abstract

Tuberculosis is a re-emerging public health threat. This article discusses the particular characteristics of tuberculosis among older adults and the use of the tuberculin skin test as a tool for diagnosis of tuberculosis infection with emphasis in long-term care facility residents. An overview of new diagnostic tests based on gamma interferon release is also included.

Key words: tuberculosis, tuberculin skin test, long-term care facilities, purified protein derivative

Key Points

- Tuberculosis remains a leading cause of morbidity and mortality in the world.
- The manifestations of the disease and its management in older adults differ from younger adults and represent a significant challenge for the clinician.
- The tuberculin skin test is a time-honoured test to detect tuberculosis infection. Its interpretation depends on patient risk factors.
- New methods based on in vivo detection of interferon gamma may also be useful in detecting tuberculosis infection.

The Tuberculin Skin Test in Long-Term Care Facilities

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Introduction

Tuberculosis, a disease that was considered in decline since the 1950s in the developed world, re-emerged in the 1980s as a consequence of the dismantling of tuberculosis control services and the HIV epidemic.[1] HIV infection caused a 100-fold increment in the risk of tuberculosis infection.[2] Tuberculosis, which is now the leading cause of death from a curable infectious disease in the world, causes nine million active cases a year and infects one-third of the global population.[3] In addition, low rates of treatment completion and poor choice of antituberculosis combinations have caused the emergence of multidrug resistant (MDR) tuberculosis (*M. tuberculosis* resistant to isoniazid and rifampin) and more recently of extensively drug resistant (XDR) tuberculosis (MDR *M. tuberculosis* also resistant to other second-line agents, as shown in Table 1).[4] This latter form of tuberculosis has not only caused lethal outbreaks in South Africa and Iran but is now also present in up to 4% of sputum isolates in the United States.[5] Hence, tuberculosis is a re-emerging public health threat.

Tuberculosis among Older Adults: A Different Animal?

Although the impact of HIV infection on the tuberculosis epidemic is unquestionable, the majority of active tuberculosis cases in developed countries occur among people older than 50, which represent the largest reservoir of the disease in the community.[6] Older adults may develop active tuberculosis following a new exposure to *M. tuberculosis* either because they were never exposed to the disease before or, in the vast majority of cases, because they have reactivation of previously acquired dormant disease.[7] Despite 80% of cases of active tuberculosis in individuals older than 65 years occurring in the community,[8] residents in long-term facilities have 5–50 times greater risk of developing active disease.[9]

The differences between tuberculosis among older adults as compared with younger adults are multiple. They are summarized in Table 2.

