Tuberculosis xxx (2015) 1–5

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

REVIEW

Tuberculosis: A disease without boundaries

Nicole Fogel*

University of Toronto, St. George Campus, Victoria College, 95 Queen's Park Crescent, Toronto, Ontario, M5S 1K7 Canada

ARTICLE INFO

Article history:
Received 30 December 2014
Accepted 29 May 2015

Keywords:
Tuberculosis
Mycobacterium tuberculosis
History
Epidemiology
Transmission
TST
IGRAs
LTBI
Immunological response
Clinical manifestation
Animal models
HIV
Treatment
BCG
MDR
Control
DOTS
Stop TB Strategy

SUMMARY

Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis* (MTB) that usually affects the lungs leading to severe coughing, fever, and chest pains. Although current research in the past four years has provided valuable insight into TB transmission, diagnosis, and treatment, much remains to be discovered to effectively decrease the incidence of and eventually eradicate TB. The disease still puts a strain on public health, being only second to HIV/AIDS in causing high mortality rates. This review will highlight the history of TB as well as provide an overview of the current literature on epidemiology, pathogenesis and the immune response, treatment, and control of TB. In this race to combat a disease that knows no boundaries, it is necessary to have a conceptual and clear understanding of TB overall with the hope of providing better treatment through novel and collaborative research and public health efforts.

1. Introduction: the history of tuberculosis from the 1800s to the present

"Just sleep and eat nutritious foods" was the advice given to patients in the 1800s infected with tuberculosis (TB), or formerly known as consumption [1], an airborne disease that usually affects the lungs leading to severe coughing, fever, and chest pains [2,3]. This mysterious disease, whose Latin-originated name describes the rod shape of the bacillus, became better understood when the German microbiologist Robert Koch announced that *Mycobacterium tuberculosis* caused TB in 1882 [1]. This revolutionary finding, along with the later discoveries of tuberculin in 1890 and the Bacillus-Calmette Guérin (BCG) vaccine in 1908 and antituberculosis drugs starting in 1943, offered hope for the eradication of a disease deadlier than the plaque.

Mortality rates significantly declined from the early to mid-20th century; however, funding for research dwindled and between 1970 and 1990, drug and vaccine developments slowed [1,3]. With the onset of the AIDS pandemic and resistant strains, TB rates rose once again, and with that, interest in TB research and prevention [1]. Though by this time, the diagnostic and treatment tools necessary to combat the disease were largely obsolete and strategies to control and prevent the disease were developed, including the Directly Observed Treatment Short-Course (DOTS) program in 1993, with the addition of a DOTS-plus program to address multidrug resistant (MDR) TB in 1998 [1,3].

Although current research in the past four years has provided valuable insight into TB transmission, diagnosis, and treatment, much remains to be discovered to effectively decrease the incidence of and eventually eradicate TB [1,4]. The disease still puts a strain on public health, being only second to HIV/AIDS in causing high mortality rates [2]. It has been reported that in 2011 alone, there were about 8.7 million new cases and 1.4 million deaths due to TB [1,2,5], with about two billion people latently infected [3]. The

* Tel.: +1 416 939 0211.
E-mail address: nicole.fogel@mail.utoronto.ca.

http://dx.doi.org/10.1016/j.tube.2015.05.017

purpose of this review is to highlight the current literature on epidemiology, pathogenesis, treatment, and control of TB, in order to better understand the disease in hopes of providing better treatment through novel research and public health efforts.

2. Epidemiology, transmission, diagnostic tools: prevalence, airborne transmission, TST/IGRAs

There are certain risk groups that are more susceptible to getting infected including: young adults (more commonly males), those in developing countries, health care workers who are around the disease frequently, and those whose immune systems are weak, as in those who have HIV or smoke [2,4]. In fact, TB is the leading cause of death in those infected with HIV and HIV-TB comorbidity has been widely studied [4,6]. Additionally, foreign-born individuals and those who reside in impoverished areas or where malnutrition is prevalent are more likely to get infected [2]. The host's own deficiency in interleukin (IL)-12 promoting the T helper (Th) 1 response may be another factor in the increased susceptibility to infection [7]. There are other conditions that may pose a high-risk for susceptibility to MTB infection such as diabetes, ageing, long-term use of corticosteroids, TNF-α blockers, polymorphism in vitamin D receptors, polymorphism in IL-12 and IFN-γ genes. However, these other conditions will not be discussed in detail here.

MTB infection is acquired by inhalation of infectious aerosol particles released from close contacts [6,8]. A majority of individuals who inhale MTB mount an effective response in the lungs leading to successful inhibition in the growth of MTB, resulting in the bacteria becoming dormant; this condition is often referred to as latent tuberculosis or LTBI [9]; immunocompetent latent individuals are infected with MTB but do not present symptoms and do not transmit the disease to others [2,6]. It is well-known that 1/3rd of the entire world's population is latently infected with MTB [6]. From latent infection, the infection can progress to an active state [5]. About 5–10% of LTBI cases are at risk to progressing from infection to active (primary) TB [6]. Those with HIV and other immunocompromised individuals, such as those with cancer or currently taking immunosuppressing medication have a higher risk of developing active TB.

