Tuberculosis (TB) is an infectious chronic disease. After decades of steadily declining prevalence, the disease has reemerged in the last 5 years. Symptoms of TB are mild and not specific and can be classified as either systemic or localized to target organs. Microscopic examination of the sputum remains an inexpensive and rapid way to identify highly infectious patients. Four different antimicrobial agents—rifampin, ethambutol, pirazinamide, and isoniazid—form the basis of currently recommended antituberculosis therapy. Tuberculosis could be an occupational risk for health care workers. Dentists must be involved in the health promotion and early detection of TB. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:267-73)

Tuberculosis was thought to be under control in the United States. In the 1980s, after decades of steadily declining prevalence of TB, public health plans were made to eliminate the disease in the United States. Despite these plans, TB control was neglected, resulting in the reemergence of the disease. Healthcare workers, including dentists, are facing an increasing number of patients that either have been exposed to TB or have acute infection. The purpose of this article is to review current concepts of the pathophysiology and medical management of TB and to describe the role of dentists in the health promotion and early detection of the disease.

EPIDEMIOLOGY

Tuberculosis is a worldwide health concern. Every year, about 8 million people develop TB, and 3 million people die of complications associated with the disease. It is estimated that 30% to 60% of adults in developing countries are infected, with TB being the first cause of death among people over 5 years of age.

Between 1985 and 1990, the amalgamation of a declining public health infrastructure, urban crowding, inadequate institutional infection control, the epidemic of human immunodeficiency virus (HIV) infection, and migratory trends resulted in the reappearance of TB in the United States, specifically multidrug-resistant strains. This reappearance manifested in 67,000 more cases of TB than would have occurred had the strategy designed by the Centers for Disease Control and Prevention (CDC) and its advisory Council for the Elimination of TB been successfully implemented. Since its peak in 1992, the incidence of tuberculosis has again decreased. In the year 2000, 16,277 cases (5.8 cases per 100,000 population) were reported to the CDC, which represents a 45 percent decrease from the peak rate in 1992 and the lowest rate in U.S. history. This improvement is largely due to comprehensive control and public health policy, resulting in a decrease of Mycobacterium tuberculosis transmission from persons with active disease.

Distribution of TB cases has been limited to specific populations, mainly in the urban and immigrant communities. However, previous decades of uncontrolled transmission of Mycobacterium tuberculosis and the continued migration from areas with high rates of TB have resulted in a large number of cases of latent TB infection. The development of active disease in persons with latent infection poses a continual threat of transmission. Approximately 5% of individuals with a primary infection will develop active TB during the first 2

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Tuberculosis: Medical management update

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years after tuberculin conversion. The probability that such individuals will develop active disease varies according to the intensity and duration of the exposure. Persons who are in frequent contact and proximity to infected individuals are at most risk for both infection and disease.

A major concern for dentists, in light of the re-emergence of the disease, is the risk for transmission of TB in the dental setting. Dentists are involved in the effort to control TB through identification and referral of patients who may require chemoprophylaxis or treatment and by developing and implementing an appropriate infection control program. The identification and treatment of oral lesions secondary to mycobacterial infection is also of importance to dental care providers.

CLINICAL PRESENTATION

*Mycobacterium tuberculosis* is transmitted mainly by airborne particles that are 1 to 5 μm in diameter. Practically all infections with *Mycobacterium tuberculosis* are due to inhalation of droplets. Transmission is influenced by characteristics of the source case, such as the number of bacteria expelled, the nature of the encounter, and the duration of exposure. These droplets are infectious particles aerosolized by coughing, sneezing, or talking and are slow to dry while airborne, remaining suspended for long periods of time. The final destination of inhaled droplets is the terminal air passages. Infection results when as few as 1 to 5 bacteria are deposited in the terminal alveolus. Primary tuberculosis, a self-limited mild pneumonic illness that generally goes undiagnosed, may develop in a subgroup of infected persons. A tenuous balance is subsequently struck between the host and the pathogen. Latency was defined by Amberson as the presence of any tuberculous lesion that fails to produce symptoms. Most patients exposed to *M. tuberculosis* produce a strong cell-mediated immune response that stops the progression of the infection. In approximately 5% of persons, the infection progresses from a latent form to active disease within 2 years after infection. The trigger to reactivation may be immunosuppression, and other factors such as malnutrition and vitamin D deficiency are involved. Although the majority of cases of active tuberculosis are thought to arise from reactivation of latent infection, exogenous reinfection with a second strain of *Mycobacterium tuberculosis* can occur, especially in immunocompromised individuals (Fig 1).

