INTRODUCTION
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There is a dread disease which so prepares its victim, as it were, for death; which so refines it of its grosser aspect, and throws around familiar looks, unearthly indications of the coming change, dread disease, in which the struggle between soul and body is so gradual, quiet, and solemn, and the result so sure, that day by day, and grain by grain, the mortal part wastes and withers away, so that the spirit grows light and sanguine with its lightening load, and, feeling immortality at hand, deems it but a new term of mortal life; a disease in which death takes the glow and hue of life, and life the gaunt and grisly form of death; a disease which medicine never cured, wealth warded off, or poverty could boast exemption from; which sometimes moves in giant strides, and sometimes at tardy pace; but, slow or quick, is ever sure and certain.


Human tuberculosis (TB) is a contagious-infectious disease mainly caused by Mycobacterium tuberculosis, which is an aerobic pathogenic bacterium that establishes its infection usually in the lungs. Progression of TB infection is fundamentally regulated by host's immune system integrity, which may succeed through microbial immediate elimination and/or latency conditioning, or fail resulting in development of active disease.

Looking the past

The captain of all these men of death that came against him to
take him away, was the consumption, for it was that brought him down to the grave.


TB, also known as the white plague, received the title of "captain of all these men of death" by John Bunyan in the second half of the XVII century, when the disease reached a high level of death rates in Europe. This malady became the principal cause of death by the end of the XIX and beginning of the XX century, and among its various victims were worldwide known people, such as Frédéric Chopin, Paganini, St. Francis of Assisi, Charlotte Brontë (and most of the Brontë family), John Keats, Lord Byron, George Orwell, Castro Alves, Alvarez de Azevedo, Cruz e Souza, Augusto dos Anjos, Noel Rosa, Eleanor Roosevelt, and Vivian Leigh, among many others. Currently, this disease still represents a global threat, as it stands as the leading cause of death due to an infectious agent among adults worldwide.

Although it was probably described for the first time in Indian texts, tuberculosis appear to be a diseases as old as human history. It has been described with different names such as the King's evil, phthisis, tapedic etc. In Rigveda which is dated 2000 B.C. tuberculosis has been described as Yakshma.

Sushruta described the disease and observed it was difficult to treat. A unique bacteriological finding of acid fast bacilli in smears taken from psoas abscess in the well preserved mummy of an inca
child from around 700 B.C. clearly documents a case of tuberculosis of lumbar spine.

Pulmonary TB is known since the time of Hippocrates as phthisis, which is derived from the Greek for "wasting away". Scrofula, a rare manifestation form of TB that affects the lymph nodes, especially of the neck, most commonly found in children and usually spread by unpasteurized milk from infected cows, was well documented during the European Middle-Age, when it was believed that cure resulted from the power of the divine touch of the kings. Pott's disease or Gibbous deformity, a rare TB manifestation, revealed only among several antique Egyptian mummies, is a destructive form of TB that leads to serious spine deformities and subsequent member paralysis.

In 1680, the French Franciscus Sylvius carried out anatomic-pathologic studies in pulmonary nodules from TB patients, which he named as "tubercula" (small knots), observing their evolution to lung ulcers (cavities). However, most of the great pathologists of his time believed these knots were some type of tumor or abnormal gland, rejecting any probable infectious origin. The first credible speculation of the infectious nature of TB was performed by the British Doctor Benjamin Marten, who proposed in 1722 that TB could be transmitted through the "breath" of a sick person, inhaled by a sound one, and thereby turning her ill. In 1689, the English Doctor Richard Morton used the term "consumption" to specifically denote TB, and finally, in
1819, the inventor of the stethoscope, the French Doctor René Laennec identified for the first time the TB manifestation unit.

