Antituberculosis chemoprophylaxis in children

Solange G. David,1 Clemax C. Sant’Anna,2 Anna M. Marques3

Abstract

Objective: to present a review of the indication of antituberculosis chemoprophylaxis during childhood based on the Brazilian National Program for the Control of Tuberculosis (Programa Nacional de Controle da Tuberculose) standards, Brazilian Ministry of Health, and on new tendencies represented by the 1st Brazilian Consensus on Tuberculosis (I Consenso Brasileiro de Tuberculose).

Methods: related literature was selected from the Medline database and from publications of the Brazilian Ministry of Health.

Results: chemoprophylaxis is an effective and safe preventive treatment for tuberculosis in children. It is not conflicting with BCG vaccination campaigns, since its objective is to prevent tuberculosis infection from developing to tuberculosis disease.

Conclusions: international recommendations and recent national tendencies have proposed an increase in the indication of chemoprophylaxis during childhood. Therefore, measures aiming at increasing preventive treatment in Brazil become necessary.


Introduction

Antituberculosis chemoprophylaxis is a measure aimed at the prevention of tuberculosis (TB) that uses a specific antituberculosis drug, the isoniazid (INH). The use of INH has the objective of reducing the risk of patients carrying latent infections to develop clinical TB. Other forms of prevention, such as BCG vaccination, health education, and, especially, proper treatment of TB patients, also contribute to keep the disease under control.1

The application of chemoprophylaxis in children does not play a significant role in interrupting the transmission of TB.2 Considering TB morbidity and mortality, however, the use of a drug that is able to prevent the disease represents a significant advantage in the fight against TB from the perspective of each single patient.

Antituberculosis preventive therapy is not conflicting with BCG vaccination campaigns for non-infected individuals.3 In Brazil, the BCG vaccine coverage is significant and, thus, healthcare professionals frequently face the need for considering the indication of chemoprophylaxis in BCG-vaccinated children who had close contact with tuberculous adults. The indication of chemoprophylaxis in this situation is fully dependent on medical criteria, since there are no national healthcare standards in this sense.
Although being effective in reducing risk for TB and one of the most effective means of prevention, chemoprophylaxis is not yet widely used in Brazil.\textsuperscript{4}

Our objectives are to underscore the importance of chemoprophylaxis as a means to control TB, to review indications of chemoprophylaxis according to the Brazilian National Program for the Control of Tuberculosis standards, Brazilian Ministry of Health, and to review expanded use of chemoprophylaxis to high-risk groups, in accordance with the recommendation of the 1997 1st Brazilian Consensus on TB.\textsuperscript{4}

**Chemoprophylaxis**

Antituberculosis preventive therapy was introduced during the 1950s, after a breakthrough in antimicrobial drugs that revolutionized TB treatment.\textsuperscript{2} During the 1950s, until 1960, a combination of INH and periodic acid-Schiff (PAS) was used in 18-month treatments. Later, in 1961, the use of INH alone was recommended in 12-month treatments.\textsuperscript{6}

In 1967, the American Thoracic Society (ATS) was the first institution to officially recommend the use of chemoprophylaxis for patients with latent infection and who were considered at high risk for developing the active form of the disease.\textsuperscript{7}

The main objective of chemoprophylaxis is to prevent latent infections from developing to clinical TB (secondary prophylaxis). Chemoprophylaxis can also be used to prevent tuberculous infections; in this case, it is named primary prophylaxis.\textsuperscript{1}

**Principles**

Preventive therapy with INH either reduces or eliminates small bacterial populations in new or residual lesions. Usually, increased numbers of bacilli are found in TB patients, which results in a larger possibility of having microorganisms genetically resistant to single-drug therapy. Infected patients who have reduced numbers of bacilli are less likely to present drug-resistant bacilli and thus more likely to present successful results in single-drug therapy.\textsuperscript{3}

INH alters the metabolism of the TB bacillus and reduces or eliminates the live or quiescent population of bacilli in tuberculous lesions. Consequently, the probability of bacilli replicating and defeating the patient’s immune defenses is reduced.\textsuperscript{3}

During the 1950s and 60s, the United States Public Health Service carried out a randomized study in 30 Alaskan communities with high rates of TB infection. The studied population was divided into two groups; one received INH treatment, and the other received placebo. Results indicated that the risk for acquiring TB was significantly reduced (60%) in the INH group during the period in which the drug was administered and for the following 6 years.\textsuperscript{8}

Despite the consensus of several studies as to what concerns the protective effect of INH administered to different populations and under a variety of conditions, there is a controversy concerning the duration of the drug protective effect.