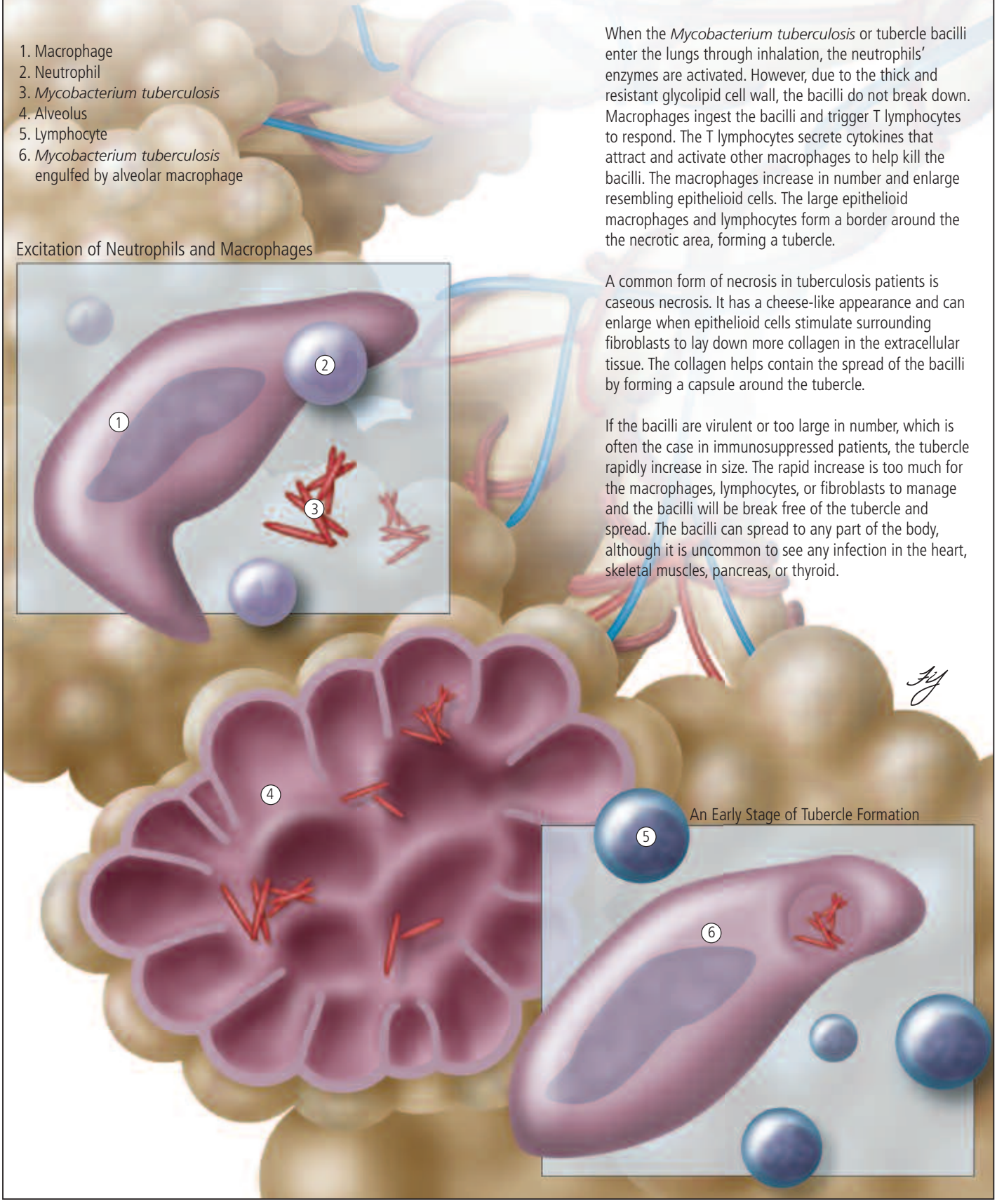
Long-term care facilities for older adults may be more prone to developing tuberculosis outbreaks due to inadequate infection control measures (such as lack of clinical suspicion in an individual with

Table 1: Definition of Resistant Strains of Tuberculosis

Type of M. tuberculosis strain	Antibiotics that are resistant against the strain
Fully susceptible tuberculosis	None
Multidrug-resistant tuberculosis	Isoniazid and rifampin
Extensively drug-resistant tuberculosis	Isoniazid, rifampin, aminoglycosides (streptomycin, kanamycin), fluoroquinolones, capreomycin

Figure 1: Tuberculosis Physiology and Its Effects on Immunosuppressed Patients

1. Macrophage
2. Neutrophil
3. *Mycobacterium tuberculosis*
4. Alveolus
5. Lymphocyte
6. *Mycobacterium tuberculosis* engulfed by alveolar macrophage

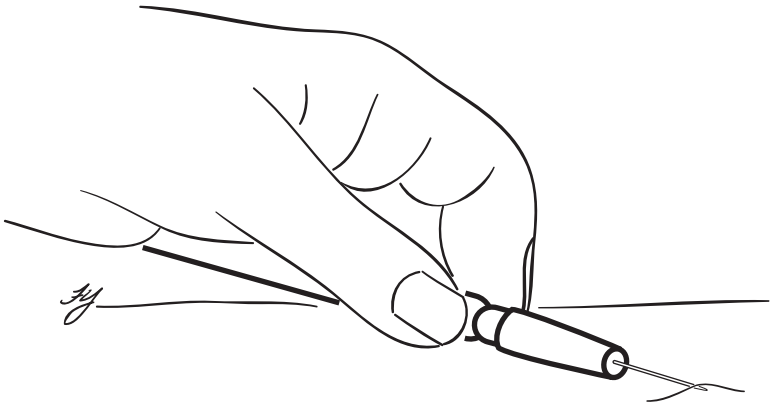


When the *Mycobacterium tuberculosis* or tubercle bacilli enter the lungs through inhalation, the neutrophils' enzymes are activated. However, due to the thick and resistant glycolipid cell wall, the bacilli do not break down. Macrophages ingest the bacilli and trigger T lymphocytes to respond. The T lymphocytes secrete cytokines that attract and activate other macrophages to help kill the bacilli. The macrophages increase in number and enlarge resembling epithelioid cells. The large epithelioid macrophages and lymphocytes form a border around the the necrotic area, forming a tubercle.