The World Health Organization (WHO) reported that “one-third of the world's population has been infected with TB” [2]. Holding true to Robert Koch's statement that the disease is deadlier than the plaque or cholera [1,6], about 9 million people were infected with TB and about 1.5 million succumbed to the disease in 2013 [2]. In 2004, TB was responsible for 2.5% of all deaths in the world [8]. The household is often the site of exposure in high- and low-burden countries, though infection rates are higher in areas such as hospitals or prisons [4]. Prevalence of the disease in such settings depends on virulence, innate immunity, and susceptibility.

While TB can be present in any society in any country, a majority of those deaths reported, about 95%, occurred in low- and middle-income countries where resources are more limited, with a majority of cases appearing in India and China [2,4]. Those with HIV are most at-risk for getting infected with TB, and about 80% of HIV-infected people with TB live in sub-Saharan Africa [4,8]. In contrast, in low-burden countries like the United States, only 10% of people with TB are infected with HIV; in 2008, only 12, 904 TB cases were reported with the incidence being 4.2 per 100,000. While diagnostic advancements have been made in the past four years, 80% of TB cases worldwide are concentrated in twenty-two countries [1] twenty-seven countries including India, China, and Russia, are responsible for about 85% of MDR TB cases [4]. Unfortunately, more recent data is not available due to the limits of global surveillance and reporting systems [8]. Additionally, there still remains an incomplete understanding how one person can acquire the disease while another doesn't, though they are exposed to the same risk factors, or how to better determine latent to active TB progression [5,7].

Since a majority of people with TB have latent infection [6], the development of new diagnostic and screening tools and standards has become necessary in order to control the disease [9,10]. Interferon-gamma release assays (IGRAs) are used to diagnose LTBI, although the tuberculin skin test (TST) still remains the most cost-effective test [9]. The TST and IGRA work by measuring the response of T cells to TB antigens [6].

2.1. TST

In the traditional TST, tuberculin purified protein derivative (PPD) mix of proteins from TB are intradermally injected into a person, causing a type IV delayed hypersensitivity skin reaction, if the individual was either previously exposed to mycobacterial proteins present in the vaccine or previously exposed to the mycobacteria infection [9]. To determine if the person is infected with TB, the size of the skin reaction is measured; the usual standard is between 48 and 72 h and a cut-off from 0.74 at 5 mm to 0.40 at 15 mm. However, the TST is known to lead to false-positive responses in those who are BCG vaccinated and to false-negative responses in immunosuppressed individuals.

2.2. IGRAs

The IGRAs are more sensitive and specific (81–88% compared to 70% sensitivity for the TST) [10]; however, they are expensive and technical [4]. They detect the release of cytokine IFN-γ from T cells that react to antigens not found in the BCG vaccine [4,10]. A blood sample is taken from an individual and the release of IFN-γ is measured. Guidelines constantly change for IGRA use. In Canada and in some European countries, it has even been suggested that IGRAs and the TST be used together to diagnose LTBI, but these tests are not definitive [9,10].

Overall, having a better understanding of how the disease develops in individuals from a latent to active TB by identifying risk factors associated with high- and low-burden countries will help lead to the development of better diagnostic tools and will improve our understanding of the immune response in TB.

3. Pathogenesis and immune response: the interactions between MTB and the host cell

de Martino et al. [7] describe the initial combat of TB once it invades the host using the quote: “All is decided the first day, which gets the longest day”. Once the bacterium *M. tuberculosis* (MTB) is inhaled via droplets spread through person-to-person contact, macrophages can phagocytose and kill the bacilli. However, if the bacilli are not killed, during that initial interaction, they can proliferate within dendritic cells and alveolar macrophages at a rapid rate, signaling the production of IL-1-α, IL-1β, and other host proinflammatory cytokines.

This response is mediated by pattern recognition receptors (PRRs) [7,11] expressed by macrophages and dendritic cells that recognize pathogen-associated molecular patterns (PAMPS) expressed on MTB [11]. Toll-like receptors (TLRs) help uptake MTB, which induces an intracellular signaling cascade to produce the cytokines. However, anti-inflammatory cytokines help the infection by opposing host cell proinflammatory responses. During the initial innate immune response, MTB proliferates within the host cell, inducing cell death via the virulence factor ESX1 type VII secretion

Please cite this article in press as: Fogel N, Tuberculosis: A disease without boundaries, Tuberculosis (2015), http://dx.doi.org/10.1016/j.tube.2015.05.017