Symptoms of TB are mild and not specific and include night sweats, fever, weight loss, anorexia, and weakness. The lack of specificity can result in a delayed diagnosis. Organ-specific symptoms of pulmonary TB include cough, pleuritic pain, and hemoptysis. Although the lung is the primary site of the disease in 80%-84% of cases of tuberculosis in the United States, extrapulmonary tuberculosis has become more common with the advent of HIV infection, and the risk of tuberculosis increases with immunosuppression.

MICROBIOLOGY

The term mycobacteria is used to designate 3 species of the genus: *M. tuberculosis*, *M. bovis*, and *M. africanum*. However, human disease due to *M. bovis* and *M. africanum* is uncommon and the terms mycobacteria and tuberculosis are considered synonymous. Humans are the only reservoir for *Mycobacterium tuberculosis*. The organism is an aerobic, nonmotile, non-spore-forming bacillus. The cell wall is complex and contains a large amount of high-molecular-weight lipids (Fig 2). This makes mycobacteria resistant to many disinfectants as well as to common laboratory stains such as Gram’s stain. The organism is slow growing, with visible growth on appropriate media taking from 4 to 6 weeks. By measuring the metabolism of palmitic acid, detection time can be reduced to
Mycobacterium tuberculosis faces the problem of establishing residence. The variety of receptors that could be utilized have demonstrated that prior tuberculin with the Fc receptor induces the production of Mycobacterium. 269 is the tuberculin skin test has been proposed. The receptor used uses to ensure that its iron supply is not limited. One example of such mechanism is the development of highly specialized iron-binding molecules that have a high affinity for intracellular iron. The only test to detect previous exposure to the Mycobacterium tuberculosis is the tuberculin skin test or purified protein derivate (PPD) and is one of the best examples of delayed hypersensitivity. The tuberculin reaction is produced via intracutaneous injection of tuberculin, a component of the Mycobacterium tuberculosis. In a previously sensitized individual or following a previous exposure to the tubercle bacilli, the T helper memory lymphocytes interact with the antigen on the surface of antigen-presenting cells, which conduces to their activation. These changes are accompanied by the secretion of cytokines, which are responsible for the expression of the delayed-type hypersensitivity. Circular areas of induration, based on length of time and intensity of exposure, are observed, and the results must be interpreted taking into consideration the prevalence of the infection in the community. Ninety percent of persons with 10 mm (diameter) of induration and virtually all with greater than 15 mm are infected by Mycobacterium tuberculosis; 5 to 10 mm reactions are suspicious for tuberculosis infection depending of the geographic area that the patient is coming from. Induration of the site of injection appears in 8 to 12 hours, reaches a peak in 24 to 72 hours, and then slowly disappears. Prior tuberculosis immunization (BCG) can complicate the interpretation of the PPD. In general, BCG vaccination in childhood does not affect the interpretation of PPD in adults, but multiple injections may produce positive results.

IMMUNOLOGY

Successful infection by Mycobacterium tuberculosis depends on the initial encounter between the pathogen and the host cell, usually the macrophage. The surface characteristics of both parties will determine the outcome. Although mycobacteria are gram positive, their wax-rich cell wall confers them unique features and thus they are classified as acid-fast bacilli. The abundant cell wall glycolipids and mycolic acids are responsible for many of the immune responses.

Mycobacterium tuberculosis has been proposed to bind to a variety of host cell receptors, including complement receptors, Fc receptors, surfactant protein receptors, CD14, and the macrophage mannose receptor via a variety of surface molecules. The receptor used to enter the macrophage affects the cellular response. For example, interaction of the Mycobacterium tuberculosis with the Fc receptor induces the production of reactive oxygen permitting phagosome-lysosome fusion. The variety of receptors that could be utilized by mycobacteria to enter host cells, led researchers to believe that there is no one “preferred route.”

