



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

A Narrative Review on Association of Anaemia with Tuberculosis

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ARTICLE INFO

Published: 23 Nov. 2024

Keywords:

Tuberculosis, Anaemia,
Association, Antitubercular
Therapy, Iron Therapy.

DOI:

10.5281/zenodo.14208593

ABSTRACT

Tuberculosis (TB) is defined as an illness which induces systemic inflammation often affecting the lungs causing fever, cough and chest pain. The most common comorbidity associated with tuberculosis is anaemia. Anaemia is a condition which results from reduced red blood cells. This review article aims to provide a better understanding of pathophysiology and role of cytokines that lead to development of anaemia in TB patients. Our study has accumulated risk factors that are involved in occurrence of anaemia in TB patients. Articles focuses on importance of ferritin and hepcidin in investigating the presence of anaemia. It has reviewed the type of treatment given to patients such as Antitubercular therapy and Iron Therapy with an objective to identify which helps in improving the severity of anaemia condition.

INTRODUCTION

Tuberculosis is caused by bacteria (*Mycobacterium tuberculosis*) that most often affect the lungs. Active TB disease associated with a breakdown in immune surveillance which explains the strong link between active TB disease and other communicable diseases (CDs) or non-communicable diseases (NCDs). Comorbid NCDs for TB include HIV, anaemia, diabetes, smoking, malnutrition, and chronic lung disease^[1]. The End Tuberculosis Strategy, a World Health Organization (WHO) initiative, set ambitious targets for 2020-2035, including a 20% reduction in TB incidence and a 35% reduction in the

absolute number of TB deaths by 2020, a 90% reduction in TB incidence, and a 95% reduction in TB deaths by 2035^[2].

Formation of granuloma is a type IV granulomatous hypersensitivity reaction. It is a protective defense reaction by the host but eventually causes tissue destruction because of persistence of the poorly digestible antigen e.g., *Mycobacterium tuberculosis*. The classical example of granulomatous inflammation is the tissue response to tubercle bacilli which is called tubercle seen in tuberculosis. Tb generally transferred through various routes such as inhalation of organisms present in fresh cough

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



droplets or in dried sputum from an open case of pulmonary tuberculosis, ingestion of the organisms, inoculation of the organisms into the skin and transplacental route. Following aerosol transmission to a new host, MTB is thought to be initially phagocytosed in the lung by alveolar macrophages and dendritic cells, after which it undergoes unrestricted intracellular replication along with infected cells traveling to draining lymph nodes in the surrounding area. After reaching the regional lymph node, MTB disseminates through the circulation and infects additional host cells, eventually re-seeding the pulmonary area. In response to cellular immunity, local pro-inflammatory reactions trigger the recruitment of more monocytes and lymphocytes, which aggregate around infected macrophages to contain MTB inside an organized cellular structure known as a granuloma^[3].

Anaemia, according to the World Health Organization (WHO) criteria, is defined as a haemoglobin (Hb) concentration less than 13g/dL for men or less than 12g/dL for women.^[30]

Many patients with active PTB have low Hb. TB infection by MTB is known to induce systemic inflammation and lung damage which results in release of cytokines such as tumour necrosis factor- α (TNF- α interleukin-1 (IL-1) etc.

Anaemia of chronic illness also known as anaemia of chronic disease (ACD) is defined as development of anaemia in patients with infectious diseases.

Microorganism invasion activates T lymphocytes (CD4+) and monocytes, which initiate immunological effector mechanisms, generating cytokines such as interferon- γ (IFN- γ) and (TNF- α), interleukin (IL) such as IL-1, IL-6 and IL-10.

One of the characteristics of ACD is to develop iron homeostasis problems, with increased iron absorption and retention among reticuloendothelial system cells. Because iron is a key growth factor for MTB, iron retention in

reticuloendothelial system is regarded as one of the host defence strategies. TNF- α , IL-1 and endotoxin generated during TB infection contribute to development of anaemia by reducing lifespan of red blood cells (RBCs).^[4]

Review:

Mechanism-

Anaemia in TB can be caused by several mechanisms:

a) Inflammation and the Acute-Phase Response

- **Cytokine-mediated inhibition of erythropoiesis:** In TB, there is a systemic inflammatory response, which is driven by the release of pro-inflammatory cytokines such as **interleukin-6 (IL-6)**, **tumor necrosis factor-alpha (TNF- α)**, and **interferon-gamma (IFN- γ)**. These cytokines can suppress the production of red blood cells by inhibiting the bone marrow.

