

# Tuberculosis: Natural History

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## ABSTRACT

Tuberculosis is a scourge of mankind. The prechemotherapeutic era has given insights into the much needed natural history of tuberculosis. Once the TB bacilli enter the system, many factors including the age, nutritional status, the host immunity, bacillary load, pathogenicity of TB bacilli and HIV status tilt the balance between infection and disease. A clear understanding of the natural history helps us understand the various presentations in both pulmonary and extrapulmonary tuberculosis.

**Keywords:** Extrapulmonary, Infection, *M. tuberculosis*, Pulmonary.

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## INTRODUCTION

The natural history of tuberculosis (TB) in children was documented from children with TB in the prechemotherapeutic era. The introduction of the first antituberculous therapy was after the second world war, initially with para-aminosalicylic acid and a few weeks later streptomycin followed by the addition of newer drugs in the early 1950s.<sup>1</sup>

The diagnosis of TB in children was possible early in the beginning of the twentieth century when it was found that tuberculin applied locally serves as a method to determine hypersensitivity to it and avoids serious systemic reactions. Among the various methods initially tried, the intracutaneous method of tuberculin injection by Mantoux was adopted by many as the results were reproducible.<sup>2</sup>

The features described by Avrid Wallgren based on life observation of a prospective follow up of one hundred children who became infected with TB along with the report of 964 children followed up to 25 years providing the clinical signs and symptoms that develop during disease progression in tuberculosis by Edith Lincoln had given the much needed natural history.<sup>3,4</sup>

The transmission of TB bacilli is mainly from the cough of an infected individual though transmission can occur when the infected person speaks, sneezes or sings expelling tiny particles containing the bacilli. Among the particles coughed out, the largest and heaviest particle having the bacilli settle quickly on surfaces such as walls, furniture, clothing, etc. Some of them, which are airborne and enter the upper airway of another individual do get trapped and removed when they spit or swallow. It is only the droplet nuclei (1–5 microns size), the smallest and lightest particle having the TB bacilli, which can start TB infection. The droplet nuclei can stay in the air in poorly ventilated spaces for hours or days and by its ability to reach the alveoli can start the infection once it reaches the gas exchange units of the lung.

TB infection starts in an uninfected child after inhalation of a single aerosol droplet which may have even less than five bacilli. Once the bacilli penetrate the terminal airway, a localized infective (pneumonic) process starts in the lung parenchyma wherein the bacilli multiply without any restraint in the initial 4–6 weeks. This primary site of infective focus is known as Ghon's focus. It can occur in any lobe of the lung. From this focus, the bacilli drain through the lymphatics into the regional lymph nodes. The size of the draining lymph node will be much larger than the primary focus. The primary focus, lymphangitis, and lymphadenitis is collectively called as Ghon's complex or primary complex of Ranke.<sup>5</sup>

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Usually, the upper lobes drain into the paratracheal nodes on the same side while perihilar and subcarinal nodes receive lymphatic drainage from the rest of the lungs. The innate immune response is inadequate to control the infection as TB bacilli grow without any restraint within the macrophages. From the regional lymph nodes, occult dissemination occurs when bacilli enter the systemic circulation via the lymphatic duct. Rarely, bacilli can also enter the circulation from the parenchymal focus. The further disease process is solely dependent on the dynamic balance between host immunity and the bacilli. Acquired cell-mediated immunity is necessary to contain and control the progression of the disease.

After the occult dissemination through the systemic circulation, the organism can sustain in various organs for a prolonged period. The child can remain asymptomatic even when bacilli are seeded in to distant organs. The risk of progression to disease depends upon a number of variables, but age appears to be the most important factor in immunocompetent children. It has been found that infants have the highest risk for progression to disease with decreasing risk in toddlers, lowest in children in the age group of 5–10 years with the risk increases again in adolescent age group. Adolescents tend to have adult type disease (Table 1).<sup>4,6</sup>

Disseminated disease is more common in those who have low immunity as in malnourished children and in very young age and in those with altered immune function as they fail to control the multiplication of bacilli in the body. TB meningitis is the most feared among the disseminated disease. Most often the immune response starts between 2 weeks and 12 weeks. The organism can persist both intracellularly (inside the macrophages) and extracellularly (in the caseous center of granulomas). The persistence of these dormant bacilli always poses a risk for reactivation whenever the dynamic balance between the bacilli and host immunity shifts in favor of the bacilli.<sup>7</sup>

**Table 1:** Age and risk of progression to disease in immuno-competent children

Age at primary infection (year)	Risk to progress to disease
<1	No disease, 50%
	Pulmonary disease, 30–40%
	Disseminated (miliary) disease or TBM, 10–20%
1–2	No disease, 75–80%
	Pulmonary disease, 10–20%
	Disseminated (miliary) disease or TBM, 2–5%
2–5	No disease, 95%
	Pulmonary disease, 5%
	Disseminated (miliary) disease or TBM, 0.5%
5–10	No disease, 98%
	Pulmonary disease, 2%
	Disseminated (miliary) disease or TBM, <0.5%
>10	No disease, 80–90%
	Pulmonary disease, 10–20%
	Disseminated (miliary) disease or TBM, <0.5%

In children, pulmonary involvement can be in many forms. They are Ghon's focus, Ghon's complex with or without cavitation, lymph node disease, a bronchial disease with airway obstruction, obstructive emphysema or atelectasis, consolidation, broncho-pneumonia, adult type disease, and miliary disease.