Studies carried out in Alaska during the 1960s and 70s that followed patients for 20 years showed that the protective effect of INH persisted for over 19 years after its administration. The results of the studies disproved the hypothesis that risk for TB was suppressed only during the administration of isoniazid, and suggested the hypothesis that the reduced risk for TB produced by the drug is lifelong.\textsuperscript{9}

The effectiveness of chemoprophylaxis has been confirmed by numerous studies carried out by the United States Public Health Service. In a randomized study with 2,750 children presenting asymptomatic tuberculous infection, results indicated a reduction of 88% of TB cases during a 10-year follow-up of patients who where administered INH in comparison to those who were administered placebo. Moreover, the protective effect against miliary tuberculosis and meningitis was of 100%. Results of another study with 15,024 children who had close contact with TB patients that were being administered INH indicated a reduction of 66% in the incidence of TB.\textsuperscript{10}

The clinical survey performed by Houston & Hsu started in 1953 and was concluded after a 30-year follow-up of 2,494 children. They described the protective effect of INH against the development of TB in children younger than 4 years of age. Due to the long period of the study, many of the followed children became adolescents; so, the protective effect of chemoprophylaxis in patients of this age group could be assessed.

All patients who present positive reaction to tuberculin test and high risk for developing TB disease can benefit from the use of INH. The positive effects of the drug persist for over 20 years and can present lifelong positive effects,\textsuperscript{11} except in cases of INH administered with the objective of preventing the installation of TB infection. In this case, INH protects patients only during the administration period.\textsuperscript{12}

The probability of infections developing to tuberculous disease depends on various factors, and many of them are patient-specific. Prior to the indication of chemoprophylaxis, it is important to consider the risks for developing the disease, the toxic effects of INH, and the positive social effects of preventive therapy in avoiding the installation of new disease foci.\textsuperscript{12}

**The use of INH in preventive therapy**

The use of INH alone is effective, safe, and does not present risk for the selection of mutants that are resistant to the drug in *Mycobacterium Tuberculosis*-infected patients, due to the reduced number of bacilli found in the focus of infection.\textsuperscript{13} In addition to the advantage of oral
administration and low cost, INH is a bactericide and presents reduced toxicity. INH is also highly effective against the M. Tuberculosis and inhibits most strains in vitro, at concentrations of 0.05 to 0.2 μg/mL. A dosage of 3-5 mg/kg/day produces a peak concentration of 5 μg/mL.\[12\]

INH is administered to children in single doses of 10 mg/kg/day, maximum 400 mg/day, for a period of 6 months. Higher doses or longer periods of administration are not necessary, according to a study performed by the WHO, in which 28,000 patients were followed for 5 years; results indicated a 65% reduction in the incidence of TB after 6 months of TB preventive therapy with INH.\[15,16\]

Asymptomatic increase of transaminase due to the use of INH occurs in less than 2% of cases, and clinical hepatitis occurs in less than 1%. Hepatitis is the most important toxic effect of INH.\[11\] In a study carried out by Dash et al., in Maryland,\[17\] with a population of 5,300 patients submitted to a 12-month chemoprophylaxis with INH, the authors verified that the need for treatment interruption due to the INH side effects increased with age. Hepatitis probability was of 0.6% in patients with less than 15 years of age, and of 4.3% in patients over 55 years of age. In this sense, routine exams with dosages of glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) are not necessary, unless the patient presents previous history of hepatic disease. It is important that the patients’ relatives be informed that the use of NIH should be interrupted in case of vomits, abdominal pain, and jaundice.\[11\]

Despite the low probability of INH-induced hepatitis, the risks for peripheral and hepatic alterations increase with age. Patients who are over 35 years of age, present alcoholism or substance abuse, are pregnant, or have chronic hepatopathy are especially sensitive to INH. Patients with higher risk for side effects should be submitted to monthly tests of hepatic function throughout the course of the preventive therapy.\[18\]

**Indication**

Chemoprophylaxis indications vary according to the epidemiological situation and health standards found in different countries. In Brazil, indications are restricted to groups presenting higher risk for the development of TB and its complications. The modalities of chemoprophylaxis are\[18,19\]:

- Primary;
- Secondary;
- Chemoprophylaxis in HIV-positive patients.

