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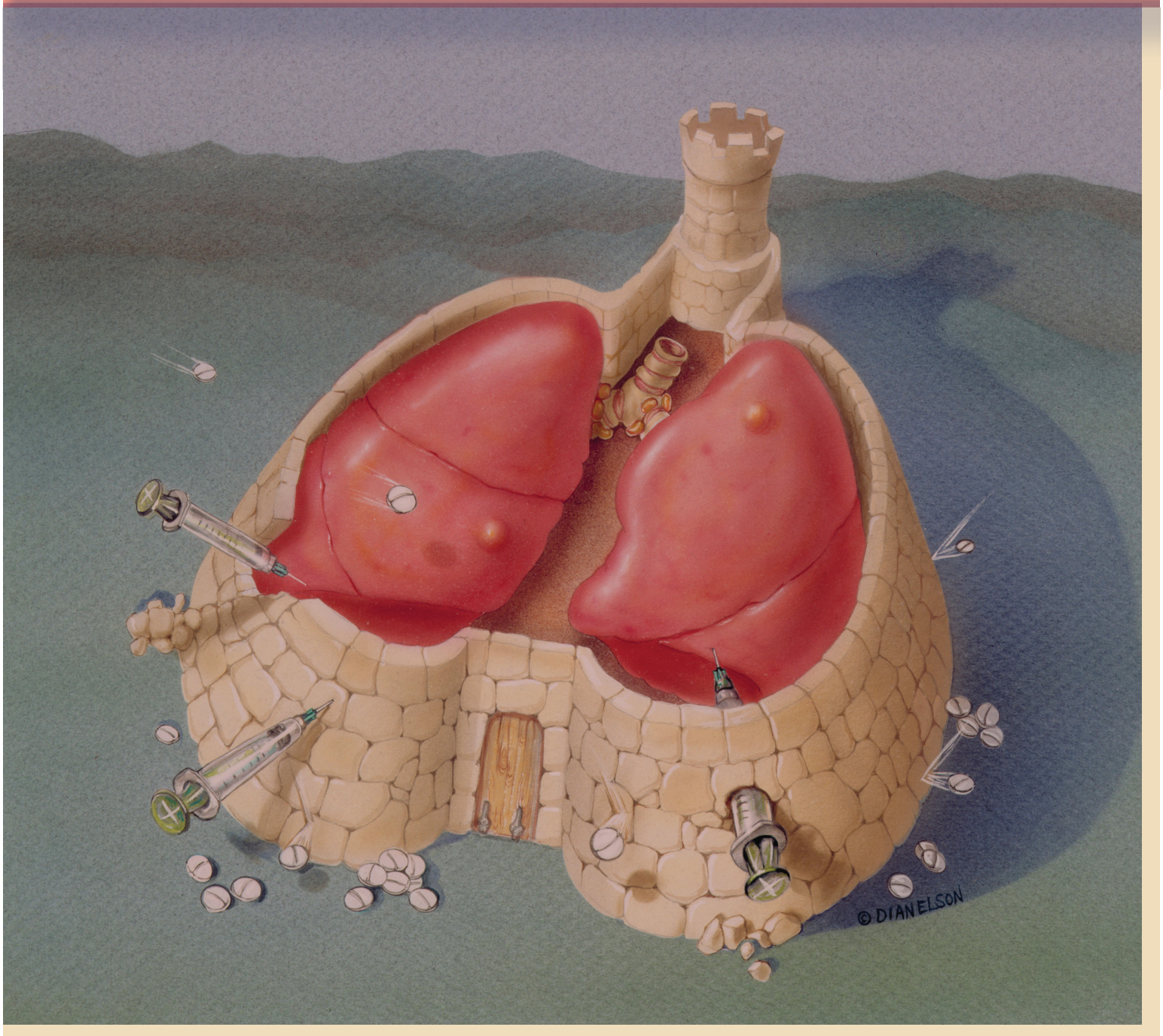
BREAK THROUGH



MULTIDRUG-RESISTANT TB

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Bodies more than 6,000 years old show evidence of tuberculosis (TB).[1,2] About 2,500 years ago, Hippocrates described TB as prevalent and deadly.[2,3] Because death was certain after the disease progressed, Hippocrates cautioned physicians that caring for patients with advanced TB might harm their professional reputation.[2]