A common form of necrosis in tuberculosis patients is caseous necrosis. It has a cheese-like appearance and can enlarge when epithelioid cells stimulate surrounding fibroblasts to lay down more collagen in the extracellular tissue. The collagen helps contain the spread of the bacilli by forming a capsule around the tubercle.

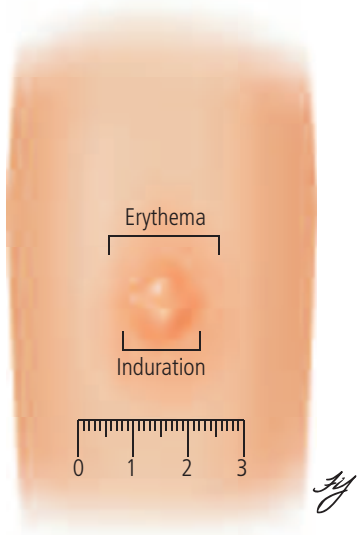
If the bacilli are virulent or too large in number, which is often the case in immunosuppressed patients, the tubercle rapidly increase in size. The rapid increase is too much for the macrophages, lymphocytes, or fibroblasts to manage and the bacilli will be break free of the tubercle and spread. The bacilli can spread to any part of the body, although it is uncommon to see any infection in the heart, skeletal muscles, pancreas, or thyroid.

Figure 2a: Visible Wheal Formation



Formation of a visible wheal is essential when applying the TST; otherwise, the subcutaneous administration of the injection may cause a false negative result.

Figure 2c: Induration Measurement



The induration (and not the erythema) caused by the injection should be measured. The measurement in millimetres should be recorded along the transverse axis of the arm.

chronic cough and absence of a non-circulating filtered air-handling system in the facility).

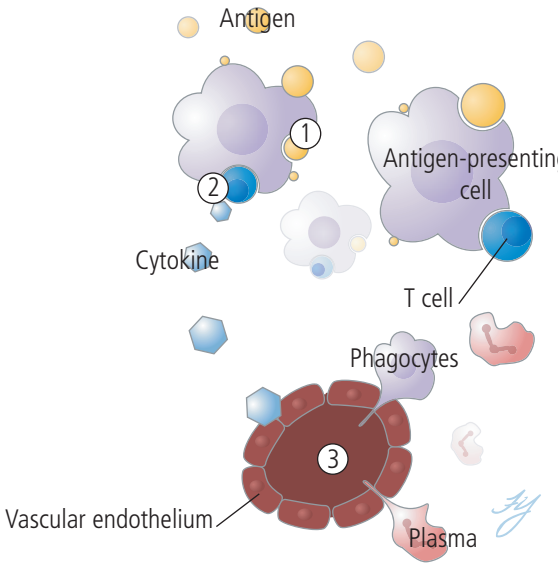
For these reasons, the diagnosis and management of tuberculosis among older adults may represent a significant challenge.

Tuberculosis physiology and its effects on immunosuppressed individuals are presented in Figure 1.

The Tuberculin Skin Test

The tuberculin skin test (TST) is a diagnostic tool used to identify individuals infected with *M. tuberculosis*. The test does not differentiate between patients with active versus latent infection.[16] The TST can be applied by multiple puncture tests or by the Mantoux test. The Mantoux test is preferred for clinical assessment and screening because it delivers uniform doses of purified protein derivative (PPD).[16] In the Mantoux test, 0.1 mL of solution containing a five-unit dose of PPD is applied intradermally. The subcutaneous administration can result in a false negative result.[17] The induration that results from the injection is a type IV hypersensitivity reaction and it is read after 48–72 hours. The induration, and not the erythema caused by the injection, should be measured and the measurement should be done along the transverse axis of the arm and recorded in

Figure 2b: A Type IV Hypersensitivity Reaction to the Injection of *M. tuberculosis* Antigen between 48–72 Hours



1. The antigen-presenting cell internalizes the antigen and displays a fragment of the the antigen on its surface for T cell recognition.
2. The T cell reacts with the antigen-presenting cell, becomes activated, and releases cytokines that interact with the endothelium of nearby vasculature.
3. The vascular endothelium will mobilize the release of phagocytes and plasma to the site of infection, forming the induration.