One of the greatest works on TB was performed in 1882 by Robert Koch, an esteemed scientist of his time. Koch isolated and cultured *M. tuberculosis* from crushed tubercles. His experimental work identified the bacterium as the TB etiological agent (Bloom & Murray 1992, Daniel 1997). In August of 1890, during The First Ordinary Session of the International Medical Congress, in Berlin, he announced the discovery of a TB therapeutic drug. Three months later, the "Deutsche Medizinische Wochen-schkit", in extraordinary edition, published a new statement of Koch, revealing that although interested in the therapeutic properties of his findings, he observed that the referred liquid, named tuberculin, could be useful as a diagnostic tool to detect the disease due to the intensified reaction developed by sick animals inoculated with this drug, as no measurable effect was ever observed in healthy ones. This concept was perpetuated for several years, until it was observed that even healthy animals could react to the drug. The veterinarians of his time clarified the fact by demonstrating that the healthy ones could be simply infected, although not ill. As a result, it was established that *M. tuberculosis*-infected animals will react to tuberculin infusion, whereas the non-infected ones will not. This drug, the first industrialized one, was called old tuberculin; subsequently, other tuberculins were produced, such as purified protein derivate (PPD), PPD-S, and PPD RT23, among others (Vaccarezza 1965, Ruffino-Netto
The tuberculin skin test became the principal tool for infection diagnosis. In the same period, Koch developed staining methods for the identification of the bacillus; these techniques were subsequently improved by the German Doctor and bacteriologist Paul Ehrlich, whose method for detection of the bacillus provided the basis for the development of the Ziehl-Nielsen staining, which still is an important tool to diagnose TB.

Koch's discovery allowed researchers to focus efforts on the development of new and more efficient therapies to treat TB patients. One of the first attempts to fight the disease was performed by Edward Livingston Trudeau, who suffered from TB and was subsequently cured. Trudeau established the first sanatorium in the United States in 1884. This institution received only TB patients, and invested in a treatment based on rest, fresh air and a healthy diet.

The variant that was administered for the first time in humans (orally), as an attempt to immunize a child whose mother died in childbirth victim of TB. Currently known as BCG (bacille Calmette-Guérin), the (intradermal) vaccine has become widely used to combat TB; it relies on a prophylactic administration of live attenuated bacilli to children.

The introduction of antibiotics, such as streptomycin (1947), isoniazid (synthesized in 1912, but introduced 40 years later) and \( p \)-amino-salicylic acid, led to a TB chemotherapy revolution, as TB mortality rates were considerably reduced (Bloom & Murray 1992,
Daniel 1997). Subsequently, other anti-TB drugs were also developed, such as ethambutol and rifampicin, among others. Since the mid-1980s, however, there has been no new first-line drug development to fight the TB causing bacilli (Petrini & Hoffner 1999).

In Brazil, it is believed that the disease was introduced by the Portuguese and Jesuit missionaries since 1500. Oral BCG was administered for the first time by Arlindo de Assis in 1927 to newborns, and intradermal vaccination was implemented in 1973, becoming obligatory for one year minors since 1976. Brazilian TB mortality rates were drastically reduced due to introduction of tuberculostatic drugs by the 1940s, including streptomycin (1948), \textit{p}-aminosalicylic acid (1949), and isoniazid (1952). The standard chemotherapy treatment recommended by the World Health Organization (WHO) to control or eradicate TB worldwide, which is based on a short-course therapy that combines the use of four anti-TB drugs, currently known as directly observed treatment short-course (DOTS), seems to be used in Brazil since 1962 by the Fundação de Serviço Especial de Saúde Pública (Sesp) in units of all complexity levels (Ruffino-Netto 2002).

Ruffino-Netto (2004) proposed an "equation" which expresses the TB charge, represented as follows:

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TbB \approx \frac{(SIN).(PHIV).(PDEF).(PR).(MIG).(OLDP)}{(AHS).(DOTS).(EDU).(NUT).(HRTB).(DPP)}
\]

where SIN: social inequality; PHIV: prevalence of HIV-positive; PDEF: percentual default of treatment; PR: prevalence of primary
resistance + acquired resistance; MIG: migrations; OLPD: age of the population; AHS: adequate health services; DOTS: directly observed treatment short-course; EDU: educational level; NUT: nutrition level; HRTb: human resources for TB control; DPP: degree of political participation of the population.

TB was responsible for millions of human deaths in the past, when there were no adequate treatment methods for infected patients. Introduction of chemotherapy and prophylactic measures led to drastic death reduction, which was maintained for various decades. However, the "good times" waned, as this disease became worldwide recognized as the one responsible for most human deaths caused by a single infectious agent. TB resumption is basically a consequence of anthropic factors, such as the recent HIV/AIDS pandemic and the development of drug-resistant strains (stemmed from inappropriate treatments and/or patient non-compliance). It thus appears to be of fundamental importance to increase investment in research, as disease control can hopefully be reached through new drug development (to be introduced in the treatment of patients with active TB), and through prophylactic and/or therapeutic vaccine optimization.