The first safe anti-TB drug, streptomycin, was developed in 1943; however, resistance to this drug was noted shortly after its introduction.[1,2] Subsequently, multidrug-resistant TB (MDR-TB) emerged, and instances of patients with resistance to all anti-TB drugs have been reported.[1,4] Isoniazid (isonicotinic acid hydrazide, INH) and rifampin are the cornerstones of TB treatment worldwide, although resistance to both is common.[5]

Although the development of anti-TB drugs was a significant milestone, some health experts attribute effective TB control to economic development.[6,7] Historical analysis suggests that declines in TB infection and disease correlate closely to government efforts to provide housing to reduce crowding.[7]

In spite of pharmacologic and social advances, TB remains widespread, and educated professionals are needed worldwide to treat people infected with TB.[8] While the prospect of treating TB in developing countries is appealing to some providers, many are ill-equipped.[8] Inadequate treatment exacerbates the problem, but in resource-poor countries with a high prevalence of MDR-TB, experts are unavailable.[8] Educating providers better may offer a solution.

Undertreated TB often evolves to MDR-TB, complicating the treatment. Undertreatment may be due to a patient's failure to take medication as prescribed or failure to prescribe appropriate medications. Patient nonadherence is addressed in programs like a Directly Observed Therapy System (DOTS), a strategy to prevent resistance by enlisting the support of another person, often a family member, to supervise the patient's medication regimen. However, drug resistance will develop even in the context of strict patient adherence if the regimen is inadequate. The prescriber's role in selecting the proper regimen is equally important.[9] Education on the proper treatment of TB to prevent MDR-TB is fundamental to successful global TB treatment.[4,8]

Epidemiology

One-third of the world's population is infected with *Mycobacterium tuberculosis* (MTB), but only 5% to 10% of these individuals develop active disease.[5,7] Less than 5% of those with active infection have signs and symptoms of the disease.[1] The incidence of active TB in 2007 was 9.27 million cases; the prevalence was 13.7 million cases.[19] Only about half of TB cases have positive sputum smears, demonstrating an important diagnostic challenge.[19] Immigrants represent most TB cases in developed countries, possibly due to immigration from high-incidence countries and poor screening practices.[10] Mortality in HIV-negative individuals due to TB was 1.3 million in 2007;

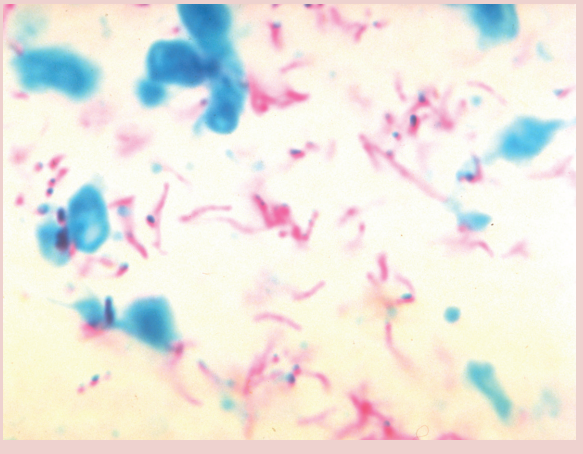
another 456,000 people who were HIV positive and infected with TB also died.[19] TB continues to be a threat to global health.

Statistics on the incidence and prevalence of MDR-TB are scarce and the figures may be much higher than generally believed. In one study of patients in rural South Africa, 10% of positive cultures were resistant to all first- and second-line drugs. Only 30% of those patients had been treated for TB previously, suggesting that most did not develop resistance as a result of undertreatment but actually contracted resistant strains.[1] Approximately 500,000 cases of MDR-TB occurred in 2007.[19] India, China, the Russian Federation, South Africa, and Bangladesh have the highest numbers of MDR-TB cases.[19] In 1993, foreign-born U.S. citizens accounted for 26% of MDR-TB cases in the United States. The number increased to 80% in 2005.[12] MDR-TB is not restricted to developing countries. A case report in New York City found that 33% of TB cases were MDR-TB.[13] Institutional outbreaks have also been reported in the United States and developing countries alike.[13]

While immunocompromised patients are susceptible to TB, most TB infections occur in otherwise healthy adults.[14] Many with TB live in resource-poor countries where HIV infection is higher.[15] People infected with HIV are at greater risk of developing active TB,[5,15,16] and TB is the leading cause of death in people who are HIV positive.[5] These statistics are cause for concern in developed and developing countries.