A type IV hypersensitivity reaction follows the injection of M. tuberculosis antigen. The antigens are recognized by TH1 effector cells, which in turn liberate cytokines and recruit phagocytes, causing a reaction that is visible.

Table 2: Different Manifestations or Findings in Younger and Older Individuals with Active Tuberculosis

Manifestation	Younger individuals	Older individuals
Symptoms	Typical: cough with productive sputum, hemoptysis, weight loss	Nonspecific manifestations may be prominent, including hyporexia, unexplained low-grade fever, fatigue, or decline in functional and mental capacity[10]
Diagnosis	Usually prompt	Diagnosis may be delayed, thus facilitating the transmission of the disease[11]
Miliary disease	Less frequent	More frequent[12]
Chest x-ray	Characteristic apical infiltrates or cavitation	Lower-lung infiltrates and pleural effusions may be prominent[13]
Tuberculin skin test	Positive	Falsely negative results may be common due to declining immunity with age[14]
Sputum smear and culture	Easily obtainable	Older individuals may be unable to provide sputum samples due to deconditioning and weakness[6]
Hepatotoxicity with isoniazid	Infrequent	Common[9]
Pharmacological interactions due to polypharmacy	Rare	Common[9]

millimeters (Figure 2a–c).[9] A pen may be used to mark the edge of the induration.

The TST is not indicated for use in the general population in North America because of the low incidence of tuberculosis but is indicated in groups that have high anticipated yields, such as residents of long-term care facilities.[16] The interpretation of the results also depends in the risk category to which each individual belongs (Table 3). For example, a long-term care facility resident will have a positive TST if the induration measures 10 mm, but an otherwise healthy adult will not be considered positive until the induration reaches 15 mm.

Because older adults have waning immunity against *M. tuberculosis* with time, a TST performed once may be falsely negative.[6] However, performing a second tuberculin injection, 1 week after the initial one, may boost their immune response with restoration of cell-mediated immunity.[18] The two-step TST is considered the standard for prevention and control of tuberculosis and it should be used among all newly admitted residents to long-term care facilities and among their health care workers (Figure 3).[9,19] The two-step test reduces the likelihood that a boosted reaction will be misinterpreted as a new positive reaction, and is helpful in identifying at least an additional 15% of older individuals with tuberculosis infection.[20]

Previous Bacille Calmette-Guérin (BCG) vaccination (extensively used in developing countries and based on an attenuated strain of *M. bovis*) can be associated with a positive TST. The impact of BCG vaccination in TST results among older adults has not been studied, but the recommendation is to interpret the test based on risk factors and independently of the history of BCG vaccination.[9,21]

Once an individual has a positive TST it should not be repeated and is usu-

Table 3: Interpretation of the Tuberculosis Skin Test According to Risk Factors

>5 mm induration	HIV-infected patients and other immunosuppressed persons (such as transplant recipients and chronic recipients of steroids)
	Recent contacts of patients with active tuberculosis
	Individuals with chest x-ray suggestive of old tuberculosis
>10 mm induration	Intravenous drug abusers
	Patients with certain comorbidities: cancer and hematologic malignancies, diabetes mellitus, chronic renal failure, silicosis, gastrectomy
	Residents or employees of "high-risk facilities": health care facilities, nursing homes, shelters, prisons
	Children or adolescent exposed to adults in high-risk categories
	Recent immigrants (less than five years' residency) from countries with high incidence of tuberculosis
>15 mm induration	Anybody

