lab findings

Classification of Childhood TB (Am. Thoracic Society/CDC 1990)

Class IV : TB Inactive

(w/ or w/o [+] exposure ;

w/ or w/o previous tx;

has CXR evidence of healed or calcified TB;

[+] TT

[-] S/S Suggestive of TB

[-] Smear or TB culture)

WHO Guidance to the NTP's in the Mx of TB in Children, 2014

Isoniazid preventive therapy (IPT)
Recommendation 21 *(new)*

Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be given 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day)

(Strong recommendation, high quality of evidence)

Source: Recommendations for investigating contacts of persons with infectious tu- berculosis in low- and middle-income countries. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Why IPT?

- Risk to develop active TB following infection is high
  - Age
  - Immune status of the child
- Progress to active TB usually occurs within 12 months of primary infection.
- **Ref: Marais B.J. Childhood Tuberculosis (Chapter 14) Pediatric Practice: Infectious Diseases, 2009 p.332**

Table 36–1.

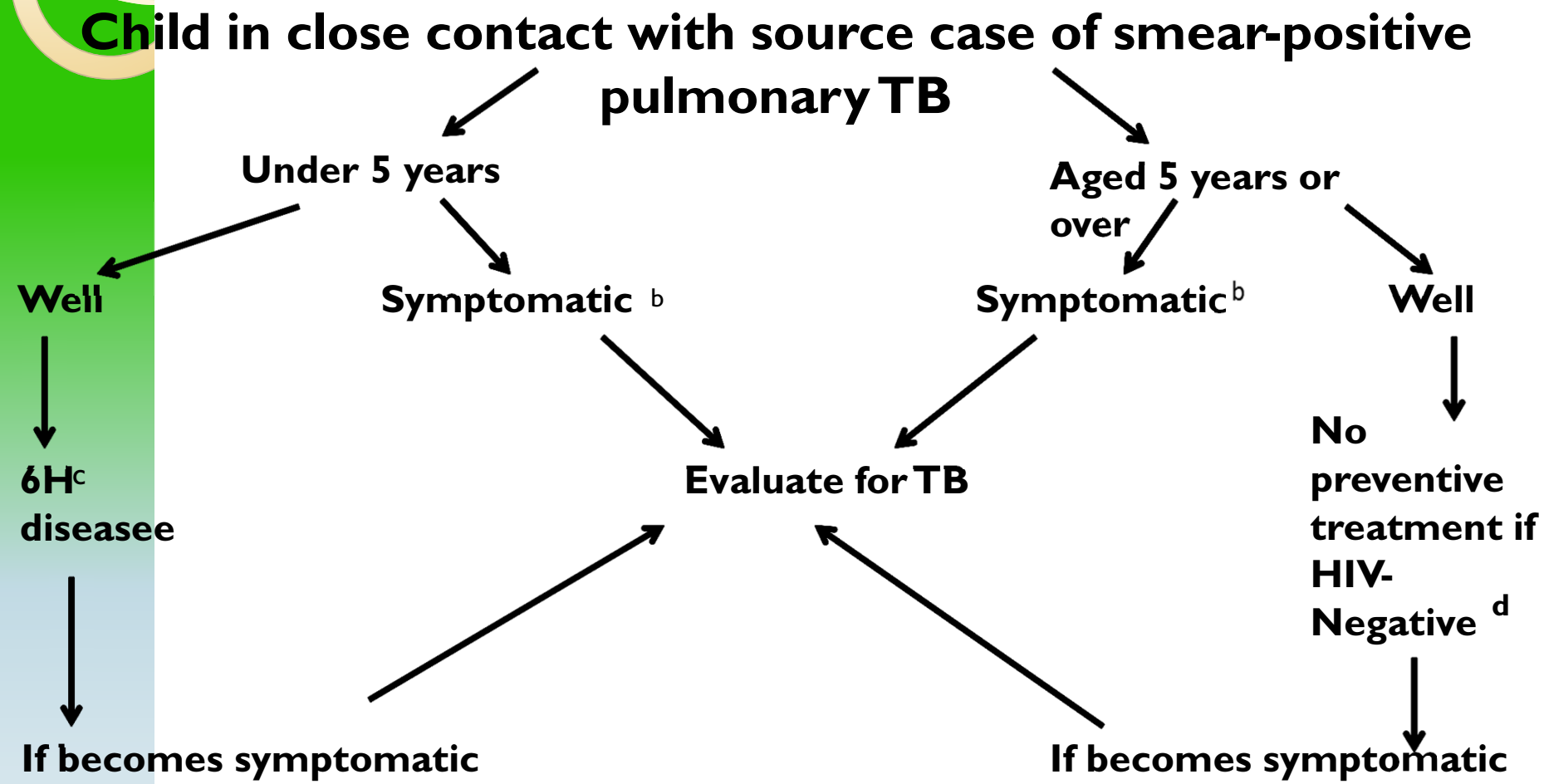
Age-Specific Risk to Progress to Disease Following Primary Infection with M. Tuberculosis in Immune-Competent Childre

Age at Primary Infection (Yr)	Risk to Progress to Disease	
<1	No disease	50%
	Pulmonary disease	30–40%
	Disseminated (miliary) disease or TBM	10–20%
1–2	No disease	75–80%
	Pulmonary disease	10–20%
	Disseminated (miliary) disease or TBM	2–5%
2–5	No disease	95%
	Pulmonary disease	5%
	Disseminated (miliary) disease or TBM	0.5%
5–10	No disease	98%
	Pulmonary disease	2%
	Disseminated (miliary) disease or TBM	<0.5%
>10	No disease	80–90%
	Pulmonary disease	10–20%
	Disseminated (miliary) disease or TBM	<0.5%

TBM, tuberculous meningitis.