- **Hepcidin production:** IL-6 also stimulates the liver to produce **hepcidin**, a key regulator of iron homeostasis. High levels of hepcidin inhibit iron absorption from the gut and prevent iron release from macrophages and stores, leading to iron sequestration and reduced iron availability for erythropoiesis, which can cause **anemia of chronic disease** (also called anemia of inflammation).

b) Nutritional Deficiency

- **Malnutrition:** TB often occurs in individuals with malnutrition, and this can contribute to iron deficiency anemia or deficiencies in other vitamins and minerals required for hematopoiesis (e.g., vitamin B12, folate, and copper).

- **Poor absorption of nutrients:** TB may cause gastrointestinal disturbances (e.g., malabsorption, diarrhea), further impairing the body's ability to absorb essential nutrients needed for red blood cell production.

c) Direct Infection of Bone Marrow



- In severe or advanced TB, the infection can sometimes affect the bone marrow directly, leading to **myelophthisis** (displacement of bone marrow by granulomas), reducing the ability of the marrow to produce red blood cells.

d) Hemolysis

- In some cases, TB or its treatment can lead to **hemolysis**, where red blood cells are destroyed prematurely. This can occur due to direct bacterial effects, autoimmune mechanisms, or as a side effect of certain anti-TB drugs like **isoniazid** or **rifampin**.

e) Chronic Blood Loss

- TB can involve organs like the lungs, and **chronic pulmonary bleeding** (hemoptysis) may contribute to a gradual loss of red blood cells, leading to anemia.

2. Mechanism of Tuberculosis (TB)

TB is caused by the bacterium **Mycobacterium tuberculosis**, and its pathogenesis involves the following steps:

a) Inhalation and Initial Infection

- TB is typically transmitted via the airborne route, and when a person inhales **aerosolized droplets** containing **M. tuberculosis**, the bacteria reach the lungs. The bacteria are engulfed by **alveolar macrophages** in the lungs.

b) Immune Response and Granuloma Formation

- **Macrophages** attempt to eliminate the bacteria but often cannot completely clear the infection. In response, a localized immune response develops. **T lymphocytes (CD4+ and CD8+)** and other immune cells (e.g., macrophages, dendritic cells) are recruited to the site of infection.
- The immune system attempts to "wall off" the bacteria in granulomas, which are clusters of immune cells that form a defensive structure around the bacteria. In some cases, **caseous**

necrosis (a cheese-like, dry, necrotic tissue) develops in the center of the granuloma as a result of the persistent infection.

- In a **latent** infection, the bacteria can persist in a dormant state inside granulomas without causing symptoms, but they can reactivate if the immune system becomes compromised.

c) Progressive TB and Tissue Destruction

- If the immune system fails to control the infection, **active tuberculosis** develops, and the bacteria spread to other parts of the lungs or extrapulmonary sites (e.g., lymph nodes, bones, kidneys, or meninges).
- In the lungs, TB causes **tissue destruction**, cavitory lesions, and inflammation. The granulomas may coalesce and lead to the breakdown of lung tissue, leading to the characteristic symptoms of TB (chronic cough, hemoptysis, weight loss, fever, and night sweats).

d) Immune Evasion

- **M. tuberculosis** has evolved mechanisms to evade the host immune system. The bacteria can survive and replicate inside **macrophages**, which normally would be able to destroy pathogens. TB also inhibits the ability of the host immune system to effectively clear the infection by manipulating the **phagosome** (the compartment inside macrophages that normally contains ingested bacteria) and preventing its fusion with the **lysosome**, thus avoiding destruction.
- The pathogen also has a thick **mycolic acid-rich** cell wall that makes it resistant to various immune system attacks, including phagocytosis and certain antibiotics.

Risk Factors:

The risk factors for anemia in TB can be divided into several categories, including those related to the disease itself, the patient's nutritional status, treatment regimen, and underlying health conditions.



