Tuberculosis (TB) in Children — Symptoms and Treatment

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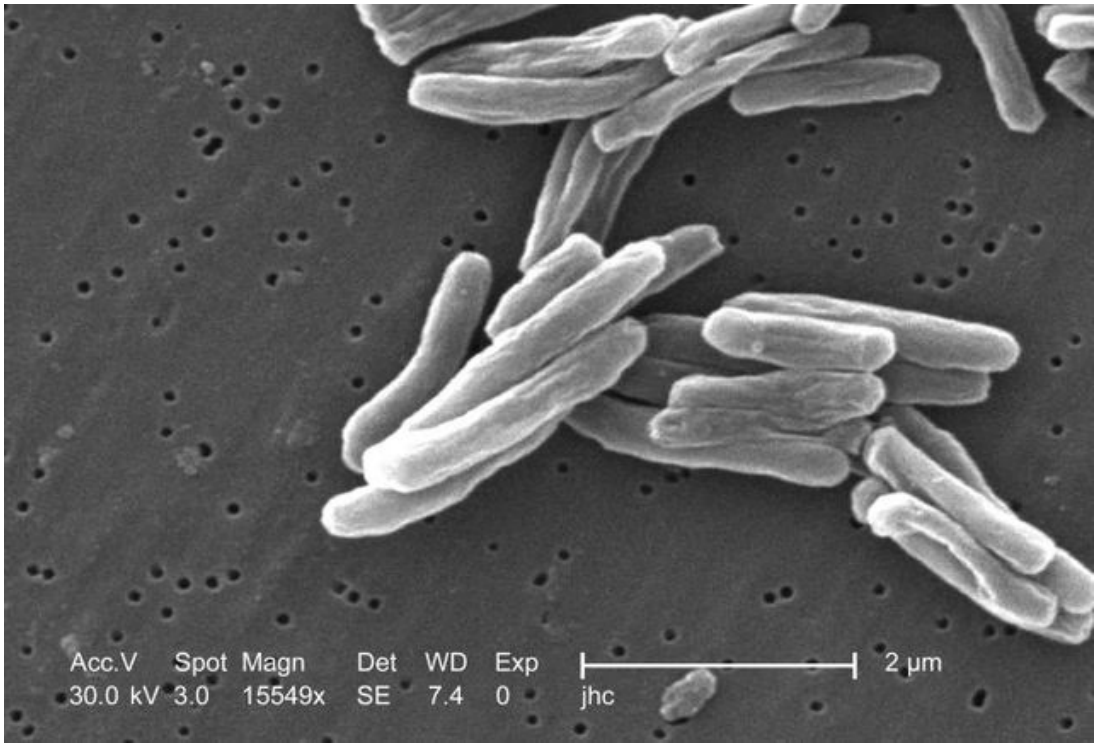
Tuberculosis in children is more common in the developing world, or in areas where tuberculosis is epidemic, such as India. The condition is caused by Mycobacterium tuberculosis. Patients present with fever, weight loss, anorexia and night sweats. The disease can be pulmonary or extrapulmonary. Anti-TB drugs combination of three or four different agents for two months, followed by isoniazid and rifampin combination therapy for another four to seven months, is indicated for the treatment of a confirmed case of tuberculosis.



Definition of Tuberculosis in Children

Tuberculosis is one of the oldest diseases to be recognized by humans. **The causative organism is Mycobacterium tuberculosis**. Other causative organisms are *M. bovinum* and *M. africanum*. Tuberculosis is any form of the disease that is caused by this bacterium which can include lung tuberculosis, tuberculosis meningitis or disseminated tuberculosis in children.

Epidemiology of Tuberculosis in Children

Children are more likely to acquire Mycobacterium tuberculosis and develop the disease tuberculosis compared to adults. Approximately, 8.7 million new cases of tuberculosis are diagnosed annually; hence, the burden of the disease in the healthcare system is huge.

Tuberculosis was diagnosed in approximately 490,000 new cases among children in 2011. Additionally, tuberculosis is one of the top ten causes of death among children. The population living in crowded areas, malnourished, homeless individuals are at risk of developing the disease.

Due to the recent increase in the incidence of the human immunodeficiency virus among children, co-infection with tuberculosis and more disseminated disease are becoming more common. Additionally, while highly active antiretroviral therapy for human immunodeficiency virus reduces the risk of disseminated tuberculosis, the risk of acquiring tuberculosis among this group of children remains high.

Another recent challenge to the management of tuberculosis in children is the emergence of multi-drug resistant tuberculosis (MDR-TB) strains. Approximately, 40,000 new cases of MDR-TB are diagnosed per year worldwide.

