
CLINICAL PRACTICE GUIDELINES

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LIGNES DIRECTRICES DE PRATIQUE CLINIQUE

Essentials of tuberculosis control for the practising physician

Tuberculosis Committee, Canadian Thoracic Society

Objective: To recommend guidelines for the management of tuberculosis (TB), particularly in high-risk groups including poor and homeless people, aboriginal Canadians, immigrants from countries where TB is highly prevalent and people with HIV infection.

Options: Diagnosis, pharmacotherapy, vaccination and chemoprophylaxis.

Outcomes: Prevention of infection and diagnosis and cure of TB.

Evidence: The evidence was gathered in late 1992 from previous guidelines, recommendations by specialist societies and new studies.

Values: Evidence was categorized into four levels: I, randomized clinical trials of therapeutic interventions or prospective studies of diagnostic strategies; II, case-control studies; III, retrospective descriptive studies; and IV, consensus of the committee members and published statements. The Tuberculosis Committee of the Canadian Thoracic Society comprises experts in TB from across Canada.

Benefits, harm and costs: The benefits of early diagnosis and prompt initiation of therapy are well documented. The cost effectiveness of antituberculous therapy in developing countries is well documented. In developed countries chemoprophylaxis has been shown to be cost effective, and directly observed chemotherapy has recently been hypothesized to have economic benefits.

Recommendations: In the appropriate clinical setting, particularly when patients are known to be at high risk of TB, clinicians should consider TB, reserve body secretions for mycobacteriologic tests and conduct other investigations such as chest radiography. Furthermore, if TB is strongly suspected or confirmed by appropriate investigation the early initiation of multi-drug therapy, including at least three first-line drugs, is strongly recommended. If drug resistance is suspected a regimen of four to five drugs, including at least two drugs with which the patient has not been treated, should be started. If the strain is found to be resistant to any of the drugs in the regimen appropriate changes should be made. Chemoprophylaxis should be considered especially in contacts with a recent significant reaction to the purified protein derivative (PPD) skin test and in people known to be at risk of reactivated TB infection, particularly those with HIV infection and a significant PPD skin-test result. Vaccination with bacillus Calmette-Guérin should be limited to high-risk groups, particularly aboriginal Canadians living on reserves.

Validation: These recommendations are based on a consensus of Canadian experts supported by other specialist societies and reference groups. They have been reviewed by the Standards Committee of the Canadian Thoracic Society.

Sponsor: The Canadian Lung Association and the Tuberculosis Committee of the Canadian Thoracic Society.

Members: Drs. J. Mark FitzGerald (chairman), consultant, Division of Tuberculosis Control, British Columbia Ministry of Health, Vancouver, BC, and Respiratory Division, University of British Columbia, Vancouver, BC; Edward A. Allen, director, Division of Tuberculosis Control, British Columbia Ministry of Health, Vancouver, BC; Anne Fanning, director, Tuberculosis Services, Alberta Health, Edmonton, Alta.; Vern Hoepfner, director, Tuberculosis Unit, Royal University Hospital, Saskatoon, Sask.; Earl S. Hershfield, director, Tuberculosis Control, Tuberculosis Central Services, Respiratory Hospital, Winnipeg, Man.; Monika Naus, medical consultant, Disease Control Service, Ontario Ministry of Health, Toronto, Ont.; Richard Menzies, assistant professor of medicine and epidemiology, McGill University, Montreal Chest Hospital, Montreal, Que.; and Donald J. MacIntosh, professor of medicine, Ambulatory Care Centre, Victoria General Hospital, Halifax, NS.

Consultants: Anna Brancker, senior analyst, Health Status Section, Canadian Centre for Health Information, Statistics Canada, Ottawa, Ont.; and Dr. C. Edward Ellis, associate medical officer of health, Health Department, Regional Municipality of Ottawa-Carleton, Ottawa, Ont.

Reprint requests to: Canadian Lung Association, 508-1900 City Park Dr., Gloucester, ON K1J 1A3

Objectif : Recommander des lignes directrices sur le traitement de la tuberculose (TB), particulièrement chez les groupes à risque élevé, y compris les pauvres et les sans abri, les Canadiens autochtones, les immigrants provenant de pays où la tuberculose est très endémique et les personnes infectées par le VIH.

Options : Diagnostic, pharmacothérapie, vaccination et chimioprophylaxie.

Résultats : Prévention de l'infection et diagnostic et traitement de la TB.

Preuves : Les preuves réunies à la fin de 1992 proviennent de lignes directrices antérieures, de recommandations de sociétés de spécialistes et d'études nouvelles.

Valeurs : Les preuves ont été classées en quatre catégories : I, études cliniques randomisées d'interventions thérapeutiques ou études prospectives de stratégies de diagnostic; II, études de cas-témoins; III, études descriptives rétrospectives; IV, consensus des membres du comité et déclarations publiées. Le Comité sur la tuberculose de la Société canadienne de thoracologie est constitué d'experts de la tuberculose de toutes les régions du Canada.

Avantages, préjudices et coûts : Les avantages du diagnostic précoce et de l'amorce rapide du traitement sont bien documentés. La rentabilité des traitements antituberculeux dans les pays en développement est bien documentée. Dans les pays industriels, la chimioprophylaxie a démontré sa rentabilité et l'on a posé récemment comme hypothèse que la chimiothérapie observée directement présente des avantages économiques.