1. Inflammation and Chronic Disease (Anemia of Inflammation)

- **Chronic Inflammation:** TB is a chronic infectious disease characterized by systemic inflammation, which can lead to **anemia of chronic disease (ACD)**. The inflammatory cytokines (e.g., **IL-6**, **TNF- α**) released during active TB suppress erythropoiesis and lead to altered iron metabolism, primarily by increasing **hepcidin** levels. This results in reduced iron availability for red blood cell production.

2. Malnutrition and Nutritional Deficiencies

- **Iron Deficiency:** Inadequate dietary intake of iron or impaired absorption due to gastrointestinal involvement (e.g., **enteritis** or **malabsorption** associated with TB) increases the risk of developing iron deficiency anemia. Iron is essential for hemoglobin production, and its deficiency can impair the body's ability to produce red blood cells.
- **Vitamin B12 and Folate Deficiency:** Malnutrition in TB patients can also lead to deficiencies in **vitamin B12** and **folate**, both of which are crucial for the production of red blood cells in the bone marrow. Deficiencies in these vitamins can contribute to **megaloblastic anemia**.
- **Protein-Energy Malnutrition:** Severe malnutrition or cachexia, which is common in advanced TB, can also lead to anemia. The body's inability to maintain adequate protein levels can result in impaired erythropoiesis.

3. Direct Effects of TB Infection

- **Extrapulmonary TB:** TB can affect organs outside the lungs, including the kidneys, liver, and bone marrow. If the bone marrow is involved (due to granuloma formation or myelophthisis), the ability to produce red blood cells may be compromised, leading to anemia.

- **Pulmonary TB with Hemoptysis:** Chronic bleeding from the lungs (hemoptysis) due to TB can result in **blood loss anemia**, which can exacerbate the condition, especially in severe cases.

4. Anti-TB Treatment Side Effects

- **Adverse Effects of Anti-TB Drugs:** Some anti-TB medications can cause or worsen anemia as a side effect. For example:
 - **Isoniazid** can lead to **hemolysis** (destruction of red blood cells) in individuals with **G6PD deficiency**.
 - **Rifampin** and **ethambutol** can cause bone marrow suppression, leading to decreased red blood cell production.
 - **Pyrazinamide** has been associated with liver toxicity, which may also affect hematopoiesis indirectly.

5. Co-Infection with HIV

- **HIV/TB Co-Infection:** TB and HIV often occur together, and **HIV infection** can worsen anemia in TB patients. HIV causes a direct impairment of bone marrow function and immune suppression, which can lead to both **anemia of chronic disease** and **anemia of bone marrow suppression**. In addition, co-infected individuals are often more susceptible to opportunistic infections, which can further compromise red blood cell production.

6. Age and Gender

- **Older Age:** Older adults with TB are at increased risk of anemia due to a combination of chronic disease burden, potential nutritional deficiencies, and comorbidities (e.g., chronic kidney disease, diabetes) that may exacerbate anemia.
- **Gender:** Women, particularly those of childbearing age, may be more prone to **iron deficiency anemia** due to menstrual blood loss or pregnancy-related demands on iron stores.

7. Underlying Chronic Diseases



- **Chronic Kidney Disease:** Patients with chronic kidney disease may be more prone to developing anemia, especially in the context of TB, because the kidneys are involved in erythropoietin production, and impaired renal function reduces the body's ability to stimulate red blood cell production.
- **Diabetes Mellitus:** Diabetes is a known risk factor for developing chronic inflammation and anemia of chronic disease, and diabetic patients with TB may have a higher risk of developing anemia.
- **Liver Disease:** If TB affects the liver, it can impair the synthesis of important proteins (e.g., erythropoietin and albumin), further contributing to anemia.

8. Advanced Disease and Severe TB

- **Advanced Pulmonary TB:** In severe cases of pulmonary TB, particularly when there is significant **cavitation** or **hemoptysis**, blood loss and nutrient malabsorption can further contribute to anemia. The severity of the infection can also overwhelm the body's ability to maintain normal red blood cell production.
- **Acute Exacerbation or Multidrug-Resistant (MDR) TB:** Patients with more advanced or treatment-resistant forms of TB, such as **MDR-TB** or **extensively drug-resistant TB (XDR-TB)**, may experience more severe inflammation, nutritional deficiencies, and side effects from prolonged or toxic drug regimens, which can increase the risk of anemia.