With permission from Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(4):392–402.

Symptom-based screening approach to child contact management



Ref: WHO Guidance for NTP's on the management of TB in children, 2nd edition 2014

Isoniazid Preventive Therapy (IPT)

- IPT for six (6) months (H: 10 mg/Kg/day)

a. Children < 5 years with (-) S/S, (-) CXR and are household contacts of

i. A bacteriologically-confirmed TB case regardless of TST results

ii. A clinically diagnosed TB case (if the child has a positive TST result)

b. PLHIV with no signs and symptoms of TB regardless of age.

Isoniazid Preventive Therapy (IPT)

- Open form 4. TB Treatment/IPT Card and register the child in Form 9. IPT register.

- Monitor and assess child at least every two months (weight, S/S, adjust dosage of H according to weight
- If with S/S, treat as TB disease

Outcome of IPT

- Completed IPT: completed, remains well or asymptomatic during the entire period
- Lost to follow-up: interrupted IPT for 2 consecutive mos. or more
- Died: a child who dies for any reason during the course of treatment
- Failed: a child who develops TB disease during the course of tx
- Not Evaluated: transferred; outcome not known

Guidelines for TB prophylaxis

Category	Population at risk of infection/disease	Duration of Isoniazid (H)
Primary Chemoprophylaxis (Class 1)	Newborn of an infected mother PPD (-) Infants and children under 5 years exposed to TB	3 Months initially; after 3 months if PPD (-) discontinue H provided the infector is under therapy and give BCG; if PPD (+) continue H for 3 months more; if abnormal chest x-ray; add 2 more drugs, e.g. R and Z and treat as disease
Secondary Chemoprophylaxis	HIV infection/persons with risk factors for HIV infection whose HIV Status in not known	6 Months

Guidelines for TB Prophylaxis

Class II	Recent tuberculin conversion (within 1-2 years) with negative chest x-ray PPD (+) not due to BCG with negative chest x-ray and no benefit of previous TB chemotherapy	6 months 6 months
Class IV	PPD (+) with stable or healed parenchymal lesion and no previous chemotherapy PPD (+) with stable or healed TB with previous chemotherapy but are at risk of reactivation due to: a. Measles/ pertussis, etc b. Conditions/drugs that induce immunosuppression (IDDM, Chronic dialysis leukemia)	6 months 1-2 months For the duration of the immunosuppression

Ref: WHO Guidelines 2014; MOP-NTPP, 2013(DOH)

Treatment of LTBI

- WHO Guidelines 2014 **6 months of**
- MOP- NTP (DOH) 2014: **INH**

Other Recommendations

(Ref: Loeb, M.et al. Evidence-Based Infectious Diseases, 2nd ed, 2012, p 92)

Current ATS/CDC/AAP: **9 months of INH**

Cochrane Review 2010
INH for Preventing TB in Non-HIV Infected Persons

- Authors: Smeija M., Marchetti C., Cook D, Smeill FM.

6H vs 12 H : difference is not statistically significant

Treatment of LTBI

- Other recommendations

(Ref: Loeb, M.et al. Evidence-Based Infectious Diseases, 2nd ed, 2012, p 92)

2 month regimen of Rifampicin **(R)** and Pyrazinamide **(Z)** should only be considered if the risks justify the benefits

RCT on INH + RPT, weekly, x3m

- Ref: Villarino, ME, et al: Treatment for preventing tuberculosis in children and adolescents: RCT of a 3 mo., 12-dose regimen of a combination of rifapentine and INH. JAMA Pediatr 2015; 169: 247-255
- 29 study sites in the US, Canada, Brazil, HK(China) and Spain, Jun 2001-Dec 2010
- N=1058, 2-17 yrs

INH + Rifapentine, weekly, x3 mos

- Results: Completion rate – 88% (INH + RPT) vs 81% (9H)
- Satisfied the "non-inferior criterion"
- Safe and effective

Reactions:

- From Dr. Ben Marais

  " Twelve-Dose Drug Regimen Now Also An Option for Preventing TB in Children and Adolescents (JAMA Pediatr, March 2015 editorial)

- From Dr Phillip Fischer, Mayo Clinic

  "A key to effectiveness of TB therapy is 'adherence', so 'real world' treatments will have to be implemented carefully. . . . ."

Summary

- IPT is recommended and for better adherence, 6H is being pushed forward.
- Cost-benefit analysis of shorter regimens are needed.