Once inside the macrophage, Mycobacterium tuberculosis faces the problem of establishing residence inside the primary host effector cell. Mycobacteria have an evolved mechanism to exploit the macrophage as an intracellular host. One of the major problems that the bacteria face is the acquisition of essential nutrients in the intracellular environment. Macrophages require iron as a cofactor in the induction of microbiocidal effector mechanisms, while bacteria themselves have an obligate requirement for iron for their intracellular survival. There are different methods that Mycobacterium tuberculosis uses to ensure that its iron supply is not limited. One example of such mechanism is the development of highly specialized iron-binding molecules that have a high affinity for intracellular iron.

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LABORATORY DIAGNOSIS OF MYCOBACTERIAL INFECTIONS

There is no single diagnostic test for tuberculosis. Several techniques should be used to generate complete and rapid information. Laboratory results should always be correlated with the patient’s clinical presentation, and the clinician should notify the laboratory when results are not consistent. Reports have demonstrated that 3% of cultures for TB are false-positives. Regardless of recent advances in molecular techniques, microscopic examination of the sputum remains an inexpensive and rapid way of identifying highly infectious patients. It allows for a quantitative estimation of the number of bacilli being excreted and therefore remains the cornerstone of infection monitoring. Smear results should be available within 24 hours of specimen collection. Although the specificity of microscopic examination is excellent (89%-100%), it presents 2 main difficulties: It is unable to distinguish tuberculosis bacilli from non-tuberculosis mycobacteria, and it has low sensitivity. Molecular testing should be used for confirmation of suspected tuberculosis cases in patients who have a positive sputum specimen by microscopic exam. Molecular tests, including PCR, transcription amplification, ligase chain reaction, and strand displacement amplification, may enhance diagnosis, particularly for patients for whom prompt treatment is imperative.

TREATMENT

Comprehensive treatment of tuberculosis requires coordination between clinical care and public health policy. All states require that cases of TB be reported to public health authorities. Recommended regimens for treatment of TB include 3 of 4 antituberculosis agents,
An additional drug, if rifampin is not available, may be added. Second-line medications either should be used, 18 months is the minimal duration of therapy, and nonnucleoside reverse transcriptase inhibitors used to treat HIV infection.

The most commonly used regimen consists of isoniazid, rifampin, cycloserine, and pyrazinamide administered daily for 8 weeks, followed by isoniazid and rifampin given daily, twice a week, or 3 times a week for 16 weeks. Unless the rate of resistance to isoniazid is documented to be less than 4% in the community, ethambutol or streptomycin should also be used until the organism is known to be fully susceptible to all drugs used.

Isoniazid should be used (in conjunction with other drugs) for the duration of the therapy because of its efficacy, low cost, and tolerability. If rifampin is not used, 18 months is the minimal duration of therapy associated with acceptable cure rates. In the absence of drug resistance, a regimen of isoniazid and rifampin administered for 9 months is curative. The addition of pyrazinamide for the first 2 months of treatment allows the regimen to be shortened to 6 months and is associated with improvement in compliance and cure rates. No regimen administered for less than 6 months has acceptable cure rates for cases of culture-confirmed tuberculosis. Of equal importance to successful therapy is the administration of medications according to a schedule conducive to adherence. A recent advancement in this respect has been the use of 6-month regimens, with an initial period of daily drug administration, followed by 2 or 3 times per week under direct observation.

Immunocompetent persons that become infected with Mycobacterium tuberculosis or become symptomatic are believed to be resistant to infection with a second strain. Therefore, isoniazid is not recommended for immunocompetent persons with previously positive tuberculin skin test who are exposed to a new case of tuberculosis. In the late 1980s, it became clear that a substantial number of patients were not completing treatment and that noncompliance was unrelated to the level of education, race or ethnic group, income, or other demographic factors. To address this problem, the American Thoracic Society and the CDC recommended that direct observation of therapy by a trained health care worker be considered for all patients as part of a comprehensive patient-centered program.

A chest radiograph should be obtained at the beginning of treatment to confirm the diagnosis. For culture-negative cases of tuberculosis, the response to therapy is monitored by reviewing the symptoms and obtaining a chest radiograph at 3 months. A chest radiograph should be obtained at the end of the treatment as a base line for future reference.