When studying the epidemiology of tuberculosis in children, one can appreciate two peaks in the incidence of the condition. Children younger than 5 years of age and adolescents older than 10 years constitute the majority of the cases of tuberculosis in children.

Pathophysiology of Tuberculosis in Children

Children who get into contact with an infected individual who has pulmonary tuberculosis might acquire the responsible bacterium Mycobacterium tuberculosis. The disease is airborne and can be transmitted by coughing, sneezing or simply being close to an infected individual for a significant duration of time; therefore, transmission of extrapulmonary tuberculosis is not possible.

Once the bacterium is acquired by the child, the usual incubation period is between 2 to 12 weeks. Because of this long incubation period due to the slow proliferation of the bacterium, the patient might forget from where he first acquired the disease or his or her recent infected contacts.

Co-infection with the human immunodeficiency virus or acquiring any other cause for an impaired immune response is believed to play a significant role in tuberculosis progression and the development of the disseminated disease. Another important risk factor for tuberculosis which is also linked to an impaired immune response is malnutrition. Because of this, tuberculosis is more common in countries and populations that are at risk of malnutrition or that have an endemic human immunodeficiency virus infection.

Once children acquire the responsible bacteria for tuberculosis, they might go on to develop latent tuberculosis infection (LTBI) or might develop active tuberculosis, known as TB. Children who have LTBI are not infectious and cannot transmit the disease to other children or to their contacts. Children with active disease, i.e. TB, can transmit the bacterium to their contacts. If the child with LTBI develops an impairment in their immune response later in life, they might progress from LTBI to TB.

Clinical Presentation of Tuberculosis in Children

Children who develop tuberculosis usually come from families of lower socio-economic status, who are recent immigrants from epidemic regions such as India, or who have had a recent travel history to epidemic areas. Additionally, a previous history of an impaired immune system, for example, due to being infected with the human immunodeficiency virus, can be elicited in up to 13% of the cases.

Patients usually complain of a chronic cough that has been persistent for more than three weeks. Fever can be present and is usually for more than two weeks. Patients presenting with this picture usually have been already investigated for pneumonia and received empirical therapy for bacterial pneumonia without any adequate response. Children usually lose weight due to the chronicity of the condition and infants can present with failure to thrive. Night sweats are common with tuberculosis.

Children who develop extrapulmonary tuberculosis usually present with systemic symptoms such as fever, weight loss, night sweats, lethargy and failure to thrive, but without pulmonary symptoms.

Children who develop pulmonary tuberculosis might present with fever, cough, and other respiratory symptoms. The child can also develop lymphadenopathy. While infants are more likely to be symptomatic when they acquire the infection for the first time, up to 70% of the children who develop new pulmonary tuberculosis are usually asymptomatic.

Children with tuberculosis can also develop meningitis due to the central nervous system involvement. Patients can present with headaches, fever, or focal neurological signs. The symptoms of meningitis in this group of children are usually milder and more chronic compared to typical bacterial meningitis.

Children who are infected with the human immunodeficiency virus, or who have an impaired immune response for any other cause, might develop disseminated tuberculosis, also known as miliary TB. Patients present with high fever, severe weight loss, lymphadenopathy, hepatosplenomegaly, and pulmonary symptoms.

Less common presentations of active TB include a bony disease that presents with localized bone pain, pericarditis, or pleural effusions and empyema.

Diagnostic Workup for Tuberculosis in Children

The diagnosis of tuberculosis in children is challenging due to the non-specificity of the presenting features. The diagnostic workup for LTBI and TB is available. Before 2001, both LTBI and TB were diagnosed based on the **tuberculin skin test (TST)** but, nowadays, more specific tests that differentiate between the two forms of the disease exist.

If TST is going to be used in the diagnosis of TB, then the following points should be taken into consideration while interpreting the results. The TST concept is simple; the presentation of tuberculin would result in a localized immune response in the skin of the patient. When the diameter of this induration response is above 10 mm and the child is older than 4 years, the child is considered as being positive for TB.

Children with a diameter of induration that is also above 1 cm, who are younger than 4 years of age and have possible risk factors for tuberculosis, are considered as having a positive test result. Finally, children with a recent contact with someone who is confirmed

to have TB, or suspected to have TB, or children with suspicious TB lesions on radiography or because of their semiology and have a diameter of induration equal to or more than 5 mm on the TST, are considered as positive for TB.