MTB

A smear of a pulmonary lesion that shows the slender, rod-shaped, acid-fast bacilli.



Source: Rubin R, Strayer D (eds). *Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008; 341.

Pathophysiology

Cell biology

Knowing MTB's pathophysiology helps in understanding why TB is a global health problem. Glickman and Jacobs define TB as "a bacterial infectious disease caused by the obligate human pathogen, *Mycobacterium tuberculosis*."[17] Studying MTB in animals is difficult because latency cannot be established. MTB is a slow-growing, acid-fast, rod-shaped bacillus, requiring 12 to 24 hours to replicate (see *MTB*).[17,18] MTB's cell wall provides hardiness against innate and acquired immunity.[17] Phagocytosis of MTB by alveolar macrophages leads to cytokine recruitment, creating an inflammatory response leading to granuloma formation and evidence of disease.[1]

The natural history of TB

Active TB is infection with MTB with evidence of infection on chest X-ray (CXR); patients with active disease may not show symptoms.[1] Latent TB is a carrier state where the organism is not killed but remains in the body, and can become active later.[15,17] (See *Active versus latent TB.*)

MTB's ability to colonize human hosts without causing active disease immediately is unique.[17] The diagnosis of latent TB is made using the tuberculin skin test (TST).[15,17] A positive TB skin test is the only sign of latent TB infection.[17] Why some people develop active TB while others do not involves genetics, cell-mediated immunity, and other factors.[1,7,17] Several genes seem to play a role in susceptibility to active TB infection.[7] Further study is needed to understand the complexities of active and latent TB infection.

Transmission

MTB is largely transmitted by airborne droplets.[1,5,18] Transmission by contact with infectious body secretions or fomites is rare.[18] Transmission from ingestion of unpasteurized milk products from TB-infected cattle has also been reported.[20] Humans alone host MTB and the disease is transmitted from person to person when hosts with active TB cough, sneeze, talk, or expectorate.[1,5,18] Living in crowded conditions increases MTB transmission.[4,7]

Resistance

Resistance to streptomycin was discovered in the 1940s, shortly after its intoduction.[1] Resistance to INH and rifampin was noted later; now resistance to all TB drugs exists.[1] Active TB should be treated with at least two drugs because the population of MTB is diverse. For example, one organism in the population may be resistant to INH but susceptible to rifampin, and for another organism, the

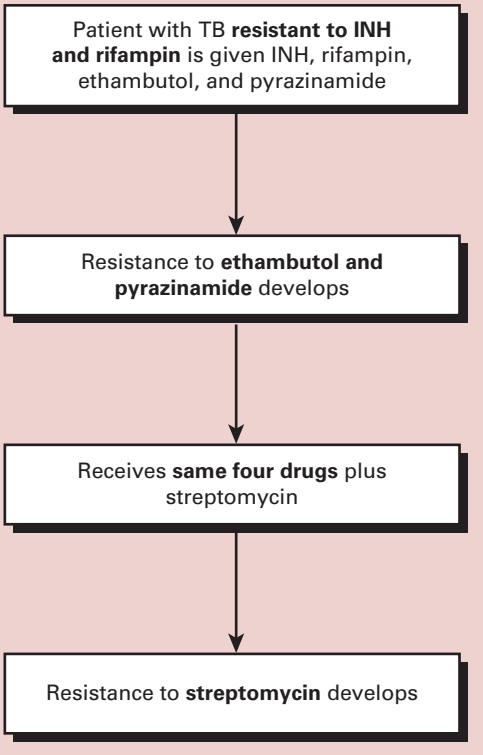
converse might be true.[18] In regions with prevalence of low drug resistance, latent TB infections—which have small MTB populations—may be treated with one drug, usually INH.[18] Drug resistance is more common among patients who have been treated for TB in the past.[11] In Peru in the 1990s, an outbreak of MDR-TB was linked to treatment with drugs that were already resistant to the disease.[4] Although many people with TB do not achieve a cure because of poor treatment compliance, this explanation does not apply to Peru, which had an effective DOTS program.[18] *Figure 1* explains why 67% of the patients in the study had TB resistant to the five first-line drugs, and why 90% of the patients who had not been cured by one or more treatments had MDR-TB (see *How resistance develops*).[4]