Timing of symptom resolution, although helpful in the assessment of an individual patient’s response to therapy, can be highly variable. Thus, in persons with positive sputum cultures, the conversion to negative cultures provides the only objective measure of successful treatment, and cultures should be obtained monthly until conversion is documented. More than 85% of patients who receive a regular regimen have negative sputum cultures within 2 months after initiation of treatment.

It is important to differentiate between chemotherapy and chemoprophylaxis. Chemoprophylaxis is the prescription of antituberculosis medications in patients who have had a positive tuberculin test in the absence of active disease. The benefit of chemoprophylaxis is highly controversial, and studies conflict between the USA and Europe. The reason for concern is the risk for toxicity, especially hepatotoxicity, from the medication. The value of chemoprophylaxis in recent tuberculin converters, especially in young individuals, is well established. However, the benefit of treatment in individuals with unknown duration of seroconversion is still

**Table I. Primary and secondary therapy**

*Medications used in the treatment of tuberculosis*

**First-line drugs**
- Rifampin
- Rifapentine
- Ethambutol
- Pirazinamide
- Isoniazid
- Rifabutin

**Second-line drugs**
- Cycloserine
- Ethionamide
- Cycloserine
- Streptomycin
- Amikacin/kamycin
- Capreomycin
- P-Aminosalicylic acid
- Levofloxacin
- Moxifloxacin
- Gatifloxacin

followed by a 4-month continuation phase in which 2 drugs are administered. In selecting a regimen for an individual patient, the clinician should consider the local rates of drug resistance and the schedule of administration that is most likely to ensure adherence.

Four anti-microbial agents—rifampin, ethambutol, pirazinamide, and isoniazid—are the basis of currently recommended antituberculosis therapy (Table I). Several studies of these drugs have shown that they have favorable therapeutic ratios. An additional drug, rifabutin, can be substituted effectively for rifampin in order to minimize interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors used to treat HIV infection. Second-line medications either have been shown to be less effective and more toxic than the first-line agents or have not been studied extensively. These medications should be used only in patients who cannot tolerate the first-line medications or who are infected with organisms that are resistant to them.

The most commonly used regimen consists of isoniazid, rifampin, and pyrazinamide administered daily for 8 weeks, followed by isoniazid and rifampin given daily, twice a week, or 3 times a week for 16 weeks. Unless the rate of resistance to isoniazid is documented to be less than 4% in the community, ethambutol or streptomycin should also be used until the organism is known to be fully susceptible to all drugs used.

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Isoniazid is the chemoprophylactic drug of choice, in a dose of 300 mg daily for 6 months. Twelve months is recommended in HIV-infected patients. Pyridoxine supplementation, 10-25 mg daily, is recommended for persons older than 65 years of age, pregnant women, patients with diabetes mellitus, chronic renal failure, or alcoholism, and persons who are malnourished. There is a potential risk of hepatotoxicity from isoniazid, estimated to occur in approximately 9% of patients.

It is widely accepted that, if not treated, about 5% of tuberculin skin test converters will develop tuberculosis within 1 or 2 years and that another 5% will develop it later. Healthy tuberculin reactors are well protected from the development of active tuberculosis if proper chemoprophylaxis is initiated.

Table II. Tuberculosis: dental considerations (adapted from Phelan et al2)

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>Establish previous history of TB exposure, medical treatment and follow-up, and any prophylactic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>May need physician consult if poor history or unclear treatment</td>
</tr>
<tr>
<td></td>
<td>Patient with history of positive tuberculin test and without signs/symptoms of active tuberculosis: Suggests previous exposure to the tubercle bacilli. In this cases detailed questions about the event, treatment if any, and medical follow-up may be asked.</td>
</tr>
</tbody>
</table>
| During treatment | Patients with active TB  
|                  | Dental emergencies only                                                                           |
|                  | Controlled environment (protective gear/respirator, pressurized air flow)                         |
|                  | Patients with signs and symptoms suggestive of TB  
|                  | Dental emergencies only                                                                           |
|                  | Consider referral for medical evaluation and workup to rule out TB                                |
|                  | Protective gear (respirator mask)                                                                  |
|                  | Patients with a history of TB  
|                  | Routine dental treatment (after establishing that the patient has been adequately treated and followed and there are no signs and symptoms of active disease) |
|                  | Patients with a positive tuberculin test with no history of TB and no signs or symptoms of active disease  
|                  | Routine dental treatment                                                                            |
|                  | Consult with physician if there is any question of the presence of active disease                  |
| After treatment  | No specific precautions                                                                            |