Recommandations : Dans le bon contexte clinique, particulièrement lorsque l'on sait que les patients courent un risque élevé d'être atteints de tuberculose, les cliniciens devraient envisager la possibilité de TB, réserver les sécrétions corporelles pour procéder à des analyses mycobactériologiques et effectuer d'autres examens comme les radiographies pulmonaires. En outre, si un cas de TB est fortement soupçonné et confirmé par une analyse appropriée, on recommande fermement la mise en oeuvre rapide d'une polypharmacothérapie comportant au moins trois médicaments de choix. Si l'on soupçonne une résistance aux médicaments, il faudrait entreprendre une thérapie à quatre ou cinq médicaments comportant au moins deux médicaments que le patient n'a jamais pris. Si l'on constate que la souche est résistante à un des médicaments, il faut modifier la thérapie comme il se doit. Il faudrait envisager une chimioprophylaxie particulièrement chez les sujets qui ont été en contact avec une personne infectée par la TB et qui ont réagi vivement à une cutiréaction récente à la tuberculine purifiée, ainsi que chez les sujets où le risque de réactivation de la TB est connu, particulièrement les personnes infectées par le VIH et les sujets qui réagissent vivement à la cutiréaction à la tuberculine purifiée. La vaccination au bacille de Calmette-Guérin devrait être limitée aux groupes à risque élevé, en particulier aux Canadiens autochtones qui vivent dans des réserves.

Validation : Ces recommandations sont fondées sur un consensus d'experts canadiens appuyés par d'autres sociétés de spécialistes et des groupes témoins. Le Comité des normes de la Société canadienne de thoracologie les a revues.

Commanditaire : L'Association pulmonaire du Canada et le Comité de la tuberculose de la Société canadienne de thoracologie.

There is a common misconception that tuberculosis (TB) has been eliminated and that there is therefore little need for further attention to control measures. This is, unfortunately, false.¹ Most physicians encounter TB infrequently and are unfamiliar with its many aspects.^{2,3} This statement provides the epidemiologic features of TB in its Canadian and international context and guidelines for the diagnosis, treatment and prevention of TB for nonspecialists. We recommend that readers refer to the Canadian Tuberculosis Standards published by the Canadian Lung Association and the Canadian Thoracic Society⁴ when a more detailed explanation of the recommendations is required. These guidelines will be of interest to all physicians, especially those caring for groups at high risk of TB. This article follows the recent recommendations for guidelines development.⁵ We reviewed the literature supporting the recommendations and categorized articles according to the following levels of evidence.

- Level I: Randomized controlled trials of therapeutic interventions or prospective studies of diagnostic strategies.
- Level II: Case-control studies.
- Level III: Retrospective descriptive studies.
- Level IV: Consensus based on the experience of committee members and previously published statements.

Epidemiologic features of TB and high-risk groups

Before the 1980s the incidence of TB had been declining in developed countries. The spread of HIV infection has reversed this decline in many countries, including the United States.⁶ In some regions of the world, notably sub-Saharan Africa,⁷ the arrival of HIV has had a tragic effect on the TB situation. In Canada after a steady decline over two decades the number of newly di-

agnosed cases of TB increased by 4.5% in 1989⁸ before falling again by 1.5% in 1990. The exact cause of the increase in cases is uncertain but the concentration of these cases in Ontario, Saskatchewan and the Northwest Territories suggests that they are probably not related to HIV infection. Based on British Columbia data, probably less than 2% of the active cases of TB in Canada since the start of the HIV and AIDS epidemic have been associated with HIV infection.⁹ However, the relative risk of TB in a person with HIV infection is higher than any other relative risk (approximately 400 times the risk of TB in most Canadians). Thus, the relatively minor effect of HIV on the prevalence of TB in Canada could easily be exacerbated if HIV becomes established in the segments of Canadian society that are disadvantaged or that have an increased prevalence of tuberculous infection, especially aboriginal Canadians¹⁰ and some immigrant groups.

Important risk groups in Canada other than people with HIV infection are aboriginal Canadians,¹¹ foreign-born people from countries with a high prevalence of TB,^{12,13} poor or homeless people,¹⁴ disaffected inner-city

residents prone to abuse of various substances, especially intravenous drugs, which may lead to HIV infection, and elderly people, especially elderly single men.¹⁵ The incidence of TB is higher in northwestern Canada and inner-city areas than in other regions of Canada, reflecting the location of these high-risk groups.

Diagnosis

A general algorithm for interventions to prevent and treat TB is presented in Fig. 1.

Approximately 85% of patients with TB present with pulmonary disease. Most active cases of TB are confirmed by culture of *Mycobacterium tuberculosis*. Cases without bacteriologic proof (approximately 15% of pulmonary cases) are diagnosed on the basis of changes on chest radiographs consistent with active TB, symptoms (discussed later) and a significant reaction to the purified protein derivative (PPD) skin test. Extrapulmonary TB may also be diagnosed on the basis of characteristic pathological findings and clinical presentation. Extrapulmonary disease is more common in patients

