Tuberculosis: a disease that is alive and kicking

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Tuberculosis is the leading cause of death from a single infectious disease, accounting for over a quarter of avoidable deaths in adults. The great majority of cases, and more than 95% of deaths, occur in the developing world.

Introduction

Tuberculosis, a multisystemic disease with myriad presentations and manifestations, is the most common cause of infectious disease-related mortality worldwide. The World Health Organization has estimated that 2 billion people have latent tuberculosis, and that in 2009, globally, the disease killed 1.7 million people. New tuberculosis treatments are being developed and new tuberculosis vaccines are under investigation. Although tuberculosis rates are decreasing in the USA, the disease is becoming more common in many parts of the world. In addition, the prevalence of drug-resistant tuberculosis is also increasing worldwide. Co-infection with the human immunodeficiency virus has been an important factor in the emergence and spread of resistance.

Brief history of an age-old disease

Tuberculosis has been present in humans since antiquity. The earliest unambiguous detection of Mycobacterium tuberculosis was in the remains of bison dated 17 000 years before the present. However, whether tuberculosis originated in cattle and was then transferred to humans or diverged from a common ancestor is currently unclear. Evidence follows a comparative genomic approach of M. tuberculosis complex in humans to M. tuberculosis complex in animals that suggests that humans did not acquire M. tuberculosis complex from animals during animal domestication as previously believed. Both strains of the tuberculosis bacteria are shown to share a common ancestor which could have infected humans as early as the Neolithic transition. Skeletal remains show prehistoric humans (4000 BCE) had tuberculosis and researchers have found tubercular decay in the spines of Egyptians dating from 3 000-2 400 BCE. Phthisis is a Greek word for consumption. In 460 BCE, Hippocrates identified phthisis as the most widespread disease of the times that involved coughing up blood and the acquisition of fever. It was almost always fatal.

The bacillus that causes tuberculosis, M. tuberculosis, was identified and described on 24 March 1882 by Robert Koch. In 1905, he received the Nobel Prize for this discovery. In 1906, Albert Calmette and Camille Guérin achieved the first genuine success in immunising against tuberculosis using attenuated bovine-strain tuberculosis. It was called bacille Calmette-Guérin (BCG). The BCG vaccine was first used on humans in 1921 in France, but it wasn’t until after World War II that BCG received widespread acceptance in the USA, Great Britain and Germany.

Epidemiology

Roughly a third of the world’s population has been infected with M. tuberculosis, and new infections occur at a rate of one per second. However, not all infections with M. tuberculosis cause tuberculosis disease. Many infections are asymptomatic. In 2007, there were an estimated 13.7 million chronic active cases, and in 2010, 8.8 million new cases and 1.45 million deaths, mostly in developed countries. China has achieved particularly dramatic progress, with an 80% decline in its tuberculosis mortality rate. The distribution of tuberculosis is not uniform across the globe. Approximately 8% of the population in many Asian and African countries test positive in tuberculin tests, while only 5-10% of the US population test positive. Tuberculosis is the world’s greatest infectious killer of women of reproductive age and the leading cause of death in people with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome. This is because worldwide, women have a larger burden of poverty, ill-health, malnutrition and disease than men. Tuberculosis results in more deaths in women than all causes of maternal mortality.
combined. More than 900 million women are infected with tuberculosis worldwide. It also kills more young people and adults than any other known infectious disease.18

The rise in HIV infections and the neglect of tuberculosis control programmes have enabled a resurgence of tuberculosis.19 The emergence of drug-resistant strains has also contributed to this new epidemic. Between 2000 and 2004, 20% of tuberculosis cases were resistant to standard treatment and 2% were resistant to second-line drugs.20 The rate at which new tuberculosis cases occur varies widely, even in neighbouring countries, apparently because of differences in healthcare systems.21 In 2007, the prevalence of tuberculosis per 100 000 people was highest in sub-Saharan Africa. It was also relatively high in Asia.22

In 2007, the country with the highest estimated incidence rate of tuberculosis was Swaziland, with 1 200 cases per 100 000 people. India had the largest total incidence, with an estimated 2 million new cases.14 In developed countries, tuberculosis is less common and is mainly an urban disease. In the UK, the national average was 15 per 100 000 in 2007. The highest incidence rates in Western Europe were 30 per 100 000 in Portugal and Spain. These rates compared with 98 per 100 000 in China and 48 per 100 000 in Brazil. In the USA, the overall tuberculosis case rate was 4 per 100 000 persons in 2007.22 In Canada, tuberculosis is still endemic in some rural areas.23