Interpreting the PPD/TST

<table>
<tr><th>≥ 5 mm</th><th>≥ 10 mm</th><th>≥ 15 mm</th></tr>
<tr><td rowspan="2">HIV</td><td>Recent immigrants from prevalent area</td><td rowspan="7">All patients</td></tr>
<tr><td>IV drug users</td></tr>
<tr><td>Recent known contact</td><td>Residents from dense populations</td></tr>
<tr><td>CXR consistent with TB</td><td>Patients with risky conditions</td></tr>
<tr><td rowspan="2">Immunosuppressed patients</td><td>Children < 4 years old</td></tr>
<tr><td>Exposure to high-risk adults</td></tr>
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Unfortunately, TST can overlap and be positive in those who have been vaccinated with the Bacille Calmette-Guerin (BCG) vaccine against TB, or those who have acquired other mycobacteria species. Because of these limitations, new tests need to be developed for the diagnosis of TB.

Interferon-gamma release assays are usually positive in patients who have active tuberculosis. The T-Spot is one type of these tests that have become available since 2008 and is considered very sensitive and specific for TB.

Isolation and culturing of Mycobacterium tuberculosis are possible but difficult in children. Repeated gastric lavage is used to isolate the organisms. Culturing of the organism allows the identification of its anti-tuberculosis sensitivity profile. Polymerase chain reaction testing for the detection of Mycobacterium tuberculosis is also available. The advantage of polymerase chain reaction testing over traditional culturing is that the bacterium load need not be very high for a positive result.

Chest X-rays and computed tomography scans of the lungs usually reveal cavitations of the upper lung lobes in patients with active TB. The presence of pleural effusion can be also noted on chest X-rays in patients with very active TB.

Treatment of Tuberculosis in Children

Once the diagnosis is confirmed by clinical examination and history taking, a positive TST or a positive polymerase chain reaction test or culture, the treatment with **anti-TB drugs is initiated**.

Drugs to treat Tuberculosis:

- **R**ifampin
- **I**soniazid
- **P**yrazinamide
- **E**thambutol
- **S**treptomycin

Combined therapy with three or four drugs for two months, followed by dual therapy for four or seven months, is indicated for the successful treatment of tuberculosis. The first phase of anti-TB regimen might include isoniazid, rifampin, rifabutin, pyrazinamide or ethambutol. If ethambutol is going to be used in a young child, routine visual assessments are indicated. Early signs of visual impairment warrant immediate discontinuation of ethambutol to prevent the development of optic neuritis and permanent visual impairment. The second phase of anti-TB therapy includes Isoniazid

combined with Rifampin for either four months or seven months.

Patients with extrapulmonary but localized TB should receive **anti-TB therapy in a regimen similar to typical pulmonary TB.** On the other hand, patients with disseminated TB should receive anti-TB therapy for a total of 12 months and corticosteroids might be needed for the alleviation of respiratory distress in the first few weeks.

If treatment fails in children, or the isolation of the causative organism provides evidence for MDR-TB, the use of second-line anti-TB drugs is indicated. Ethionamide, cycloserine, streptomycin and other anti-TB drugs are available. Unfortunately, the safety of these drugs in children is not well-established.

Different regimes for different circumstances

Circumstances	Regimen
Conventional therapy for susceptible organisms	First 2 months: rifampin + isoniazid + pyrazinamide Next 4 months: rifampin + isoniazid
Possibly resistant organisms or patients with HIV (RIPE, RIPS or RIPES)	Rifampin + isoniazid + pyrazinamide + ethambutol or streptomycin
Tuberculosis resistant to Isoniazid	Rifampin + ethambutol for 12 months + pyrazinamide
Multi-Drug resistant organisms	Combination of at least 3 drugs to which organisms are susceptible

Complications of Tuberculosis

Complications include:

- Pulmonary complications- pneumothorax, pleural effusion, blocking of the bronchus leads to atelectasis, the collapse of lungs, and bronchoesophageal fistula.
- Miliary disease and tubercular meningitis are the deadliest complications.
- Tuberculosis of the intestines may complicate as enterocutaneous fistula, perforation and obstruction of bowels and severe malabsorption.
- Pericardial effusion.
- Renal complications include hydronephrosis.
- TB in the spine may result in paraplegia.

Prognosis

- Prognosis of the disease depends on the severity of the disease and the starting of the treatment.
- Prognosis is poor with disseminated disease, miliary disease, and tubercular meningitis.
- Multidrug-resistant cases have a high mortality rate of more than 70%. 3 million deaths occur all over the world per year due to tuberculosis.

References

Esposito S, Tagliabue C, Bosis S. Tuberculosis in Children. *Mediterranean Journal of Hematology and Infectious Diseases*. 2013;5(1):e2013064. doi:10.4084/MJHID.2013.064.

Notes