The cornerstone of tuberculosis management is a six month course of Isoniazid, Rifampicin, Pyrizinamide and Ethambutol. Compliance is Crucial for curing Tuberculosis. Adverse Effects often negatively affect the compliance, because they frequently require a
change of treatment, which may have negative consequences for treatment outcome. **Isoniazid**, the first line drug of tuberculosis can cause peripheral neuritis and hepatic toxicity. INH-induced increase in the excretion of Pyridoxine in Urine and decrease in the Peripheral Utilization of Pyridoxine in the Patients treated with INH is also reported. Hepatitis is also the major adverse effect and the risk may be increased if **Rifampicin** with INH is used in patients with underlying liver disease. Occasional adverse effects include rashes, GIT disturbances, Dizziness and fatigue. Rifampicin may accelerates the metabolism of other drugs such as oral contraceptives, anticoagulants and protease inhibitors used in HIV patients which may result in therapeutic failure.

**Hepatotoxicity** is the major adverse effect in about 15% of Pyrazinamide (PZA) recipients. PZA may cause hyperuricamia and possibly acute gouty arthritis. Therefore this is also becoming very significant to study the toxic effect of drugs together in this study. Other adverse effects include nausea, vomiting, anorexia and fever.

The Prolonged treatment of **Ethambutol** can also cause neuritis impairing visual acuity and red-green color discrimination. Ethambutol decreases renal excretion of urates and may precipitate gouty arthritis. GIT intolerance, rashes, fever and dizziness are also possible with Ethambutol therapy. Pyrazinamide another drug of Antitubercular drug combination is also found impairing the Renal functions and have also found in some cases causing the episodes of
Gout. Since we found a common relationship between Pyrazinamide, Gout and Allopurinol a primary drug of Gout, it is a thought of interest to understand the other toxic effects of Allopurinol. We visualize a clinical condition of a patient who was kept on Antitubercular treatment for a long time, developed Gout as a result of Pyrazinamide and was given Allopurinol to overcome the affects of urate deposition. It is a thought of interest to see whether Allopurinol also play a role in Hepatotoxicity and worsening the condition?

Since hepatotoxicity, renal impairment and musculoskeletal involvement is becoming common with the treatment of Allopurinol and drugs of tuberculosis; it is significant to make a rational review of toxicity by the following biochemical & Pathological Parameters.

1- Alkaline Phosphatase
2- Alanine Transaminase
3- Bilirubin (Total)
4- Ra Factor
5- ASO titre
6- Erythrocyte Sedimentation Rate (ESR)
7- Urea
8- Creatinine
9- Uric Acid

Antioxidant is a substance that inhibits oxidation and can guard the body from the damaging effects of free radicals. Molecules with one or more unpaired electrons, free radicals can destroy cells and play a role in many diseases. They may help in preventing macular degeneration and other serious eye diseases. Well known antioxidant include a number of enzymes and other substances such
as Vitamin C, Vitamin E and beta-carotene that are capable of counteracting the damaging effects of oxidation. **Beta Carotene the Precursor of Vitamin A and Tocopherol (Vitamin E)** both are lipid soluble oxidant scavengers that protect biomembrane. Ascorbic acid is important water-soluble antioxidants. It has been reported that people who took supplement of Vitamin A or beta Carotene, Vitamin E, Vitamin C. Copper and selenium were 37% less likely to develop cataract and blindness. Much research has recently focused on how antioxidant Vitamins may reduce cardiovascular disease risk. Antioxidant Vitamins-E, C and beta-carotene have potential health promoting properties.

Therefore the study of the toxic effects by Allopurinol, Isoniazid, Rifampicin, Ethambutol and Pyrazinamide and the control of these toxic effects by antioxidants therapy is having a significance in the national interests and can contribute in the already available information by discovering a new approach towards the understanding of gout treatment and anti-tubercular treatment.

It has been reported that the generation of free radical is associated with the side effects of many drugs including the drugs of gout and tuberculosis and it has been a thought of interest that if these free radicals are controlled by non-enzymatic antioxidant therapy whether the other effects may also be controlled by the use of such therapy. It is very much relevant to throw a light on general characteristics of antioxidants before concluding the introduction of
this synopsis. The purpose of this study is to see the overcome of toxic effects of above quoted drugs, If they are used along with antioxidant therapy. Therefore this study is planned and performed to understand a better approach in the light of following objectives.

- **To assess the extent of toxicity created by Allopurinol and anti-tubercular drugs.**

- **To Study the effect of antioxidant Vitamins C and E to reduce the toxicity created by Allopurinol and anti-tubercular drugs.**