Journal of Infectious Diseases & Preventive Medicine

Rosenthal and Fisher, J Anc Dis Prev Rem 2013, 1:2
DOI: 10.4172/2329-8731.1000104

Review Article Open Access

Tuberculosis: Ancient History, Modern Scourge

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Abstract

Tuberculosis, one of the most common infectious diseases worldwide, caused by the etiologic agent *Mycobacterium tuberculosis*, was first isolated by Robert Koch in 1882. This organism has an extensive history, with modern molecular techniques having identified this organism in Bison during the Pleistocene period, 17000 years before present and in ancient Egypt during predynastic and early dynastic periods. Although progress has been made with modern chemotherapeutic agents, we now must contend with multidrug resistant, extensively drug resistant, and pan-resistant strains of *M. tuberculosis*. This coupled with increased transmission due to greater population density has nearly set us back to a time in history when no viable treatment options existed.

Keywords: Tuberculosis; Multidrug resistance

Past History

As sir William Osler stated at his dedication address at the Boston Medical Library in 1901, "the student who dates his knowledge of Tuberculosis (TB) from Koch may have a very correct, but a very incomplete appreciation of the subject" [1,2]. Phthisis, Greek for "wasting away", originally described by Hippocrates as an ulceration of the lungs was surmised to be contagious by Aristotle and Clarissimus Galen [2]. In 1804, medical student Rene Laennec argued the term "tuberculosis" should replace "phthisis," as extra-pulmonary involvement was common based on his 400 plus autopsies performed on patients who died of tuberculosis [3]. It was formally demonstrated a contagious disease by transmitting to animal hosts by Jean-Antoine Villemin in 1865; and almost twenty years later, the etiologic agent was isolated by Robert Koch using a methylene-blue based dye which revealed the "very fine rod-like form [in] fresh growing grey tubercles from the lung of animals…" thereby greatly advancing the field of mycobacteriology by identifying the tubercle bacillus. Paul Ehrlich then improved upon this staining method using a fuschin and gentian violet mixture with a decolorizing step and heat fixation; Ziehl included carbolic acid, and Neelsen advocated for sulphuric acid, creating the Acid-alcohol fast bacillus (AAFB) and Ziehl-Neelsen stains, respectively [4].

Although, in the late 1890s, Koch had failed to prove his glycerin extract from tubercule bacilli, or "tuberculin", was a cure for tuberculosis, it was this extract applied subcutaneously which allowed pediatrician Clemens Freiherr von Pirquet to show, what he termed, "latent tuberculosis" [5].

Treatment options were limited. The touch of the royalty for "King's evil" employed primarily for the treatment of tuberculous adenitis or scrofula, was extremely popular though the late 1600s. As the curative power of the king's touch did not improve morbidity or mortality, a novel regimen of fresh air, nutrition and bed rest started in Poland in the 1860s and became common throughout Europe. In these sanatoria, patients were often placed on bed rest for up to a year. In the United States, the first sanatorium was opened in 1882 by Dr. Edward Livingstone Trudeau in Saranac Lake, NY [6]. As understanding of the disease process evolved with the recognition of the formation of cavitary pulmonary lesions late in the process, treatment was then directed to eradication of the cavity.

Albert Calmette and Camille Guerin made a serendipitous observation in 1908 that *M. bovis* grown in an ox-bile containing culture became avirulent on the 39th passage and provided protection against *M. tuberculosis* (MTB) infection when injected into animals; after refinement and clinical trials, it became widely utilized as a human vaccine bearing their initials, (Bacillus Calmette Guerin, or BCG) with its greatest efficacy in preventing children under 5 years of age from extra-pulmonary TB [6].

Once effective chemotherapy was introduced, earlier, ineffective treatments were rapidly abandoned and the sanatorium became obsolete. In 1946, streptomycin (SM), an aminoglycoside antibiotic which inhibits protein synthesis, was shown effective in reducing early mortality in clinical trials; however at 5 years out, the mortality data was similar to the non-treated group due to resistance mediated by altered ribosomal binding [7]. Additionally, it is inactive against intracellular bacilli, and monotherapy was associated with relapses. Combination of SM with p-aminosalicylic acid (PAS), a folic acid inhibitor, reduced the development of resistance [8]. Isoniazid (INH), bactericidal against replicating MTB and bacteriostatic against latent MTB, was introduced in 1952 allowing for effective, 3 drug combination regimens (SM, PAS, INH) and widely adopted in Europe. In 1968, Rifampin (RIF), known as Rifampicin in Europe, was introduced clinically. It was shown that pyrazinamide plus rifampicin added to a six month regimen of INH was effective and became the standard in the 1970s [9].

Current treatment regimens utilize a tiered approach, with first line bactericidal therapy (except for Ethambutol, which is bacteriostatic), showing greatest efficacy and least toxicity. These agents include INH, Rifampin, Ethambutol, and pyrazinamide, a nicotinamide analogue. Second line therapeutic agents exhibit less efficacy and/or greater toxicity and include quinolones (ofloxacin, levofloxacin, moxifloxacin), other aminoglycosides (capreomycin, kanamycin, and amikacin), linezolid, cycloserine, ethionamide, and PAS.