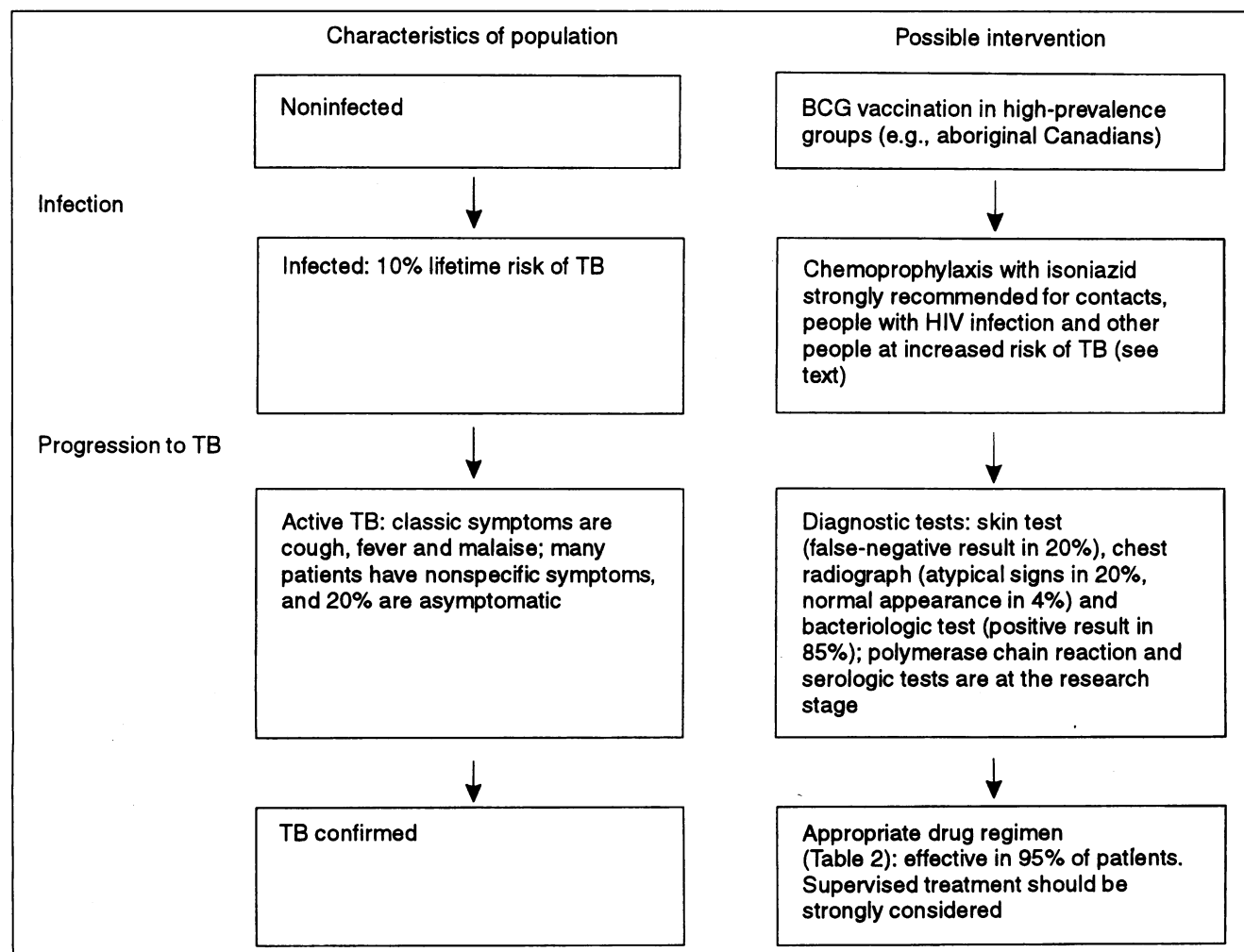


Fig. 1: Algorithm for interventions at various stages of tuberculous infection and disease. TB = tuberculosis, BCG = bacillus Calmette-Guérin.

with HIV infection⁶ and those from certain ethnic groups, including Asians and aboriginal Canadians, than in other patients.¹⁶ Primary forms of TB, such as the primary complex in the lung and thoracic lymph nodes, pleural effusion, cervical lymphadenopathy and tuberculous meningitis, continue to appear in pediatric disease. However, these conditions are becoming increasingly evident in adults and even elderly people as patients tend to acquire infection later in life than has historically been the case.

The diagnosis of TB involves a careful review of symptoms, the time-course of the condition (nonspecific subacute and chronic symptoms are characteristic of TB), exposure to TB, history of active TB and the adequacy of previous treatment. TB should be suspected in the presence of the aforementioned characteristic lifestyle and demographic features associated with increased risk, and physicians should be alert to the diseases, drugs and conditions that predispose an infected patient to active TB (discussed later). Following a complete physical examination, the traditional investigations are the tuberculin skin test, radiography of the chest or other appropriate area and collection of appropriate specimens for mycobacterial culture.

Symptom review

The classic symptoms of TB, such as cough, hemoptysis, fever and night sweats, may be absent, particularly in elderly patients (level I evidence),¹⁵ and a significant minority of patients with TB (20% in a recent series, level I evidence¹⁷) are asymptomatic. However, TB should always be considered if the classic symptoms are present in a patient from a high-risk group or if unexplained cough and constitutional symptoms persist for more than a few weeks or pneumonia fails to resolve in any patient. As well, symptoms in extrapulmonary TB may be nonspecific.

Tuberculin skin test

The standard dose in the PPD skin test is 5 tuberculin units. Doses of 1 TU and 250 TU are not biologically standardized; they have limited indications and are not recommended for routine use.^{5,18} The result is determined between 48 and 72 hours after injection through measurement of the transverse diameter of induration in millimetres (the surrounding erythema should be ignored). It is insufficient to describe the test result simply as "positive" or "negative." These designations are arbitrary; they have different meanings in different periods and regions and are affected by the local prevalence of cross-reactions and test materials used.