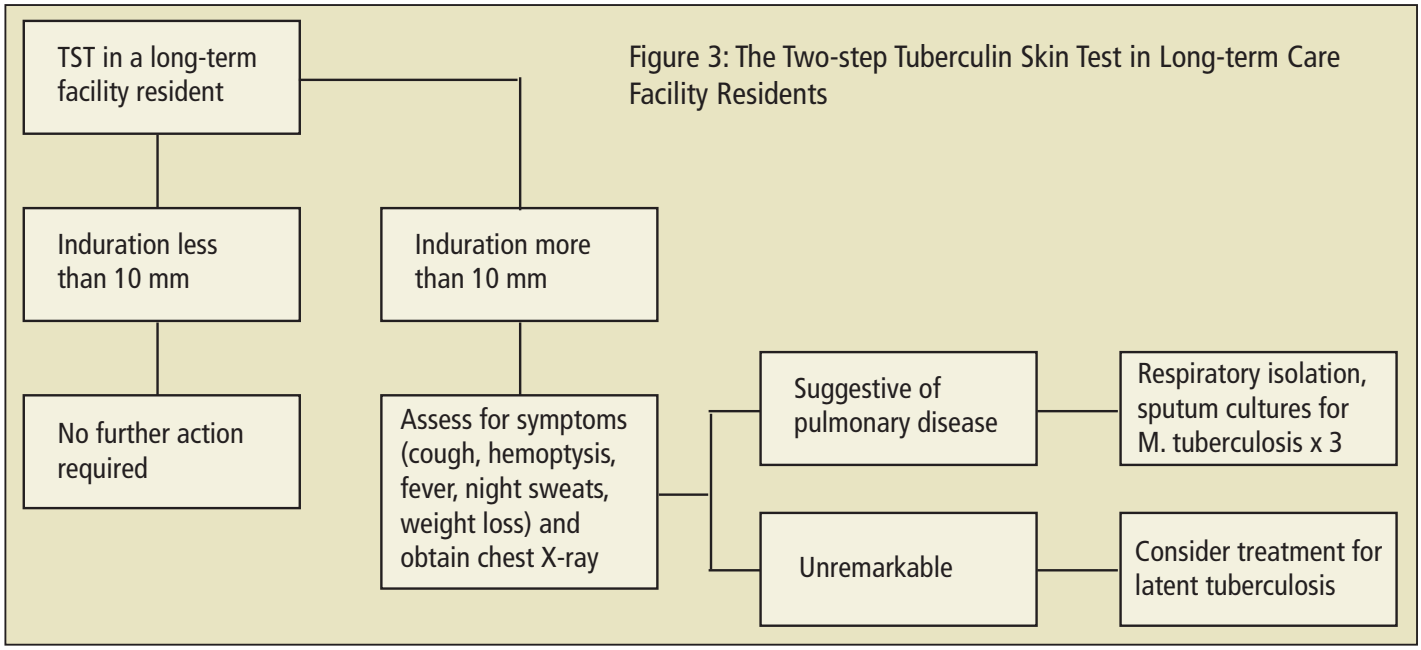


Figure 3: The Two-step Tuberculin Skin Test in Long-term Care Facility Residents

ally positive for life. In the long-term care facility setting, a chest x-ray is not a good screening test for activation of tuberculosis and should be repeated only when new symptoms develop.

What to Do if the TST Is Positive?

If the TST is positive, the first step is to rule out active infection. The majority of older adults with active tuberculosis will still present with classical symptoms including fever, cough, night sweats, and weight loss; however, up to 25% of them may have extrapulmonary disease (particularly the disseminated form, although meningitis, genitourinary, and bone disease may also be common).[7,10] If cough is present, there is usually no productive sputum or frank hemoptysis (unless cavitating disease is present). Weight loss may be erroneously attributed to normal aging or may prompt a search for malignancy. Unusual presentations, which range from absence of all symptoms to abnormal mental status, may also occur.[11,15] Although the chest radiograph in the majority of older patients with active pulmonary tuberculosis will show a classic apical infiltrate with or without cavitation, more unusual patterns such as miliary tuberculosis, isolated mediastinal or hilar lymphadenopathy, and basal or middle-lobe infiltrates have also been described.[22] If there is active disease, the affected individual should be placed in an airborne-infection isolation room (or transferred to a facility with one), and empirical treatment with four drugs should be started immediately (Table 4).