In the Ghon's complex, the manifestation depends upon the dynamic balance between the bacilli and the immune status of the host. In unsuccessful containment within the lung parenchyma, the bacilli proliferate in the Ghon's focus leading to destruction

and formation of the cavity. This is also known as a progressive primary disease.<sup>8</sup> This happens most often in infants and immunocompromised children. Ghon's focus can occur anywhere in the lung and the involved lymph nodes are most often the hilar and subcarinal nodes, the enlargement of which compresses the airway extraluminally. Progressive primary complex indicates that the disease has spread beyond the primary focus and the draining lymph node by bronchogenic spread leading to various disease manifestation of tuberculosis in the lung.

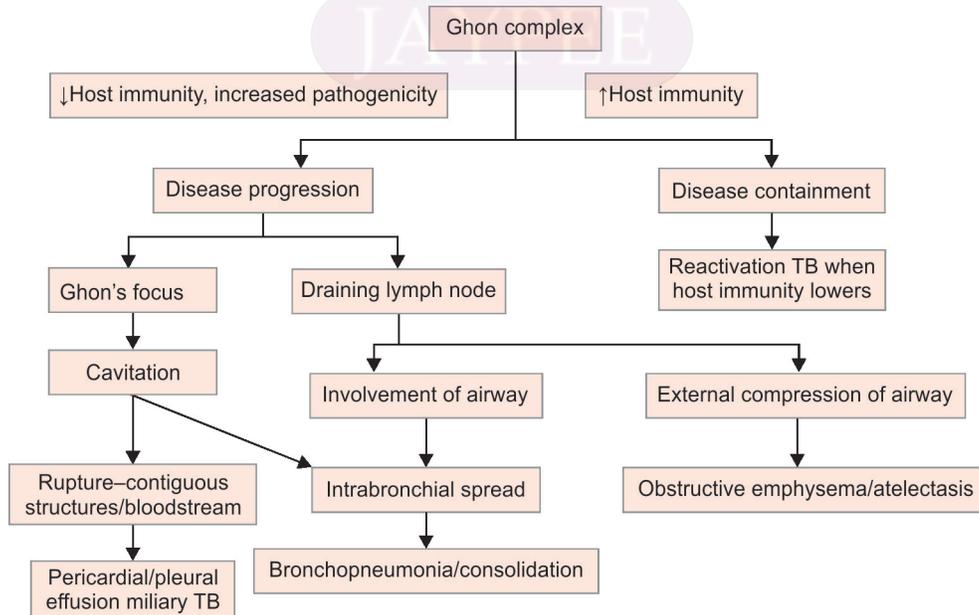
In the lymph nodes, the effects can be due to the sheer size of the lymph nodes itself or due to erosion into the airways. The severity of the airway obstruction, dose, and virulence of the bacilli aspirated and the immune status of the host determines the degree of pathology. Partial obstruction leading onto segmental or lobar hyperinflation and finally atelectasis when the obstruction becomes complete are the end results. This is seen in chest X-ray as collapse-consolidation or segmental tuberculosis.

The lymph nodes can erode into the lumen of the airway and discharge the bacilli into the lung distal to it or the caseous material from the lymph node can cause exuberant granulation tissue formation in the airway leading to pneumonia or consolidation. Further progression is based on the number of bacilli discharged into the airway. A progressive, expansile, caseating pneumonia can ultimately cause parenchymal destruction and cavitation.

In young children, lymph node disease with its attendant complication is common. In adolescents, a parenchymal disease with cavitation is more common, and the bacilli proliferate in the cavities and disseminate to other parts of the lungs through the endobronchial spread.

The involvement of pleura can happen by direct spread from subpleural focus or lymph node but rarely can be from the hematogenous route too. Pleural effusion occurs as a hypersensitivity reaction to the caseous material in the pleural cavity with very few bacilli in the pleural fluid.

The average time for the different manifestations of the disease after the primary infection is described by Wallgren in five different phases. Phase 1 which occurs 3–8 weeks after the primary infection has hypersensitivity manifestations in the form of fever, erythema



**Fig. 1:** Ghon's complex and its fate

nodosum with Mantoux becoming positive and chest X-ray showing the primary complex. Phase 2 usually is noted 1–3 months after the primary infection after the spread of the organism through the bloodstream. Younger children in this phase have the highest risk for miliary and tuberculous meningitis but both these conditions can occur at any time period. In phase 3, which occurred 3–7 months after primary infection, a bronchial disease in less than 5 years age and pleural disease in older children are seen. Phase 4 was seen one to three years after the primary infection during which osteoarticular involvement in under 5 years aged children and adult type TB in adolescents occurred. Phase 5 occurred three years after the primary infection in which reactivation tuberculosis developed. But one has to accept that this timeline need not be followed by TB bacilli. Figure 1 gives a bird's eye view of the fate of the primary TB.

The cell-mediated response usually appears about 2–12 weeks after the initial infection along with tissue hypersensitivity and most often those with the infection do not go on to develop active TB. Once the lymphocytes are able to recognize the mycobacterial antigens after the TB bacilli enter the macrophages, secretion of lymphokines and other mediators occur. They not only attract the other lymphocytes but also activate the macrophages to produce a high concentration of lytic enzymes to increase their mycobactericidal capacity. Both T helper cells and T suppressor cells help to modulate the immune response to develop specific cell-mediated immunity (CMI) thereby preventing the progression of the infection. CMI enhance intracellular killing while tissue hypersensitivity enhances extracellular killing. Granuloma forms when antigen load is small, and tissue hypersensitivity is high. Caseation occurs when antigen load and tissue hypersensitivity are high. Dissemination occurs when tissue hypersensitivity is low.

TB is a curable disease. The natural history of the disease helps in understanding the disease pathology clearly. The way the host immune system handles the infection influence the disease manifestation in children.

Understanding this helps us to diagnose TB early and treat correctly so that morbidity and mortality is reduced.

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