Other agents include clofazamine, amoxicillin-clavulanate, imipenem, clarithromycin, high-dose INH, and Thioacetazone [10]. Recommended treatment regimens are constantly being updated (http://www.who.int/tb/).

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Received April 17, 2013; **Accepted** May 31, 2013; **Published** June 03, 2013

Citation: Rosenthal M, Fisher B (2013) Tuberculosis: Ancient History, Modern Scourge. J Anc Dis Prev Rem 1: 104. doi:10.4172/2329-8731.1000104

With improved molecular techniques such as PCR amplification and spacer-oligo typing (spoligotyping), consisting of PCR amplification of 43 nonrepetitive short space sequences in the Mycobacterium genome helped differentiate between *M. tuberculosis* and *M. bovis,* it became clear that a tuberculosis clearly existed long before the tubercle bacillus was first identified and described. Mycobacterium tuberculosis complex DNA (consisting of *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti* and other non-human mycobacterium pathogens) was isolated from a 17,000 year-old Pleistocene era bison bone and more closely resembled *M. tuberculosis* or *M. africanum* than *M. bovis* [11,12]. Additional serendipitous findings revealed 9,000 year old human remains of a mother and infant with bony lesions containing MTB DNA from human *Mycobacterium tuberculosis* lineage [13]. Additional evidence of skeletal MTB has been isolated in skeletal bone from three geographically distinct populations in predynastic and early dynastic periods in ancient Egypt [14].

History of Present Illness: What is Old is New Again

TB was on the decline until the late 1980s and 1990s when the Human Immunodeficiency Virus (HIV) epidemic hit, causing a resurgence in TB due to the synergy between HIV and TB infection [15]. Multiple issues surround timely diagnosis and treatment, the slow growth of *M. tuberculosis* in culture, access to appropriate therapy, adherence to therapy, and development of resistance during treatment. In 1993, WHO declared the TB epidemic a global emergency with directly Observed Therapy, Short-Course (DOTS), with renewed political commitment, case detection, standardized treatment, effective drug supply, and monitoring and evaluation was instituted [16].

Multidrug resistant TB (MDR-TB), defined as *M. tuberculosis* resistant to INH/Rifampin, became a challenge in the early 1990s, especially in the HIV positive population [17-20]. The DOTS-plus program was advocated and included adding additional second-line medications on an individualized basis [21].

The emergence of extremely drug resistant TB (XDR-TB) in March 2005, defined as *M. tuberculosis* resistant to INH and RIF, the fluoroquinolones, and at least one of the injectables: amikacin, capreomycin, or kanamycin, pose greater treatment challenges [22]. One of the most recent additions to the treatment armamentarium of MDR-TB is the newly approved antituberculous medication bedaquiline, a diarylquinoline [23].

Two Italian patients were reported to have acquired MDR TB and developed pan-resistance to twelve first and second line agents over the course of multiple treatment regimens [24]. In 2009, 15 patients in Iran had MTB resistant to all second line drugs tested: (aminoglycosides, polypeptides, fluoroquinolones, thioamides, serine analogues, and salicylic acid derivatives); and this advanced drug resistance profile was termed "totally drug resistant TB" (TDR-TB) [25]. Shortly thereafter, in 2012, the first patients from India with TDR-TB were described [14].

In March 2012, WHO convened an expert panel in Geneva, Switzerland to discuss the definition, identification and treatment strategies regarding TDR-TB. The panel concluded that a new definition of resistance beyond XDR-TB was not recommended given the lack of standardization of susceptibility, and given the accurate and reproducible definitions and susceptibility testing methods, MDR-TB and XDR-TB treatment regimens should take precedence [26].

Currently, in the US in 2012, 9,951 new TB cases were reported, an incidence of 3.2/100,000, which represents the 20th consecutive year of declining rates [27]. However MDR-TB and XDR-TB (including pan-resistant strains) remain a world-wide treatment challenge, especially in resource-limited settings.

Future Direction

A priority must be placed on accurate and fast diagnosis of both latent and active TB, effective and safe treatment, including development of new anti-tuberculous agents, control of TB transmission to susceptible hosts, and ultimately, development of an effective vaccine.

Molecular drug susceptibility testing may offer future benefit; however, due to limitations in knowledge of resistance patterns, this method will not currently replace current phenotypic methods.

Investigational new drugs need to be further developed and studied for use as second and third line agents. Randomized Clinical trials are still needed to answer the question of which regimens are best in XDR and pan-resistant infections.

With a multipronged approach, we can hopefully one day list MTB as an eradicated disease, although significant challenges arise in eradicating this fastidious, slow-growing, organism that may remain undetected in persons with no obvious symptoms of infection.

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