Extensively drug-resistant TB (XDR-TB), a more recent worldwide phenomenon, is MDR-TB that is also resistant to the most effective second-line therapeutic drugs used to treat MDR-TB: fluoroquinolones and at least one of three injectable second-line drugs used to treat TB.[37] The CDC formed a task force to address the growing problems of MDR-TB and XDR-TB in the United States, but there is a great need to address these issues on an international level.[37]

Active versus latent TB[1,15,19]

Type of TB infection	Percentage represented	Subjective findings	Objective findings
Latent	5% to 10% of TB population	Asymptomatic	Positive TST, negative CXR, or old, healed infection
Active	90% to 95% of TB population	Symptomatic or asymptomatic	Positive TST, evidence of disease on CXR, and sputum smear

How resistance develops[4]



Presentation

History

Presentation depends upon disease stage. The classic presentation of productive cough, fever, cachexia, dyspnea, and abnormal lung sounds is uncommon in the developed world.[10] Sputum production varies according to the infection's severity; 10% of patients expectorate blood.[1] The review of systems should include questions about fever, weight loss, cough, shortness of breath, and sputum production.[1,10,17] A history of bacillus Calmette-Guerin (BCG) vaccination, recent travel, immigration, or incarceration of the patient or family members should be gathered in the history. Patients working in high TB-exposure areas, such as hospitals, prisons, and homeless shelters, should be screened for TB.

A list of previously prescribed TB drugs is a key part of the history of a patient with possible MDR-TB.[8] An accurate patient drug history can help practitioners avoid prescribing drugs the patient may have already developed resistance to, which prevents further development of resistance.[8] This may be done by obtaining previous medical records and involving family and others in the treatment plan.

Physical exam

Most active TB infections are asymptomatic; therefore, the physical exam may be unrevealing.[18] General observations of cachexia or fever and examination of the lungs for adventitious sounds and consolidation, indicating lung disease, are important components of the physical exam.[17]

Diagnosis

This article focuses on pulmonary TB. Although disseminated infection occurs, its discussion is beyond this article's scope. A high index of suspicion is required to diagnose TB in developed countries where the incidence and prevalence are low.[19] Diagnosis of pulmonary TB must be

How to interpret a Mantoux TST[24]

Induration of 5 mm or more is considered positive in

- HIV-positive persons
- Recent contacts of TB case patients
- Persons with fibrotic changes on CXR consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients (receiving over 15 mg/day of prednisone for 1 month or more

Induration of 10 mm or more is considered positive in

- Recent immigrants (that is, within the last 5 years) from high-prevalence countries
- Injection drug users
- Residents and employees* of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with AIDS, and homeless shelters
- Mycobacteriology lab personnel
- Persons with clinical conditions that place them at high risk, such as silicosis, diabetes mellitus, chronic kidney disease, some hematologic disorders (for example, leukemias and lymphomas), and other specific malignancies
- Children younger than 4 years of age or infants, children, and adolescents exposed to adults at high risk

Induration of 15 mm or more is considered positive in

- Persons with no known risk factors for TB

* For persons who are otherwise at low risk for TB and who are tested at the start of employment, a reaction of 15 mm is considered positive.

Source: Public Domain Reproduced from http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm.

First-line TB drugs[1,4,18]

Isoniazid

- Contraindicated in acute liver disease or isoniazid-related liver damage
- May cause hepatotoxicity and hepatitis
- Monitor liver function studies
- Give pyridoxine (vitamin B_6) to prevent peripheral neuropathy, especially in malnourished patients
- Pregnancy risk category C

Rifampin

- May cause hepatotoxicity, use with caution in patients with liver disease
- Monitor liver function studies
- Induces cytochrome P450 enzymes, may cause drug interactions
- Advise patient that drug causes red-orange discoloration of body fluids
- Pregnancy risk category C

Pyrazinamide

- Contraindicated in severe hepatic disease and acute gout
- May cause hepatotoxicity
- Monitor liver function studies and uric acid levels
- Advise patient that drug may cause darkened urine, yellow discoloration of skin and eyes, and arthralgia
- MTB strains may produce pyrazinamidase
- Pregnancy risk category C