The incidence of tuberculosis varies with age. In Africa, tuberculosis primarily affects adolescents and young adults.24 However, in countries where its incidence is low having previously been high, such as the USA, it mainly affects older people or the immunocompromised.25

Microbiology

The main cause of tuberculosis is *M. tuberculosis*, a small, aerobic non-motile bacillus or less commonly, the closely related *M. bovis*.26 The high lipid content of this pathogen accounts for many of its unique clinical characteristics.27 It divides every 16-20 hours. This is at an extremely slow rate compared with other bacteria, which usually divide in less than an hour.28 Since *M. tuberculosis* has a cell wall but lacks a phospholipid outer membrane, it is classified as a Gram-positive bacterium. However, if a Gram stain is performed, *M. tuberculosis* either stains very weakly Gram-positive, or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall.29 *M. tuberculosis* can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured in the laboratory.30

Using histological stains on expectorate samples from phlegm (also called sputum), scientists can identify *M. tuberculosis* under a regular microscope. Since *M. tuberculosis* retains certain stains after being treated with acidic solution, it is classified as an acid-fast bacillus (AFB).31 The most common acid-fast staining technique, the Ziehl-Neelsen stain, dyes AFBs a bright red that stands out clearly against a blue background. Other ways to visualise AFBs include an auramine-rhodamine stain and fluorescent microscopy.

The *M. tuberculosis* complex includes other tuberculosis-causing mycobacteria: *M. bovis*, *M. africanum*, *M. canetti* and *M. microti*.29 *M. africanum* is not widespread, but in parts of Africa it is a significant cause of tuberculosis.33,34 *M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurised milk has largely eliminated this as a public health problem in developed countries.35 *M. canetti* is rare and seems to be limited to Africa, although a few cases have been seen in African emigrants.36 *M. microti* is mostly seen in immunodeficient people, although it is possible that the prevalence of this pathogen has been underestimated.37 Other known pathogenic mycobacteria include *M. leprae*, *M. avium*, *M. kansasi*, *M. pinnipedii* and *M. bovis* BCG. The latter two are part of the nontuberculous mycobacteria group. Nontuberculous mycobacteria do not cause either tuberculosis nor leprosy, but they can cause pulmonary diseases that resemble tuberculosis.38

Clinical disease

Tuberculosis is a common, and in many cases, lethal infectious disease, caused by various strains of mycobacteria, usually *M. tuberculosis*.39 It is spread when people who have an active *M. tuberculosis* infection cough, sneeze or otherwise transmit their saliva through the air.40 Most infections in humans result in an asymptomatic, latent infection. Approximately one in 10 latent infections eventually progresses to active disease, which if left untreated, kills more than 50% of infectees. The classic symptoms are a chronic cough with blood-tinged sputum, fever, night sweats and weight loss. Infection of other organs causes a wide range of symptoms. Diagnosis relies on radiology (commonly chest X-rays), a tuberculin skin test, blood tests, as well as a microscopic examination and microbiological culture of sputum or bodily fluids. Treatment is difficult and requires long courses of multiple antibiotics. Social contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in extensively multidrug-resistant tuberculosis. Prevention relies on screening programmes and vaccination, usually with the BCG vaccine.

When tuberculosis becomes active, 75 of cases involve infection in the lungs, namely pulmonary tuberculosis. Symptoms include chest pain, haemoptysis and a productive, prolonged cough for more than three weeks. Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, pallor and fatigue.41 Extrapulmonary infection sites include the pleura in the case of tuberculosis pleurisy, the central nervous system in the case of meningitis, the genitourinary system in the case of urogenital tuberculosis and the bones and joints in the case of Pott’s disease of the spine. When it spreads to the bones, it is also known as osseous tuberculosis,42 a form of osteomyelitis.1 An especially
serious form is disseminated tuberculosis, more commonly known as military tuberculosis. Extrapulmonary tuberculosis may co-exist with pulmonary tuberculosis.43