The majority of those with a positive TST will not have active symptoms or radiological abnormalities and will be classified as having latent tuberculosis. Although there are not specific studies of older adults, treatment of latent tuberculosis confers a protective efficacy (against developing active disease) of approximately 90% among the general population (and 93% among HIV-infected patients).[23,24] So it seems appropriate to offer treatment to all older patients.

The standard treatment for latent tuberculosis infection (LTBI) is 9 months of isoniazid, which is preferred over the previously recommended 6-month regimen (6 months gave only a 69% protection).[25] Other combinations are seldom used (Table 5). In the past, isoniazid use was restricted in patients older than 35 years due to the increased risk of hepatitis;[26] however, isoniazid is currently recommended regardless of the age. Addition of vitamin B_6 supplement while using isoniazid is important in aging adults, because they may have higher risk of developing peripheral neuropathy.[27] Although monitoring of liver enzymes is not strictly advocated while receiving treatment for LTBI,

Table 4: Common Treatment Regimens for the Management of Active Pulmonary Tuberculosis among Older Adults

Regimen	Initial phase	Continuation phase
1	Isoniazid, rifampin, ethambutol, and pyrazinamide 5 or 7 days per week for 8 weeks	Isoniazid and rifampin 5 or 7 days per week or twice weekly for 18 weeks
2	Isoniazid, rifampin, ethambutol and pyrazinamide 7 days per week for 2 weeks, then twice weekly for 6 weeks	Isoniazid and rifampin twice weekly for 18 weeks
3	Isoniazid, rifampin, ethambutol and pyrazinamide 3 times weekly for 8 weeks	Isoniazid and rifampin 3 times weekly for 18 weeks

many older patients will have comorbidities that will make monthly biochemical monitoring appropriate.[9]

Beyond the PPD Test

The TST is an inexpensive test that does not require any special laboratory equipment to be performed; unfortunately, it may have several drawbacks, including:

- False positive results among recipients of BCG vaccination and in populations with a high prevalence of nontuberculous mycobacteria.[28]
- False negative results among immunosuppressed individuals and older adults.[29]
- Patients not returning for the test to be read.[30]
- Person-to-person variability in reading the results and variability depending on the time the result was read.[31]

In order to overcome these potential disadvantages, two new tests that measure the production of interferon gamma by T-cells exposed to *M. tuberculosis* antigens have become commercially available (Figure 4). QuantiFERON-TB Gold has been approved by the Food and Drug Administration in the United States and T SPOT-TB is approved for use in Canada and Europe. The first one is a whole-blood enzyme-linked immunosorbent assay (ELISA) and the second, a peripheral blood mononuclear cell enzyme-linked immunsorbent spot (ELISPOT). Both use the same rationale: host cells are exposed in vitro to the culture filtrate protein 10 (CFP-10) and the early secretory antigenic target 6 (ESAT-6), two highly specific antigens of *M. tuberculosis*. Then, the amount of interferon gamma produced by the exposed cells is measured. The test can be reported as positive, negative, or indeterminate (this last result may occur when there are few circulating lymphocytes in the blood sample, such as in HIV infection or malignancies, or due to improper handling of the specimen).[32]