**Primary chemoprophylaxis**

Primary chemoprophylaxis is indicated for patients who have not been previously infected with M. Tuberculosis. The most important indication is for newborn patients who had close contact with adults carrying bacillary TB. In this case, a protective effect of 80% is described.

In primary chemoprophylaxis, INH is administered for 3 months, and a tuberculin test is carried out during the 3rd month. If the patient is positive for tuberculin test, the INH therapy is maintained for 6 months. If the patient is negative, the INH therapy is quitted, and BCG vaccination is administered.

**Secondary chemoprophylaxis**

Secondary chemoprophylaxis is indicated for patients previously infected with the TB bacillus, in the following situations:

- Children younger than 5 years of age, non-BCG vaccinated, asymptomatic, with normal chest X-ray, positive for tuberculin test, and who had close contact with adults carrying bacillary TB.
- Special clinical situations, with patients presenting a high risk for developing the disease, such as in cases of immunodepression, use of immunosuppressants, or long-term corticotherapy in patients who had contact with bacillary TB at home, all according to appropriate medical criteria.

**Chemoprophylaxis in HIV-positive patients**

Chemoprophylaxis in HIV-positive patients is indicated in the following situations:

- Patients who had contact, at home or outside home, with bacillary TB, independently of the tuberculin test result.
- Patients positive for tuberculin test (induration of 5 mm or more) and asymptomatic.
- Patients negative for tuberculin test (induration of less than 5 mm) and with CD4 below 350 cells/mm\(^3\), or total lymphocyte count lower than 1,000 cells/mm\(^3\).
- Patients with cicatricial lesions on X-ray or with positive tuberculin test results.

The 1st Brazilian Consensus on TB\[4\], promoted by the National Coordination of Sanitary Pneumology and by the Brazilian Lung and Tuberculosis Society in April of 1997, aimed at developing recommendations for the main tuberculosis-related problems and matters in Brazil. The Consensus reviewed and changed the content of the National Program for the Control of Tuberculosis standards and broadened the spectrum of chemoprophylaxis indication for the following situations:

- Patients who used to be in close contact with active TB and who are positive for tuberculin test (5 mm), independently of BCG vaccination. It is also recommended that patients in close contact with active TB and negative for tuberculin test be submitted to a new test after 2 or 3 months.
- Patients recently converted from absence of reactivity to strong reactivity in PPD findings (up to 2 years).
- Patients positive for PPD and with clinical statuses associated with immunodepression and/or with high-
risk TB incidence factors, such as alcoholism, insulin-dependent diabetes, silicosis and serious nephropathy, lymphomas, antineoplastic chemotherapy, long-term use of corticosteroids, intestinal by-pass, HIV+ or AIDS, and substance abuse.

- Patients with chest X-ray (fibrotic lesion) compatible with inactive TB and without previous history of proper chemotherapy.
- Patients presenting high risk situations for developing TB, such as in cases of close contact with the TB contamination source in HIV+ newborns, independently of the tuberculin test.

**Contra-indication**

During infancy, there are few restrictions to preventive therapy, since children can tolerate INH. However, cases of previous history of allergic reactions, hepatic lesion associated with INH, or any acute liver disease represent risk situations for serious toxic complications.²⁰

**Chemoprophylaxis in antituberculosis campaigns**

Preventive INH therapy against TB is aimed, mainly, at patients who present with tuberculous infection. Also, it does not oppose to BCG vaccination campaigns, which aim at the protection of noninfected individuals. One of the difficulties in implementing preventive INH therapy against TB is the availability of treatment funding, since most resources are destined for the treatment of tuberculous patients.