9. Poor Compliance or Inadequate Treatment

- **Inadequate or Delayed Treatment:** If TB treatment is not initiated promptly or if the patient is non-compliant with the treatment regimen, the infection can progress to a more severe state, increasing the risk of complications, including anemia. Incomplete or interrupted treatment can also lead to drug

resistance, requiring more toxic regimens that can have hematologic side effects.

Investigations:

In tuberculosis (TB) patients, the investigation for anemia typically involves a combination of laboratory tests to determine the **type** and **cause** of anemia, as well as any underlying factors related to the TB infection or its treatment. Here's an outline of the common investigations for anemia in TB patients:

1. Routine Blood Tests

a) Complete Blood Count (CBC) with Reticulocyte Count

- **Hemoglobin Level (Hb):** This is the primary measure to determine if a patient is anemic and to assess the severity of anemia.
 - **Mild anemia:** Hb 10–11 g/dL
 - **Moderate anemia:** Hb 7–9.9 g/dL
 - **Severe anemia:** Hb <7 g/dL
- **Reticulocyte Count:** This is important to assess the bone marrow's response to anemia. An increased reticulocyte count suggests active red blood cell production, while a low count may indicate poor marrow response or bone marrow suppression.
- **Mean Corpuscular Volume (MCV):** The MCV helps classify the type of anemia:
 - **Microcytic anemia** (low MCV): Often associated with iron deficiency or chronic disease.
 - **Normocytic anemia** (normal MCV): Common in anemia of chronic disease (ACD) and could also be due to bone marrow suppression or blood loss.
 - **Macrocytic anemia** (high MCV): Suggestive of vitamin B12 or folate deficiency, or sometimes a side effect of TB drugs like isoniazid.
- **Other CBC indices:** **Mean corpuscular hemoglobin (MCH)** and **red blood cell distribution width (RDW)** can provide

additional insights into the nature of the anemia.

b) Peripheral Blood Smear

- A peripheral blood smear can provide further information on the morphology of red blood cells, which can help in differentiating types of anemia. Common findings in TB-related anemia include:
 - **Microcytic hypochromic cells** (suggestive of iron deficiency or anemia of chronic disease)
 - **Macrocytic cells** (suggestive of vitamin B12/folate deficiency)
 - **Target cells** (common in certain types of anemia, such as thalassemia)

2. Iron Studies

a) Serum Ferritin

- **Ferritin** is an indicator of iron stores. In anemia of chronic disease, ferritin levels are typically **normal or elevated** due to the inflammatory response, even though iron may be sequestered in macrophages and not available for erythropoiesis. **Iron deficiency anemia** would typically show low ferritin levels.

b) Serum Iron and Total Iron-Binding Capacity (TIBC)

- **Serum iron** is often low in both iron deficiency and anemia of chronic disease.
- **TIBC** is usually high in iron deficiency anemia but may be normal or low in anemia of chronic disease.

c) Transferrin Saturation

- The transferrin saturation (serum iron / TIBC) is usually low in iron deficiency anemia and may be normal or low in anemia of chronic disease.

d) Soluble Transferrin Receptor (sTfR)

- **sTfR** levels are often elevated in iron deficiency anemia, as transferrin receptors are upregulated when iron stores are low.

3. Inflammatory Markers

a) C-Reactive Protein (CRP)

- **CRP** is an acute-phase reactant that is elevated during inflammation. High CRP levels in a TB patient can indicate ongoing inflammation, which may contribute to anemia of chronic disease (ACD).

b) Erythrocyte Sedimentation Rate (ESR)

- **ESR** is another non-specific marker of inflammation that is typically elevated in active TB and anemia of chronic disease. It helps to assess the degree of inflammation but is not specific for anemia or TB.

c) Interleukin-6 (IL-6) and Hepcidin

- **IL-6** is a cytokine that stimulates the liver to produce **hepcidin**, which regulates iron homeostasis. High hepcidin levels inhibit iron absorption and release, leading to iron-restricted erythropoiesis.