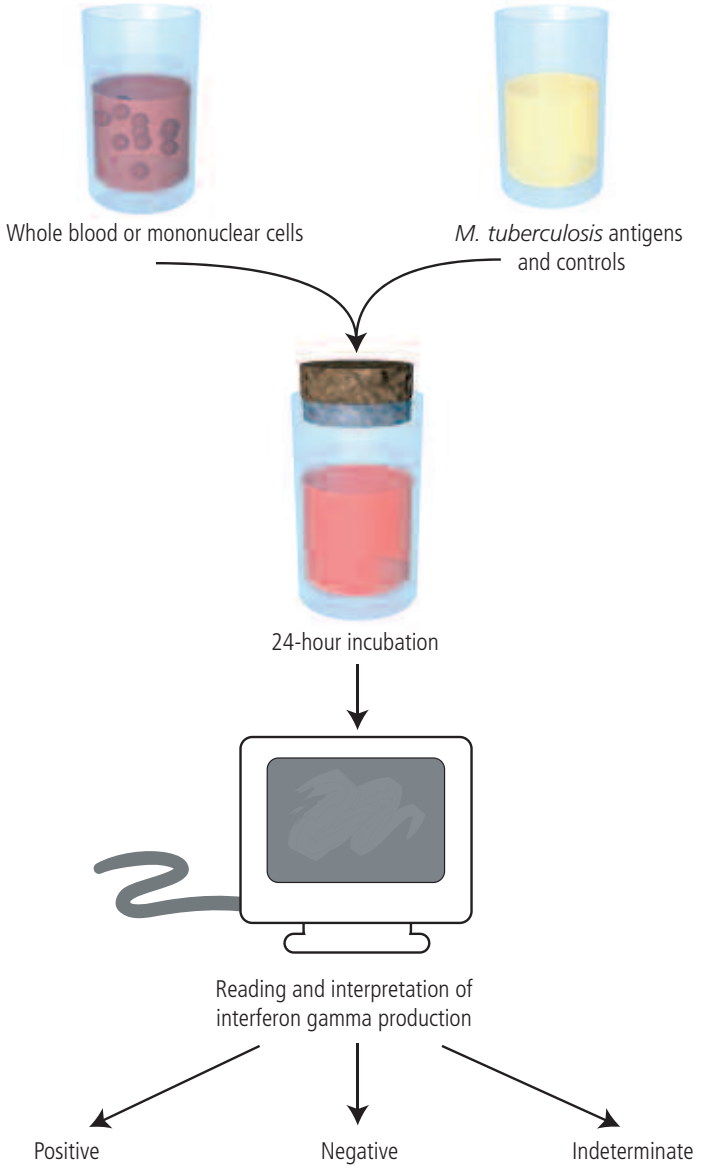
The benefits of performing these in vitro tests (as compared with the in vivo TST) include[33]

- Higher specificity due to selected *M. tuberculosis* antigens employed. Hence, no false positive results will occur among BCG vaccine recipients.
- Higher objectivity and standardization of the test, decreasing the chances for interpersonal variability in the reading.
- Need for only one blood draw, thus not requiring the patient to return for a second visit.

Although promising, the interferon gamma-based assays still have several disadvantages:

- The test is several times more costly than the TST and requires specific laboratory infrastructure to be performed.
- The chances of a false-positive result are lower than with the TST, but not zero. Infections with *M. kansasii, M. szulgai, M. marinum,* and perhaps *M. leprae* may give false positive results.

Figure 4: Interferon Gamma Based Assay for Detecting Tuberculosis Infection



Aliquots of whole blood or peripheral blood mononuclear cells are incubated with the test antigens for 16–24 hours. Test kits include *M. tuberculosis* test antigens and controls. After incubation, the concentration of interferon gamma is determined. The amount of interferon gamma released is determined by subtracting the amount released as compared with the controls. These results can be calculated by using specific software.

Table 5: Suggested Treatment Regimens for Latent Tuberculosis Infection in Older Adults

Highly recommended	Isoniazid daily for 9 months
Alternative	Isoniazid daily for 6 months
	Isoniazid twice weekly for 9 months
	Isoniazid twice weekly for 6 months
Less commonly used	Rifampin plus pyrazinamide daily or twice weekly for 2 months*
	Rifampin daily for 4 months

* High potential for hepatotoxicity

– Indeterminate results in immunosuppressed patients are common.

Similar to the TST, the interferon gamma-based assays do not discriminate between latent and active infection, but it seems that with time they will become more widely used to detect tuberculosis infection. In fact, it is already becoming the test used for the yearly evaluation of healthcare workers in several hospitals across North America.[34] The performance of these tests have not been studied specifically among older adults yet.

Conclusion

Tuberculosis is a re-emerging infectious disease that may be difficult to diagnose and treat among older individuals. The tuberculin skin test is an old but still valuable method to assess for the presence of tuberculosis infection. The caveat among residents of long-term facilities is that a two-step test (to boost the waned immunity) is required for proper diagnosis. New laboratory methods based the detection of interferon gamma by T-cells exposed to *M. tuberculosis* antigens may replace or complement the use of the tuberculin skin test in the future.

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