In the case of children, there are particular characteristics as to what concerns risk for infection. Usually, the contact with TB occurs at home, and it may also occur at school or day care centers. During the initial stage of contact with tuberculous adults, children are asymptomatic, present normal chest X-ray and negative tuberculin test. It is not possible to diagnose *M. Tuberculosis* infection during the initial stage of contact, since hypersensitivity to tuberculin test is delayed, and manifestation may occur up to 3 months after lung infection. The duration of exposure required for contamination with TB depends on the nature of infection source, on general air circulation, and on the interaction between the tuberculous adult and the child.²¹

Reactivity to tuberculin test is an indication that TB infection has occurred.²² The distinction between infection and disease is much more clear in adult patients than in children, since they usually present symptomatology and altered chest X-ray. Also, about 40% of infected, non-treated children are at risk for developing tuberculous disease during the first 2 years following the infection. During infancy, alterations in chest X-rays may be sudden, and children may be asymptomatic in 50% of cases.²¹

Preventive TB therapy during infancy has caused some controversy. Considering the effectiveness of INH described in the treatment of tuberculous infections and in the prevention of the TB progression, questions have been raised as to why the preventive treatment is not widely used in developed countries.

Both BCG vaccination and chemoprophylaxis strategies present implementation problems and difficulties. BCG vaccination, for example, does not confer absolute immunity and does not prevent primary infection with *M. Tuberculosi*s.

Chemoprophylaxis, in turn, although being effective, is a long-term treatment, and the adherence to the therapy is considered a problem. In the USA, it is estimated that less than one-third of patients carry out the treatment appropriately.²³

McAnulty et al.²⁴ determined the extent to which opportunities for prevention were missed among 153 patients with tuberculosis. Results indicated that 90 cases (59%) of TB could have been avoided, and that although 73% of the patients presented risk factors for developing TB, none of them were submitted to screening for tuberculosis. The authors observed that chemoprophylaxis failure due to non-adherence occurred in 11% of the study population.

In a multi-centered study carried out in 1985 in three different regions of the USA, Glassroth et al.²⁵ presented the following causes for the failure of tuberculosis prevention: patients were out of the healthcare system when developed tuberculosis; patients had access to the healthcare system, but were either not screened for tuberculous infection, or, when screened, were not offered preventive therapy when it was appropriate; patients whose tuberculin test was negative. The causes for failure of TB preventive therapy indicates that the successful prevention of tuberculosis requires the accomplishment of several different steps, and not simply the prescription of INH.

Fitzgerald & Gafni² assessed the cost-effectiveness of INH prophylaxis in Canada, in 1988. The studied population included low-risk patients with positive Mantoux skin tests. The authors observed that the preventive treatment costs could be considered reasonable, and thus the treatment was cost-effective. In this sense, the results indicate that preventive therapy is highly cost-effective for high-risk patients in contact with TB, which corroborates the indication of chemoprophylaxis.

In 1975, in the city of Ribeirão Preto, State of São Paulo, Ruffino Netto²⁶ evaluated the cost and impact of BCG vaccination campaigns and chemoprophylaxis for the Brazilian population in general and for different age groups. The implementation of BCG vaccination and chemoprophylaxis campaigns promotes an important impact on the number of expected cases of TB among patients either positive or negative for tuberculin test. A 10% increase in the coverage of these two types of programs, for example, would promote a different impact in each case. Chemoprophylaxis promotes an impact whose results are three times faster than those of BCG vaccination.
Considering healthcare funding, however, the ideal combination for an antituberculosis campaign, in Brazil, has to offer the lowest costs possible. Consequently, the study indicates that, in Brazil, healthcare funding should be first destined to BCG vaccination campaigns, and secondarily to chemoprophylaxis preventive therapies.

The implementation of chemoprophylaxis is not up to par yet in both developed and developing countries. The main problems described in the literature, which are related to low adherence to treatment, late or no prescription of chemoprophylaxis, are similar to those of developing countries, which face additional difficulties due to lack of healthcare funding.

The 1st Brazilian Consensus on Tuberculosis also recognized that chemoprophylaxis has been underused in Brazil and suggests its use expansion by including it into routine procedures of healthcare units. One of the possible causes indicated for underusing chemoprophylaxis is that BCG vaccination coverage has protective effect, and thus reduces the use of the tuberculin test as an indicator of infection. The Consensus considered this hypothesis unjustifiable, since the protective effect of BCG vaccination is optimally of 80% for the general population, and not for individuals at high risk of developing TB. In addition, the tuberculin test in individuals in close contact with TB patients can be overestimated, even in BCG-vaccinated individuals, since the reactivity to tuberculin test decreases with time. The risk for hepatitis, which may follow the use of INH, was considered minimal; so, it does not justify the underuse of preventive therapy. Other difficulties, such as adherence to treatment and unfeasibility for examining all apparently healthy individuals in contact with TB, in addition to the inadequate structure of many healthcare centers, were recognized as serious problems that will be difficult to overcome.