4. Vitamin and Mineral Deficiencies

a) Vitamin B12 and Folate Levels

- **Vitamin B12** and **folate** deficiencies can lead to **macrocytic anemia**. In TB patients, especially those with poor nutrition or gastrointestinal involvement, these deficiencies may be present.
 - **B12 deficiency** may also result from malabsorption or the use of certain medications like **isoniazid** (which can interfere with vitamin B6 and B12 metabolism).
 - **Folate deficiency** can occur due to inadequate dietary intake or due to TB treatment, especially if the patient is on **isoniazid**, which can interfere with folate metabolism.

5. Bone Marrow Examination

In cases where the anemia is **severe** or when the underlying cause of anemia is unclear despite the initial investigations, a **bone marrow aspiration and biopsy** may be necessary. This is particularly relevant when there is suspicion of:



- **Bone marrow involvement by TB** (e.g., granulomatous infiltration or myelophthysis).
- **Aplastic anemia** or **bone marrow suppression** from anti-TB drugs.
- **Hemophagocytic lymphohistiocytosis (HLH)**, a rare but potentially serious complication in patients with chronic infections like TB.

6. Co-Infection Testing

a) HIV Testing

- TB and **HIV co-infection** are common, and **HIV** can contribute to anemia through direct effects on the bone marrow or via opportunistic infections. In co-infected patients, HIV-related anemia may be due to both **chronic disease anemia** and **bone marrow suppression**. HIV testing is especially important in TB patients from high-risk groups.

b) Screening for Malaria or Other Co-Infections

- In endemic areas, **malaria** or other parasitic infections can contribute to anemia. Testing for malaria, especially if the patient presents with fever and fatigue, might be warranted.

7. Tuberculosis-Specific Investigations

Although anemia is a secondary concern in TB, understanding the severity and extent of TB infection is essential to determine the context of anemia:

- **Chest X-ray**: To assess the extent of pulmonary involvement and check for complications such as cavitary lesions or pleural effusion.
- **Sputum smear microscopy and culture**: For confirmation of **Mycobacterium tuberculosis** infection (especially in suspected active TB cases).
- **GeneXpert or PCR for TB**: A rapid molecular test to detect **M. tuberculosis** and resistance to **rifampicin**, especially in cases of

multidrug-resistant TB (MDR-TB), which may require a different treatment regimen.

8. Kidney and Liver Function Tests

• Renal Function Tests (Creatinine, eGFR):

Chronic kidney disease (CKD) can contribute to anemia through reduced erythropoietin production, and TB can sometimes involve the kidneys.

• Liver Function Tests (ALT, AST, bilirubin):

If there is suspicion of **liver involvement** due to TB or anti-TB drug toxicity, liver function tests are necessary to monitor liver health, as impaired liver function may worsen anaemia

Oliveira et al. conducted a descriptive longitudinal study that was published in 2014. The study included 166 TB patients in whom various inflammatory parameters were measured. Ferritin and ESR were high in patients with ACD [5]. Mishra et al. conducted a study with 100 adult TB patients who were compared with 60 healthy individuals in which serum CRP and ferritin were found to be raised [6].

CONCLUSION

This review paper discusses the link between TB and anaemia. Articles aims to put light on contributory factors involved in development of anaemia in tuberculosis patients. Cytokines and inflammatory markers including TNF- α , IFN- γ , hepcidin, and ILs plays crucial role in development anemia in patients with chronic diseases. ACD can be diagnosed with different parameters such as Hb, transferrin, hepcidin, TIBC, ESR, CRP, and sTFR. Anemia in TB patients falls between the mild-to-moderate range and tends to resolve after the completion of ATT alone, and treating anemia with iron therapy during the active phase of the disease is not recommended. A multidisciplinary approach including routine follow-ups, regular screening practices, early diagnosis, and medication compliance along with treatment of the underlying



cause goes a long way in reducing the incidence of TB-associated anemia.

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HOW TO CITE: Kavitha Sekar*, Divyashree N, Aarabhi I U, Madeeha Abrar, Sadiya Samreen, A Narrative Review on Association of Anaemia with Tuberculosis, *Int. J. of Pharm. Sci.*, 2024, Vol 2, Issue 11, 953-960. <https://doi.org/10.5281/zenodo.14208593>