Ethambutol

- Contraindicated in patients with optic neuritis
- Use with caution in patients with impaired renal or hepatic function, cataracts, or diabetic retinopathy
- Monitor for vision changes
- Resistance due to cell wall lipid changes
- Pregnancy risk category C

Streptomycin

- An aminoglycoside that may cause nephrotoxicity, ototoxicity, and neurotoxicity
- Use with caution in patients with renal disease
- Monitor renal function
- Pregnancy risk category D

based on sputum tests, CXRs, clinical presentation, and risk factors because a negative result for one of these elements does not preclude disease.[10] In the United States, all 50 states have laws that require certain health professionals to report cases of TB.[13] Time frames for reporting vary from the time of diagnosis to 1 week later.[13] NPs should be familiar with the mandatory reporting laws in their states. The CDC has detailed recommendations for reporting at http://www.cdc.gov/mmwr/preview/mmwrhtml/00030715.htm.

Lab tests

TST

In the United States, screening for latent TB is based on a positive intradermal TST.[18] The Mantoux TST is performed by injecting tuberculin purified protein derivative (PPD) into the inner surface of the forearm. Ideally, the TST should be repeated after 1 to 2 weeks because the initial injection can prompt immune memory of latent TB. TB screening programs should focus on groups at high risk for TB transmission and infection; this is known as targeted tuberculin testing.[21] Mass screenings of people at low risk for TB are unnecessary and can affect the sensitivity and specificity of the test.[21] Healthcare providers who may be exposed to TB should be routinely screened according to their state's recommendations.[21] (See *How to interpret a Mantoux TST.*)

Previous vaccination with the BCG vaccine may cause a false-positive reaction to the skin test.[18] The likelihood of

a false-positive reaction decreases over time, and a positive result 5 years or more after receiving BCG is much more likely to be due to TB infection than to BCG.[22] Previous vaccination with BCG does not preclude TST, and providers should not make the mistake of failing to perform TST because a patient has been vaccinated with BCG.[22] The TST should be interpreted in the same manner regardless of BCG vaccination status.[23] False negatives are possible in immunosuppressed patients.[1]

QFT-G

The newer, more expensive QuantiFERON-TB Gold (QFT-G) test is a blood test that detects the release of interferon-gamma by white blood cells following incubation of the patient's blood sample with antigens that are synthetic peptides similar to *M. tuberculosis proteins*.[25] QFT-G can be used to screen for latent TB, diagnose active TB, and as a follow-up test for a positive TST in a less subjective manner. Problems with QFT-G include issues with sensitivity, specificity, and adequate lab facilities.[25]

CXR

A CXR with anterior-posterior and lateral views reveals disease status.[18] Active TB infection appears as adenopathy of the hilar nodes, fibrous texture, lobar atelectasis, and tracheal deviation.[1] Older, healed TB infections present as calcifications and are difficult to differentiate from TB that has reactivated.[1] In some cases, the CXR is normal, and others show massive disease with effusions and consolidation of lobes evidenced by air fluid levels.[1]

Sputum smear

The sputum smear is the classic test used to quickly diagnose pulmonary TB.[15] However, this test is commonly negative in people who are infected with HIV.[15] Performing the sputum smear repeatedly and concentrating the sputum increases the sensitivity of the test. Using hypertonic saline to stimulate production of the sputum ensures higher bacterial counts.[15] Respiratory therapists and pulmonary specialists are excellent resources for the NP who needs a sputum sample. Lab contamination can lead to false-positive culture results; a rise in the number of negative smears that are positive on culture should arouse suspicion.[15] Caminero states that cultures should be tested through direct sensitivity testing (DST) for first-line drugs.[8] DST has inconsistent reliability, and history of previous TB drug regimens may be more useful than DST for second-line drugs and in resource-poor settings where DST can take 4 to 5 months.[8] Cultures should be kept for at least 8 weeks because MTB multiplies slowly.[1]

Other labs

Complete blood cell count and inflammatory markers in patients with active TB may show leukocytosis (particularly, monocytosis), normochromic normocytic anemia, elevated erythrocyte sedimentation rate, and elevated C-reactive protein.[1] These tests can support the diagnosis but are nonspecific.