It is strongly recommended that the dose be injected intradermally and that the safeguards described in the manufacturer's insert be followed. The PPD skin test is a valuable epidemiologic tool. As a diagnostic tool it

is limited by technical aspects, the interpretation of the reaction, associated conditions that may affect the reaction temporarily or permanently (Table 1) and by its specificity and sensitivity in a particular epidemiologic situation. A full description of the quality of evidence for studies establishing the diameter of induration considered significant in the different risk groups is beyond the scope of this article.¹⁹ An assessment of the significance of the skin-test reaction must always take into account the circumstances under which the skin test is used and the purpose intended.

In epidemiologic terms an area of induration of 10 mm or more in diameter has customarily been considered significant in establishing infection with *M. tuberculosis*. However, in diagnosis an area of 5 mm or more in diameter is considered significant. Several important considerations must be borne in mind when physicians use the skin test diagnostically. Approximately 20% or less of patients with active TB, particularly those with advanced pulmonary disease or tuberculous serositis, may temporarily (until 2 to 3 weeks of drug therapy have been given) have an area of induration of less than 5 mm in diameter.¹⁷ Therefore, an insignificant skin-test result does not by itself exclude a diagnosis of TB. As well, patients with HIV infection or other immunosuppressive conditions, infants a few months of age and seriously ill patients may not react to the skin test.

Furthermore, a skin-test reaction may be caused by a cross-reaction to bacillus Calmette-Guérin (BCG) or mycobacteria other than *M. tuberculosis*. The likelihood of a cross-reaction decreases with increasing diameter beyond 10 mm.^{20,21} Evidence from a study in Quebec suggests that BCG given at birth is unlikely, by itself, to cause an area of induration larger than 10 mm (level II evidence).²² Previous BCG vaccination, even if there is a typical scar present, should be ignored in assessing skin-test reactions in immigrants from countries where the incidence of TB is intermediate or high. Casual exposure to *M. tuberculosis* is common in such countries, and a skin-test reaction in patients from them probably repre-

Table 1: Diameter of area of induration from purified protein derivative (PPD) skin test with 5 tuberculin units considered significant in different patients¹⁸

Patient	Diameter, mm
Person with HIV infection	≥ 5
Close contact (especially child or young adult) of patient with TB	≥ 5
Person with an insignificant PPD skin-test reaction in the previous 2 years	≥ 10
Person with documented previous active TB that was untreated or treated inadequately	≥ 10
Person with signs of apical scarring on chest radiograph	≥ 10
Person with other risk factor ¹⁸ (see also section on chemoprophylaxis)	≥ 10

sents a response to both organisms. These difficulties in interpreting the results of the PPD skin test are impossible to unravel; patients who may be infected and who are at high risk of disease are best managed according to broad guidelines for certain clinical contexts and corresponding cut-off points for the area of induration from the skin test (Table 1).

The skin-test reaction wanes with increasing time after infection²³ and increasing age.²⁴ In some such previously infected and older patients the reaction can be boosted by the performance of a second test of the same dose a week or more after the first. Boosting reduces the risk that a subsequent skin test performed within a year or so after the first will be falsely interpreted as a recent conversion. However, repeated boosting in elderly patients may yield an increasing number of patients with a significant reaction, making it difficult to judge the significance of conversions in the elderly.²⁵ Still, an area of induration of 10 mm or more in diameter indicates a greater likelihood of current or future TB.²⁶ The prognosis for patients with a boosted reaction is unclear, since there are no longitudinal studies assessing the risk of TB in those with an initial insignificant skin-test reaction and a significant boosted reaction.

Chest radiography

Postprimary tuberculous lesions in the lungs are characteristically located in the posterior segment of the right upper lobe, apicoposterior segment of the left upper lobe and apical segments of the lower lobes. However, the radiographic findings have been described as atypical in the presence of diabetes mellitus (level III evidence)²⁷ and HIV infection (level I evidence).⁹

A common presentation of primary TB is an acinar lesion (pneumonia) with enlargement of the ipsilateral lymph nodes. In children such a presentation is especially common²⁸ and is often accompanied by atelectasis. Occasionally the only finding is a pleural effusion. In reactivated pulmonary TB the lesions are more commonly seen in the upper lobes; however, they may appear in any lobe.¹⁷ Radiographic examination is unreliable in determining the activity of the lesion. Such a determination requires serial radiographs and examination of sputum for the presence of bacilli. A normal chest radiograph does not exclude a diagnosis of TB.²⁹ Chest radiographs in patients with bacteriologically proven pulmonary TB appear normal in a minority of patients; however, this occurs more often in the presence of HIV infection.⁹ Therefore, sputum should be collected for mycobacteriologic tests from patients at high risk who have appropriate symptoms.

Bacteriologic tests

The gold standard for the diagnosis of TB is a positive result of culture for *M. tuberculosis*. Therefore, the

proper collection, handling and identification of each specimen is extremely important.⁴

Three specimens of sputum (respiratory mucus rather than saliva) should be collected on successive days. However, physicians should not discard saliva, especially if the patient is unable to produce mucus, since it may yield a positive result when cultured.³⁰ Gastric washings are a useful method of obtaining specimens in children³¹ or in adults who cannot produce sputum. Three washings should be collected on successive mornings before feeding in the case of an infant or after an overnight fast. If these procedures fail to produce a positive result and suspicion remains, sputum induction or bronchoscopy may be required, and appropriate referral is indicated.^{32,33} If genitourinary or disseminated TB is suspected three early-morning mid-stream urine samples should be collected on successive days.