It is also pertinent to include in the chemoprophylaxis category the treatment of persons in contact with active cases. In young patients the benefits exceed possible risks, as toxicity from isoniazid is lower and the likelihood of recent infection is greater. To address the risk to health care workers accidentally exposed to tuberculosis, Stead52 reviewed 33 previously investigated hospital and nursing homes outbreaks. He concluded that a tuberculin conversion greater than 15 mm (rather than greater than 10 mm as recommended by the CDC) is a definitive indication for preventive therapy after exposure. In HIV-positive health care workers preventive therapy should be started even before retesting.

DENTAL CONSIDERATIONS

Tuberculosis has been recognized for many years as an occupational risk for health care workers. However, with the advent of chemotherapy and the apparent reduction in the incidence of the disease in the mid-1980s, awareness of the problem declined. Tuberculin testing indicates that there has been a 50% increase in Mycobacterium tuberculosis contacts among health care workers in New York during the past 8 years.33 In the general dental evaluation of patients with tuberculosis, it is important to distinguish persons with active tuberculosis (symptomatic with other findings confirmatory of TB) taking appropriate chemotherapy, from active tuberculosis without treatment, and from those infected with Mycobacterium tuberculosis but not with active disease (positive tuberculin test). The oral healthcare worker should question the patient with a history of positive tuberculin test without active infection about occupational exposures and the type and length of treatment, if any. Recent contact with the primary physician must be included in the chart.

Only persons with active disease are infectious to others. (Table II) The medical history should include the signs and symptoms of pulmonary TB, which include cough, production of sputum and blood (hemoptysis) and chest pain. Other nonspecific symptoms, such as anorexia, fatigue, weight loss, fever and night sweats, are often associated with active TB.34

Patients who report that they have been diagnosed with TB have to be questioned regarding status of the disease. It is vital to make a distinction between asymptomatic infection, remote inactive disease, and active disease on therapy. Asymptomatic individuals with a positive tuberculin skin test and no evidence of active pulmonary disease do not present a risk for transmission of TB but may be candidates for preventive therapy.35 Patients with a positive skin test and evidence
of prior active TB by chest radiograph are also not infectious but, if not treated in the past, may also be candidates for prophylactic therapy. Patients with active disease should be on appropriate chemotherapy. Patients should be questioned about the type of medication they are taking, the duration of the treatment, and the compliance with drug therapy. Anti-TB therapy rapidly reduces the infectivity of the individual, and 2 weeks is usually considered adequate to label a patient as non-infectious. Adverse reactions to TB medications may occur. The clinician should avoid medication interactions such as acetaminophen and isoniazid because of the potential for hepatotoxicity. The CDC published in 2003 the most recent “Guidelines for Infection Control in Dental Health-Care Settings,” including considerations for TB. The CDC guidelines highlight administrative controls such as delineation of policies and procedures, engineering controls such as ventilation and air flow, and personal respiratory protection.

For dental care facilities that provide care to populations at high risk of TB, engineering controls to decrease the risk of transmission should be considered. These include high efficiency ventilation and air flow (Table II).

Oral lesions usually appear secondary to primary tuberculosis infection elsewhere, although primary infection of the oral mucosa by Mycobacterium tuberculosis has been described. Lesions are found commonly in the posterior part of the mouth, possibly related to lymphatic distribution. The clinical presentation of the tuberculosis lesions of the oral mucosa varies widely, including ulceration, diffuse inflammatory lesions, granulomas and fissures. The tongue is a prevalent site of presentation, but lesions have been noted in the buccal mucosa, gingiva, floor of the mouth, lips and palate. Tuberculosis lymphadenitis may involve the cervical lymph nodes. Atypical mycobacteria are involved in cervical lymphadenitis in children while Mycobacterium tuberculosis is more likely found in adults.

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