Human immunodeficiency virus

Individuals who are infected with HIV are at increased risk of acquiring tuberculosis, beginning within the first year of HIV infection.44 Based on historical data, the initiation of antiretroviral therapy (ART) decreases the risk of developing tuberculosis in these patients.45 The risk of tuberculosis remains higher in the first three months after starting ART. The risk was highest in patients with a baseline CD4 count of less than 200/μl, higher baseline HIV-1 RNA level (relative hazard 1.93 for every log increase in baseline HIV-1 RNA), a history of injection drug use and male sex.46

In a study in Durban, nearly 20% of patients who started ART had undiagnosed, culture-positive pulmonary tuberculosis. Neither coughing nor an AFB smear were sufficiently sensitive for screening. Tuberculosis sputum cultures should be attempted before ART initiation in areas with a high prevalence of tuberculosis.47

Patients with tuberculosis must be tested for HIV. Patients with HIV need periodic evaluation for tuberculosis with tuberculin skin testing or chest radiography. Patients with HIV and a positive tuberculin skin test result develop active tuberculosis at a rate of 3-16% per year.

Prevention

As of 2011, the only currently available vaccine is the BCG, which while effective against disseminated disease in childhood, confers inconsistent protection against pulmonary disease.48 It is the most widely used vaccine worldwide. More than 90% of children have been vaccinated with it.49 However, the immunity that it induces decreases after approximately 10 years.49 Part of the reason against use of the vaccine is that it makes the tuberculin skin test falsely positive and is thus of no use in screening.50 A number of new vaccines are in development.49

The WHO declared tuberculosis to be a global health emergency in 1995,49 and in 2006, the Stop Tuberculosis Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between its launch and 2015.51 A number of targets that they have set are not likely to be achieved by 2015 because of the increase in HIV-associated tuberculosis and multidrug-resistant tuberculosis.49

Prognosis

Progression from tuberculosis infection to tuberculosis disease occurs when the tuberculosis bacilli overcome the immune system defenses and begin to multiply. These dormant bacilli can produce tuberculosis in 2-23% of latent cases, often many years after infection.51 The risk of reactivation increases with immunosuppression, such as that caused by infection with HIV. In people who are co-infected with M. tuberculosis and HIV, the risk of reactivation increases to 10% per year.51 Studies that utilise DNA fingerprinting of M. tuberculosis strains have shown that reinfection contributes more substantially to recurrent tuberculosis than was previously thought.52 Between 12% and 77% of cases are attributable to re-infection, instead of reactivation.53

Childhood tuberculosis

Children are most commonly infected with M. tuberculosis as a result of transmission from an adult, often a family member, with smear-positive disease. Most children remain asymptomatic. A positive tuberculin test may be the only evidence of infection. The patterns of extrapulmonary tuberculosis in children and the diagnostic problems that are encountered are similar to those described in adults, although meningitis makes up a higher proportion of extrapulmonary tuberculosis cases in young children. The diagnosis of childhood pulmonary tuberculosis has always been difficult because children rarely produce sputum for smear examination. Therefore, usually diagnosis requires a combination of clinical features, a history of contact with a sputum-positive case, growth faltering, chest X-ray changes and a reactive tuberculin skin test. Chest X-ray findings on their own are non-specific, as are clinical features, but the most important symptoms are weight loss and poor appetite. Given the problems with diagnosis and the low frequency of routine childhood screening, the real burden of childhood tuberculosis in sub-Saharan Africa is not known. One nationwide study in Malawi found that 12% of all registered tuberculosis cases were children who were less than 15 years of age.54

Conclusion

Important steps toward the elimination of tuberculosis include the expanded use of skin testing and preventative therapy in persons who are infected with HIV. The BCG vaccine should be offered to populations that are at increased risk of side-effects from isoniazid, in whom infection with multidrug-resistant tuberculosis might occur, or for whom compliance with skin testing and preventative therapy is difficult. Laboratories must be encouraged to use rapid diagnostic methods to identify M. tuberculosis or establish links with facilities where these tests are available. Treatment completion rates should be maintained through the use of case management and incentives. Only a concerted effort will prevent future tuberculosis cases and eliminate this ancient and still deadly disease.

References

Review: Tuberculosis: a disease that is alive and kicking


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