In some cases tissue samples are required for biopsy. Cervical lymphadenopathy caused by tuberculous infection is a noteworthy example. Such lymphadenopathy in Canadian-born children except for aboriginal children is usually caused by mycobacterial species other than *M. tuberculosis*.^{20,34} In contrast, cervical lymphadenopathy in aboriginal Canadians and immigrants from countries with a high incidence of TB is almost invariably tuberculous. It is extremely important that some tissue collected is reserved for bacteriologic tests and sent to the laboratory in normal saline and that a portion of the sample is not immersed in formalin. Close liaison with the surgeon or radiologist is required to obtain the needed tissue for bacteriologic testing, since the sample is essential to identification of the organism and its susceptibility to drugs, and hence to diagnosis and proper treatment. The distinction between lymphadenopathy caused by *M. tuberculosis* and lymphadenopathy caused by other mycobacteria is important because therapy for each differs.

New technologies

Several research tools, which are not yet used routinely in clinical settings, may prove useful in diagnosing TB. The polymerase chain reaction³⁵ is the most promising of this group of tools. With the use of synthesized primers (templates) of *M. tuberculosis* DNA this technique can identify organisms in samples with a low bacteria count (less than 10 bacilli) within a short period (24 to 48 hours) after collection of the sample. Its main disadvantages are its high sensitivity and the risk of contamination of the sample. The practical problems associated with polymerase-chain-reaction testing of various body secretions and tissues are rapidly being overcome.^{36,37}

The technique is also useful in distinguishing between *M. tuberculosis* and other mycobacteria when smears are positive for acid-fast bacilli.³⁵ Rapid species identification is particularly valuable in patients with

HIV infection, because most of the mycobacterial isolates in such patients are not *M. tuberculosis*.⁶

Serologic techniques using purified antigens³⁸ or monoclonal antibodies or both have shown encouraging results in identifying extrapulmonary and pediatric pulmonary TB.^{39,40} The sensitivity of some of these techniques is similar to that of smears in identifying pulmonary TB. The main advantage of serologic examination is that blood is easily obtained when sputum is not available. The main disadvantage is the degree of overlap between normal and abnormal test results in the very situations in which such testing would be useful, such as extrapulmonary TB, in which secretions may not be available for culture.

Treatment

The fundamental goal of all TB control programs should be early diagnosis and prompt initiation of an optimal and, if resources allow, supervised drug regimen (level I evidence).⁴ It has recently been argued that the goal of programs should be directly observed therapy,^{41,42} although others have argued for a more selective approach to supervised treatment.⁴³

Because approximately 1 per 10⁶ bacilli of *M. tuberculosis* mutate to become drug resistant, treatment with a combination of drugs is essential. Use of a single drug can cause selection of a particular drug-resistant strain, which is likely to lead to development of drug-resistant disease in the patient. If drug resistance is a concern treatment should include at least two new drugs to which the patient has not been exposed. In Canada it is customary to determine the sensitivity of TB strains to the main drugs in patients with a positive culture result.

Once sensitivities are established the therapeutic regimen should be adjusted accordingly.

Patients likely to have been infected before the introduction of antimicrobial therapy for TB are less likely to exhibit resistance.¹³ If results of mycobacteriologic tests are positive for an undue length of time (more than 3 months) a repeat study of the strain's susceptibility to the full range of anti-TB drugs should be requested.

Drug resistance should be anticipated in patients from groups with a high prevalence of drug-resistant and often multi-drug-resistant TB caused by poor compliance or poorly prescribed treatment; such groups include drug addicts, people with HIV infection, people who have not received adequate medical treatment and immigrants from countries with a high prevalence of drug-resistant TB.⁴⁴ Drug resistance is also a concern in patients previously treated for TB who have had a relapse and in contacts of a known case of drug-resistant disease.

The optimal initial regimen is three to four drugs,⁴ including isoniazid, rifampin, pyrazinamide and ethambutol or streptomycin, with daily doses determined by the weight of the patient (level I evidence)⁴⁵ (Table 2). A four-drug regimen should be considered, especially if drug resistance is a possibility (as discussed earlier). In the presence of alcoholism, diabetes mellitus or pregnancy or if there is concern about the patient's nutritional status, 25 mg of vitamin B₆ should be added to the daily regimen. After 2 months of therapy pyrazinamide is usually discontinued if culture results indicate the presence of a fully sensitive organism, and isoniazid and rifampin can be given twice weekly. A twice-weekly schedule lends itself to fully supervised, directly observed therapy. This optimal regimen should last at least 6 months in total, and close supervision is ideal. A total

Table 2: Doses of and common adverse reactions to first-line antituberculous drugs (level I evidence)⁴⁵

Drug	Daily dose in adults (and children), mg/kg	Usual daily dose, mg	Twice weekly dose, mg	Adverse reactions* (comments)
Isoniazid	5 (10–20)	300	900–1200	Hepatitis, paresthesia
Rifampin	10 (10–20)	600	600	Hepatitis, flu-like illness (reduced effect of certain other drugs)
Pyrazinamide	15–30 (15–30)	1500	2500	Hepatitis, elevated serum uric acid level, arthralgia
Ethambutol†	15–25	800–1200	2400	Retrobulbar neuritis
Streptomycin†	15 (20–40)	1000	1000	Vertigo, tinnitus, renal failure
Vitamin B ₆		25	Optional	

*All drugs may cause rash, nausea and fever.