Treatment

Treatment regimen design for MDR-TB is controversial.[8] At least three effective drugs should be used to treat MDR-TB; four or more drugs are often used.[1,8] First-line drugs (isoniazid, rifampin ethambutol, pyrazinamide) should be used when possible, and treatment should last 18 to 24 months after the patient has negative cultures when second-line drugs are used.[1,26] These drug regimens are complex.

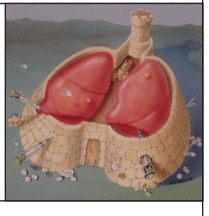
Second-line treatments include ethionamide, kanamycin, amikacin, capreomycin, cycloserine, ciprofloxacin, and ofloxacin.[18] These drugs either have more adverse reactions or are less effective in treating TB.[18] Second-line drug testing in randomized controlled trials of TB treatment is lacking.[1] Since the second-line drugs are expensive, the WHO has established the Green Light Committee to provide second-line drugs at a lower cost through an application process.[19] New drug development is paramount in fighting MDR-TB.[8]

Special populations

HIV infection

Care of patients with both HIV and TB should be undertaken by providers with knowledge in both areas.[27] The care provider must be aware of interactions between antiretrovirals as well as monitor for toxicity and interaction with TB drugs. Rifampin, a first-line TB drug, induces many of the antiretrovirals through the CYP450 pathway.[28] Rifabutin is as effective in treating TB and causes fewer drug interactions than rifampin, making it a viable treatment alternative.[28] Rifabutin is not available in many areas where TB and HIV coinfection are common.[28]

Respiratory therapists and pulmonary specialists are excellent resources for the NP who needs a sputum sample.



Pregnancy or lactation

Treating MDR-TB in pregnant women is complicated because most second-line drugs are potential teratogens.[27] However, not treating TB in pregnancy is more dangerous than the treatment itself.[29] Pyrazinamide, streptomycin, kanamycin, amikacin, capreomycin, and fluoroquinolones should not be used in pregnant women.[27,29] Vitamin B_6 supplementation is important with INH use in pregnancy and lactation.[29] Breastfeeding is safe with first-line TB drugs because the low drug levels do not cause toxicity in the infant; breastfeeding during TB treatment is not effective in treating infants with TB.[29] Counseling about the effects of TB drugs on the fetus is important in women who have HIV or MDR-TB because the benefits of TB drugs may outweigh the risks.[28,29]

Children

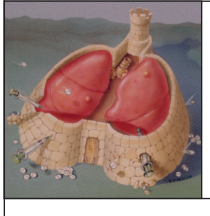
Research on TB drugs and children is scarce. A provider who specializes in TB should be involved in the care of children with MDR-TB.[27] Fluoroquinolone use over extended periods has not been studied in children, but many specialists in TB treatment recognize the importance of fluoroquinolone use in children with MDR-TB.[27] Refer to http://www.cdc.gov/tb/publications/factsheets/treatment/drugresistanttreatment.htm for appropriate pediatric treatment regimens.

DOTS

DOTS is a TB treatment strategy in which another person ensures that the patient is properly taking his or her medications.[9] Shin et al. notes that nurses are "… the central coordinators of patient care[and] critical to the care of patients with MDR-TB."[26] The extent of supervision often depends on what is acceptable to each patient and their environment; certain individuals such as prisoners, drug-users, and people with certain mental illnesses may need more support with their treatment.[30] DOTS also holds healthcare providers accountable for proper treatment.[30] Correct use of DOTS results in an 80% cure rate.[9] DOTS assures maintenance of an effective TB drug supply, holds governments responsible for TB treatment, and assists with public health data collection.[1,30] Having a reliable supply of drugs, not missing treatments, and providing free drugs to those with TB (because their treatment protects the public) are all part of WHO's strategy to control TB and prevent MDR-TB.[30]

Farmer notes that the S in DOTS actually stands for "short course" therapy, which includes INH and rifampin.[4] Farmer, Kim, and colleagues discovered many patients who were infected with TB resistant to these drugs in Lima, Peru, in 1996.[3,4,26] Peru has an excellent DOTS program, but the researchers questioned the WHO policies of repeating failed treatment with the same drugs, believing that this practice was worsening resistance.[4,6] A chart review of 2,000 patients with MDR-TB over 8 years found selection of a weak treatment plan for retreatment to be the most frequent medical mistake.[31] The team in Peru used DOTS basics but tailored the therapy to individual patients using culture and DST, curing 85% of their patients with MDR-TB (who had previously been considered to have terminal disease).[4] They set a precedent in TB treatment in developing countries, and their strategy was later adopted by the WHO as DOTS Plus.