The Consensus estimates a reduction of 80% in the incidence of TB among patients in contact with bacillary TB following chemoprophylaxis. The Consensus also emphasizes the advantages of preventive INH treatment and its cost-effectiveness.

Limitations of chemoprophylaxis

Numerous operational problems present difficulties for the identification and treatment of all patients with positive tuberculin test. Even if it were possible to identify and treat all patients positive for tuberculin test, many of these treatments would be unnecessary, since among infected patients it is not possible to diagnose those who will develop TB disease.

Another difficulty in a hypothetical treatment of all infected patients would be the material and human resources required for the preventive program, which would probably deviate resources from TB treatment programs, especially in developing countries.

Adherence to preventive treatment is a difficulty that has to be faced by healthcare professionals, who should work towards convincing parents or persons in charge of children about the importance of following a long-term treatment in apparently healthy individuals.

Different perspectives in chemoprophylaxis

It is important to distinguish between patients infected with *M. Tuberculosis*, who present a greater possibility of developing TB disease, from those infected with tuberculous bacilli that cannot develop clinical TB. Future advances in molecular biology and immunology may help understand the factors that cause TB infection to develop to TB disease.

Experimental studies and clinical examinations using alternative therapeutic methods – 2-month long rifampicin and pyrazinamide treatment, or 4-month long rifampicin treatment – have presented promising results. These alternative treatments have reduced the duration of the preventive therapy and its toxicity, but it has not reduced its effectiveness, though. Another alternative presented is intermittent chemotherapy.

Immune systems made stronger through the activation of macrophages carrying intracellular bacillus, with the use of immunomodulators, may present a positive outlook for the prevention and treatment of TB.

A definite chemoprophylaxis scheme has not yet been determined for individuals in contact with patients presenting multiresistant tuberculosis. The concept of multiresistant tuberculosis, which is recognized in Brazil, is partially related to operational procedures. Since 1979, the Brazilian National Program for the Control of Tuberculosis standards have recommended that patients unsuccessfully submitted to scheme I (isoniazid, rifampicin, and pyrazinamide) and/or IR (isoniazid, rifampicin, pyrazinamide, and ethambutol) be indicated E3 (streptomycin, ethambutol, pyrazinamide, and ethionamide). The *in vitro* resistance to rifampicin and isoniazid and to one or two other drugs in the E3 scheme define the bacteriological concept of resistance.

In Brazil, multiresistant TB occurs mainly due to treatment failure, low therapeutic potential, and non-adherence or inconsistent adherence to treatment, with a yearly incidence rate of 0.4%. The total number of multiresistant TB patients in Brazil is reduced, and 50% of these patients are located in Rio de Janeiro and São Paulo.

Moreover, in Brazil, a definite scheme for the treatment of patients with multiresistant TB is not defined. It is understood that the best form of avoiding multiresistant TB is the adequate administration of scheme I (RHZ); to individuals in contact with patients carrying multiresistant TB, the association of pyrazinamide and ethambutol is recommended. In the USA, the Centers for Disease Control and Prevention (CDC), in turn, have suggested the use of pyrazinamide and quinolones as prophylactic drugs. The
sensitivity to tuberculostatics found in the index case can be used to provide guidelines for preventive therapy among individuals in contact with TB patients. The recommended duration of chemoprophylaxis is 6 months for healthy individuals and 12 months for patients with HIV infection.

Considering the effectiveness of chemoprophylaxis in avoiding the development of TB, the susceptibility of children in contact with bacillary TB, and the safety of INH administration in children, we have concluded that the indication of chemotherapy should be increased and more frequent. The increased number of situations to which preventive therapy is recommended, as suggested by the Consensus, is an appropriate response to assist healthcare professionals in their difficulties related to patients in contact with adults carrying bacillary TB, positive for tuberculin test, and BCG-vaccinated. In addition, the Consensus provides answers for different situations, allowing a better administration of chemoprophylaxis.

References

Correspondence:
Dr. Solange Gonçalves David de Macêdo
Rua Ari Parreiras, 689/904 - Icarai
CEP 24230-321 – Niterói, RJ, Brazil
Phone/fax: + 55 21 711.7868