†Dose may need to be adjusted if renal failure occurs.

of 9 months or more should be considered if clinical, radiologic or bacteriologic findings show a slow response. If second-line regimens are required, and particularly if there is a concern about drug resistance, the opinion of a consultant or an expert from the local health unit should be sought. In such cases much longer courses of treatment (15 to 18 months) are required, and regimens of 18 months or longer are needed if isoniazid or rifampin are excluded.

Drug monitoring and adverse reactions

All patients should be monitored closely for adverse reactions, for compliance with therapy and for the progress of the disease. In adults hematologic and biochemical screening must be carried out before therapy and at intervals (usually monthly) during therapy.⁴ This level of monitoring is not usually recommended in children. A fourfold increase in liver enzyme levels is not unusual, occurring in up to 20% of patients taking isoniazid, and should not, by itself, be a reason for stopping therapy. However, the direction of change in these enzyme levels should be watched closely after they have become abnormal. Progressive elevation of liver enzyme levels, particularly if accompanied by symptoms of liver dysfunction, calls for withdrawal of all hepatotoxic drugs and cautious sequential reintroduction once liver function has returned to normal. Every effort must be made to identify the culpable drug; drugs should not be discontinued without reason, since this condemns the patient to a more prolonged course of treatment with drugs of lesser value.

Approximately 7% of patients taking pyrazinamide will experience some arthralgia, which usually responds to simple analgesia, and most will have a rise in the serum uric acid level without symptoms. If possible pyrazinamide should be continued for the first 2 months because of its valuable role in sterilizing the lesion. Exclusion of pyrazinamide necessitates substitution with ethambutol for the first 2 months and at least 9 months' therapy in total. Ethambutol is often included at the outset of treatment until drug susceptibility results are available not specifically for its antimycobacterial effect but to cover the possibility of resistance to isoniazid or rifampin.

Adjunct therapy

Prospective controlled trials have shown that corticosteroids may be useful as an adjunct in treating tuberculous meningitis and pericardial disease (level I evidence).⁴⁶ They may also be useful in treating extensive pulmonary disease and in managing drug fever (level III evidence).⁴⁶ Although corticosteroids speed up the resorption of fluid and resolution of fever in pleural disease, such therapy has little effect on long-term outcome.

Sufficient detail for physicians to provide safe and effective adjunct therapy is beyond the scope of this article. Physicians treating TB are urged to refer to the Canadian Tuberculosis Standards⁴ and another appropriate reference.⁴⁶

Drug interactions

For a full discussion of potential interactions between antituberculous drugs and other agents readers are referred to a standard reference.⁴⁷

Special situations

HIV infection

TB in association with HIV infection is characterized by atypical clinical and radiologic presentations (level I evidence).⁶ Its diagnosis is often missed as a result of failure to obtain appropriate secretions⁴⁸ and send them for mycobacteriologic tests. Although therapy in such patients is associated with a higher rate of adverse reactions than in other patients with TB, standard regimens are usually successful.⁹ Care of these patients is complicated by their propensity to acquire other opportunistic infections, including infection by other mycobacterial species, that may cause confusion in diagnosis.

Guidelines regarding HIV infection and TB have recently been published;⁴⁹ a number of points merit emphasis. Physicians should strongly consider conducting serologic tests for HIV infection in all patients with TB, especially those from groups at known risk of HIV infection. In the presence of a positive result of a serologic test for HIV, patients should be screened for active and inactive TB. If there is no evidence of TB yet tuberculous infection is confirmed through a PPD skin test (area of induration 5 mm or more in diameter) chemoprophylaxis should be initiated.⁶ In Canada,⁹ unlike the United States,⁵⁰ multi-drug-resistant TB has not been identified in patients with HIV infection;⁹ however, prevention of multi-drug resistance requires the use of optimal drug regimens and close supervision of therapy.

Tuberculous infection spreads and progresses rapidly to TB among patients with HIV infection and health care workers.^{50,51} As a result, physicians should be alert to the possibility of TB in such patients and should initiate appropriate isolation procedures and physical measures, such as negative-pressure rooms, no recycling of room air and the use of ultraviolet light, until TB is ruled out.

Such precautions are also necessary during sputum induction or aerosol administration of pentamidine.⁵² Finally, a smear that is positive for acid-fast bacilli should be assumed to indicate *M. tuberculosis* infection, and therapy for *M. tuberculosis* should be started until the mycobacterial species has been identified.

Pregnancy

The management of TB during pregnancy has recently been comprehensively reviewed.⁵³ Apart from streptomycin, which may cause fetal ototoxic effects, there is no absolute contraindication to any of the first-line anti-TB drugs. Data on the fetal safety of pyrazinamide are limited; therefore, although there is no evidence that pyrazinamide is teratogenic and it appears to be safe to use in pregnancy, caution should be exercised in selecting this drug.