Guidelines for management of MDR-TB are available from the WHO.[11] An example of a standard course of DOTS is 6 months of INH and rifampin with 2 months of pyrazinamide; often another drug is used at the beginning of treatment and should always be used when MDR-TB is suspected.[1] Patients should be cautioned that improvement of symptoms may take 2 weeks and that the CXR should improve in 3 to 5 months.[1]



Poverty and geographic location are risk factors for infection and death due to TB.

Global concerns

Many factors contribute to the high TB incidence in developing countries. Stopping treatment, drug resistance to INH and rifampin, new infection with TB, loss of more than 15% of body weight, and limited education were correlated with death from TB in Mexico.[9] Active disease is more likely in people with poor T-cell function, such as people with HIV infection.[1]

Poverty and geographical location are risk factors for infection and death due to TB.[11,26,32] Crowded living conditions, poverty, and inadequate governmental support contribute to TB infection globally.[1,7,8,14]

Prevention

The following three areas are important in preventing the spread of TB and the development of drug resistance: (1) identifying people with both active and latent disease, (2) treating them quickly with appropriate drug regimens, and (3) isolating people with active TB to prevent airborne transmission.[1,10] Poor prescribing, unreliable drug

supplies, inadequate treatment, and low compliance can have profound effects on the development of drug resistance.[5] TB outbreaks vary according to the prevalence of HIV and MDR-TB, wealth, and public health infrastructure.[6] Vision in MDR-TB prevention requires a comprehensive view of disease contributing factors.

Preventing airborne transmission

Airborne precautions are important in preventing transmission of TB.[33] Transmission in acute care settings is problematic, and the CDC requires airborne isolation and three negative sputum smears 8 to 24 hours apart before airborne precautions can be discontinued.[34] The CDC recommends at least 2 weeks of multidrug treatment before precautions are discontinued if infectious TB is still suspected after three negative sputum smears.[34] One study found that patients with MDR-TB had positive cultures longer than other patients with drug-susceptible TB.[33] Isolation rooms to prevent airborne transmission and rooms for procedures with a higher risk of transmission (sputum induction) are important.[35] Negative-pressure rooms are used and special masks such as N-95 respirators are worn in healthcare settings in the United States.[36] Proper fitting and use of these protective devices is imperative.[35]

Closeness of contacts and amount of time spent with patients contributes to the probability of disease transmission; about 25% of household contacts are infected.[1] Recent reports of transmission of TB on airplanes have received considerable media attention and have captured the attention of the public.[1] The probability of transmission in such cases is low; the WHO has guidelines for air travel on their website. Attention to the patient's feelings in regard to isolation is important, as is the case with any disease that carries social stigma. Having separate waiting areas in outpatient settings for patients with known TB or MDR-TB may protect other patients from becoming infected. Signs in waiting rooms reminding patients about preventing the spread of infection are helpful.[35]

BCG vaccine

The BCG vaccine has been used since 1921 and has consisted of many different strains; the current reference strain is the Pasteur vaccine.[1] The variability of the BCG vaccine limits its usefulness.[18] BCG is currently used in many countries where TB prevalence is high to prevent serious TB infections in children.[22] The vaccine causes a local inflammatory response and a scar at the injection site.[1] Development of host immunity depends on the following factors: strain of vaccine, environment, genetics, and individual responses.[1] A more effective vaccine to prevent TB is needed because current BCG vaccines vary in their protectiveness from 0% to 80%.[7]

Conclusion

Understanding the history, pathophysiology, epidemiology, diagnosis, treatment, and prevention of MTB infection is important for all healthcare providers. MTB is an airborne bacteria, and the urgency of treating MDR-TB must not be underestimated.[3,4] The world cannot afford to view MDR-TB, an airborne disease, as simply a problem of poorer countries; MDR-TB is a global issue. NP

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