Ethionamide and prothionamide are teratogenic and should be avoided. Amithiozone (also known as thi-acetazone) and cycloserine appear to be safe.⁵⁴

Although not contraindicated during pregnancy, chemoprophylaxis is best postponed until post partum. However, as an exception to this recommendation, chemoprophylaxis should be started in a pregnant woman who is seropositive for HIV and has evidence of tuberculous infection (level IV evidence).⁵³

Pediatric TB

In Canada pediatric TB affects mainly aboriginal Canadians and immigrants, particularly those from Pacific Rim countries, to a greater extent than adult TB.⁵⁵ Most pediatric patients present with primary disease and are discovered in the course of contact tracing. The management of pediatric TB has recently been comprehensively reviewed from both the Canadian (level III evidence)³¹ and global perspectives (level IV evidence).⁵⁶

Prevention

There are two main methods for preventing TB: chemoprophylaxis with isoniazid and vaccination with BCG.

Chemoprophylaxis

Chemoprophylaxis with isoniazid is started after infection but when current active TB has been excluded by bacteriologic and other appropriate investigations. Candidates should have a significant PPD skin-test reaction with or without evidence of healed TB. (Radiologic evidence of healed TB is present in patients who have never been treated or have been treated inadequately.) If adequate treatment has been prescribed and taken prophylaxis is not indicated.

To date, the only drug submitted to extensive trials and in common use for prevention is isoniazid (level I evidence).⁵⁷ Alternative regimens (e.g., rifampin alone and combinations of drugs) are being reviewed, but their value has not been confirmed (level III or IV evidence).⁵²

The use of isoniazid alone is based on the assumptions that the population of bacilli is relatively small and that secondary drug resistance is unlikely if the indica-

tions for chemoprophylaxis have been followed and the patient has fully complied with therapy. It is reasonable to treat with multiple drugs if drug resistance is possible or if the stability of apparently inactive disease is in doubt, even if data are not yet available.

The effectiveness of preventive therapy with isoniazid has been confirmed in several studies (level I evidence).⁵⁷⁻⁵⁹ There has been controversy about its risks and benefits (mainly in patients at low risk of active TB) and its cost effectiveness. However, a recent Canadian study has confirmed the cost effectiveness of this intervention.⁶⁰

Physicians prescribing chemoprophylaxis must consider the drug to be given, its dose, the duration of therapy (12 months of isoniazid confers maximum benefit, whereas 6 months confers a lesser benefit but a greater level of compliance),^{61,62} contraindications and precautions, the level of patient understanding and motivation and the requirements for adequate monitoring.

After weighing the risks, the benefits and any other special considerations physicians should consider the following groups for preventive drug treatment.⁴

- Recent contacts of active infectious pulmonary TB cases or patients with tuberculous and concurrent HIV infection in whom a skin test yields an area of induration of 5 mm or more in diameter.

- People who have converted from an insignificant to a significant skin-test result within the previous 2 years.

- People with inactive TB or apical lung scarring and a significant skin-test reaction who have not been adequately treated in the past.

- Infected patients with a condition predisposing to active TB: a condition necessitating immunosuppressive therapy, hematologic or reticuloendothelial malignant disease (e.g., lymphoma, Hodgkin's disease), a condition necessitating corticosteroid therapy (particularly over prolonged periods and in high dosages), silicosis, diabetes mellitus (particularly severe and unstable diabetes), chronic renal insufficiency (necessitating long-term dialysis or renal transplantation), recent gastrectomy or gastrointestinal bypass surgery, conditions associated with nutritional deficiency and substantial weight loss, and intravenous drug abuse. In some of these conditions the risk of TB has not been well defined. If the predisposing condition persists after the normal course of chemoprophylaxis, there is no reason to continue prophylaxis.

- Patients with a significant skin-test reaction, without additional risk factors, especially infants, children and adolescents. In Canada a significant skin-test reaction in a patient in this group should lead to investigation for a source case, particularly if the patient was born in Canada.

Given its proven effectiveness, isoniazid chemoprophylaxis is underused in Canada (level III evidence).⁶³ Compliance is a major hurdle. Because chemoprophyl-

axis is an elective therapy in a country where the health care resources are adequate, it is important that it be as risk-free as possible, that the results be optimal and that isoniazid resistance not be induced. Hence, considerable care should be taken in selecting and educating patients and in providing personnel time and other resources, especially if such a program affects the management of active cases of TB.

BCG vaccination

BCG vaccination is currently offered as a voluntary program for all newborn aboriginal children living on reserves in Canada. It is also considered in the following groups.

- People who are unavoidably exposed repeatedly to untreated or inadequately treated TB.
- People in groups or communities with unusually high rates of new infection or disease, especially if alternative measures (treatment or chemoprophylaxis) are difficult to apply or are unavailable. This indication may apply to people planning to live in high-incidence countries for prolonged periods.
- Health care workers who are frequently exposed to unrecognized pulmonary TB or laboratory workers who handle bacilli.
- Newborn infants one or both parents of whom have infectious TB at the time of delivery; these children are separated immediately from their mothers for their protection. This indication particularly applies if the parent has drug-resistant TB.

Although there is controversy about the precise role of BCG vaccination in TB control,^{64,65} a number of studies in Canada (level II evidence) have shown a significant protective effect against pulmonary TB^{66,67} and, in particular, the more lethal forms of miliary TB and tuberculous meningitis (level III evidence).⁶⁸ Despite these benefits, acceptance of BCG vaccination by parents and primary care physicians is falling owing to concerns about adverse reactions and the effect on subsequent skin testing. Both of these concerns are, in general, exaggerated.^{22,69} Decreasing rates of tuberculous infection in aboriginal populations in Canada will likely soon lead to more selective vaccination and may allow the BCG vaccination program for this group to be phased out.

In Canada BCG vaccination is not recommended for infants of people with HIV infection or AIDS (level IV evidence).⁴ Other contraindications include other types of immune impairment, extensive skin disease or burns. Vaccination with BCG in a person who has a significant skin-test reaction is not harmful but has been avoided.⁴

Since BCG vaccination does not provide complete and lasting protection, TB should be considered in the differential diagnosis of any recipient of the BCG vaccine.

Conclusions

The world situation has led to increased immigration and global travel, which affect the long-term outlook for the control and eventual elimination of TB in Canada. Its large number of immigrants, especially from countries with a high prevalence of TB, means that Canada is exposed to the prevalence of TB in these countries.

TB will not be eliminated quickly; cases will continue to occur until well into the next century. Even if a highly effective, long-lasting vaccine and a highly effective, safe, preventive drug treatment of very short duration were found, the target populations are so large that it would be unrealistic to expect comprehensive adoption of such measures in the short term. It can be expected, therefore, that the large reservoir of infected people (approximately 6% of the Canadian population [Tuberculosis Registry, Division of Tuberculosis Control, British Columbia Ministry of Health: unpublished data, 1993]) and those with untreated or poorly treated inactive disease will continue to feed the annual incidence of active TB for many years.⁷⁰

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May 29-June 2, 1994: Canadian Society of Clinical Chemists Annual Scientific Congress (cosponsored by the Société québécoise de biochimie Québec and the Canadian Association of Medical Biochemists)

Quebec

Dr. J.-C. Forest, Service de biochimie, Hôpital Saint-François-d'Assise, 10 de l'Espinay St., Quebec, PQ G1L 3L5

May 30-June 4, 1994: 1st World Congress on Medicine and Philosophy — Sciences, Technologies and Values (organized by the European Society for Philosophy of Medicine and Health Care and the Association Descartes; in conjunction with the 8th Annual General Assembly of the ESPMH)

Paris, France

Professor Henk ten Have, Secretariat ESPMH, Department of Ethics, Philosophy and History of Medicine, School of Medical Sciences, Catholic University of Nijmegen, PO Box 9101, 6500 HB, Nijmegen, The Netherlands; tel 011-31-80-615320, fax 011-31-80-540254

May 31-June 2, 1994: Centre for Studies of Children at Risk Inaugural Symposium — Improving the Life Quality of Children: Options and Evidence

Hamilton, Ont.

Peggy McAlpine, administrative coordinator, Centre for Studies of Children at Risk, Chedoke-McMaster Hospitals and McMaster University, PO Box 2000, Stn. A, Hamilton, ON L8N 3Z5; tel (905) 521-2100, ext. 7358; fax (905) 574-6665

Du 1^{er} au 3 juin 1994 : Association canadienne d'oncologie psychosociale assemblée annuelle et congrès — Éthique, économie et empathie : les défis à relever dans les soins en oncologie

Ottawa

Services d'éducation, Hôpital Royal Ottawa, 1145, ave. Carling, Ottawa, ON K1Z 7K4; tél (613) 724-6521, fax (613) 725-0446

June 1-3, 1994: Canadian Association of Psychosocial Oncology Annual Meeting and Conference — Ethics, Economics and Empathy: the Challenge in Oncology Care

Ottawa

Education Services, Royal Ottawa Hospital, 1145 Carling Ave., Ottawa, ON K1Z 7K4; tel (613) 724-6521, fax (613) 725-0446

Du 2 au 4 juin 1994 : Association pulmonaire 94^e congrès annuel : Mieux respirer pour mieux vivre (comprend les assemblées générales annuelles de la Société canadienne des infirmières en santé respiratoire, de la Société de physiothérapie cardio-respiratoire du Canada, de l'Association pulmonaire du Canada, de l'Association pulmonaire du Québec et de la Société québécoise des infirmières en santé pulmonaire)

Québec

Crédits en éducation médicale continue offerts.

Association pulmonaire, Bureau national, 508-1900, ch. City Park, Gloucester, ON K1J 1A3; tél (613) 747-6776, fax (613) 747-7430

June 2-4, 1994: Lung Association 94th Annual Conference: Breathe Better to Live Better (includes the annual general meetings of the Canadian Nurses' Respiratory Society, the Canadian Physiotherapy Cardio-Respiratory Society, the Lung Association, the Quebec Lung Association and the Quebec Nurses' Respiratory Society)

Quebec

Study credits available.

Lung Association, National Office, 508-1900 City Park Dr., Gloucester, ON K1J 1A3; tel (613) 747-6776, fax (613) 747-7430

June 3-4, 1994: Alcohol and Other Drugs in Pregnancy: Issues for Families and Communities — a Conference to Address Fetal Alcohol Syndrome and Neonatal Abstinence Syndrome (cosponsored by Sunny Hill Health Centre for Children)

Vancouver

Study credits available.

Alcohol and Other Drugs in Pregnancy, Continuing Education in the Health Sciences, University of British Columbia, Rm. 105, 2194 Health Sciences Mall, Vancouver, BC V6T 1Z3; tel (604) 822-2626, fax (604) 822-4835

June 3-4, 1994: Hastings Center's 25th Anniversary Celebration

New York

Hastings Center, 255 Elm Rd., Briarcliff Manor, New York 10510-2255; tel (914) 762-8500, fax (914) 762-2124

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