

Tuberculosis: A Forgotten Foe, with a Dangerous Proposition

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ABSTRACT

The subject of 'Tuberculosis'. Something of a challenge, but it has been ignored recently in much of the medical training media. Here we present an educational script that aims to discuss and give a refresher on biology of mycobacteria with a brief mention of leprosy and environmental mycobacteria, epidemiology of TB: historically, recently, concept of roles of nutrition in immunology, latent infections, a short presentation of TB. Further discussing current guidelines, covering topics such as BCG, treatments, role of fluoroquinolones and MDR. With an examination of the social aspect by reviewing the awareness of prevalence in migrants, refugees, and its links to HIV. Finishing it with an original set of quiz questions that focuses on diagnosis, side effect of BCG vaccine, recent arrival from Africa with underlying retrovirus.

Keywords

Mycobacterium tuberculosis, Treatment, Guidelines, Mycobacteria, Question.

Biology of Mycobacteria

Tuberculosis (TB) is a worldwide infectious disease caused by *Mycobacterium tuberculosis*, a bacteria subspecies of the *Mycobacterium tuberculosis* complex (MTBC) [1]. TB is transmitted via respiratory droplets from a person with an active infection, and typically causes a productive cough, fever, weakness, night sweats, and weight loss [2]. The MTBC is comprised of other mycobacterium subspecies, most notably *Mycobacterium africanum* and *Mycobacterium bovis*.

The *Mycobacterium* genus also includes the *Mycobacterium leprae* complex, which causes Hansen's disease, also known as leprosy [3]. Leprosy is transmitted via respiratory droplets and has an average incubation period of 5 years [4]. When symptoms do develop, they are primarily skin, peripheral nerve, and mucosal manifestations [5].

Bacteria in the *Mycobacterium* genus are aerobic bacilli. Perhaps the most notable common feature is that they are acid-fast [6]. Their cell wall has an outer layer of lipids surrounding a peptidoglycan-polysaccharide layer, making the bacteria hydrophobic and

especially resistant to treatment [7]. Interestingly, while many *Mycobacteria* are environmental, both *M. tuberculosis* and *M. leprae* are both obligate parasites. The environmental sources of *Mycobacterium* include water, animals, and soil [8]. A study testing the bacteria in soil and in humans revealed that though the bacteria exist in the soil, it is not as virulent as mycobacterium transmitted in respiratory droplets, and therefore likely not a source of infection in humans [9].

The Epidemiology of TB:

In 2018, There were 10 million newly diagnosed cases of TB and 1.5 million mortalities due to TB, making it more deadly than HIV/AIDS [1]. Of the 10 million new cases worldwide, 90% were over the age of 15 and 9% were in patients with HIV [2]. Additionally, 66% of these new cases were from India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa [3]. The incidence rate of TB worldwide has been decreasing at approximately 3% per year, but the WHO aims to accelerate this reduction in incidence rate to 5% per year as a part of its End TB Strategy, which aims to have an overall 90% reduction in new cases of TB by 2035, as compared to 2015 [4,5]. Already, the End TB Strategy has achieved a 33% decrease in TB mortality from 2000 to 2017 [6].

It is estimated that one-quarter of the world's population is currently infected with latent TB [7]. People with latent TB are at risk of developing active TB and becoming severely sick, but that risk increases in people who have a history of tobacco use or are immunocompromised, such as having HIV/AIDS, diabetes mellitus, or on immunosuppressant medication [8]. Nutrition is also an important factor, as malnutrition is a known risk factor for developing active TB. In fact, people who have a BMI > 25, and even > 30, had a significantly reduced risk of developing active TB as compared to those with a normal BMI (18.5 to < 25) [9]. In addition to maintaining adequate caloric intake, studies show maintaining adequate levels of Vitamin D and Iron help reduce the risk of developing active TB, likely due to the role of macrophages in fighting off infection [10,11].

The WHO recommends treating those with latent TB with 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine + isoniazid, or a 3-month regimen of daily isoniazid + rifampicin [12]. The guidelines have to offer alternative treatment methods because there is an increase in drug-resistant TB. In fact, a 2016 study estimated that 11% of latent TB infections are resistant to isoniazid [13]. According to the 2020 WHO Consolidated guidelines on tuberculosis, both 1-month regimen of daily rifapentine + isoniazid (1HP) and (4R) are now recommended options for preventive treatment.

Presentations of TB

Primary pulmonary tuberculosis is often asymptomatic, but in patients who do experience symptoms, fever is most common. Fevers typically resolve in 14-21 days, and are often not accompanied by other symptoms. Less commonly, patients experience either pleuritic or retrosternal chest pain, and even rarer are symptoms like fatigue, cough, and arthralgia [15].

In patients with reactivation pulmonary TB, typical clinical symptoms include cough for greater than two weeks, fever for greater than two weeks, weight loss, and/or hemoptysis [16]. These typical symptoms are non-specific and only present in about 22-23% of patients with reactivation pulmonary TB [16,17]. Other, less common pulmonary symptoms include isolated hemoptysis, chronic cough, COPD, and pneumonia. Few patients experience symptomatic pleural effusion. About 15% of patients experience extra pulmonary symptoms including but not limited to lymphadenopathy, inguinal hernia, and arthritis [17]. Additionally, patients often do not have any symptoms at all: one study reports that 14% of subjects with reactivated pulmonary TB were asymptomatic and less than half had positive sputum smears [18].

In most patients with either primary or reactivation pulmonary TB, abnormalities are found on chest radiographs [19,20]. In primary pulmonary TB, hilar and mediastinal lymphadenopathy is common, and lesions are usually localized to the lower and middle lobes [21]. The combination of lobar pneumonia with hilar or mediastinal lymphadenopathy on radiography strongly suggests

a diagnosis of primary tuberculosis, though absence of these findings cannot be used to rule out the infection as not all patients have these findings [22] (Figure 1). The majority of patients with reactivation pulmonary TB exhibit involvement of the anterior and/or posterior segments of the upper lobe of either lung on chest x-ray, and many of the lesions seen in these regions are cavitory with air-fluid levels [23]. It is important to note that while much of the literature differentiates between primary and reactivation TB by location of lesions, with primary TB localizing to lower and middle lung lobes and reactivation TB localizing to upper lobes, one study finds little to no difference in radiographic presentation of primary and reactivation disease [24].

Endobronchial tuberculosis is a less common manifestation of TB infection, with nonspecific symptoms that present similarly to airway obstruction. Endobronchial TB often exists alongside pulmonary TB, so symptoms of both are usually seen [25]. Laryngeal TB makes up less than 1% of TB cases, and usually manifests as dysphonia and weight loss (26, 27). As with endobronchial TB, laryngeal TB is often associated with underlying pulmonary TB [26].

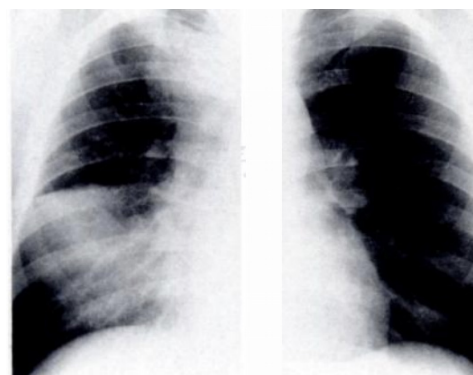


Figure 1: Primary pulmonary TB causing lobar consolidation and hilar lymphadenopathy in a 23-year-old man, Lee et al. [22].



Figure 2: reactivation TB causing cavitory lesions with air-fluid levels in the upper lobe of the left lung, Curtis et al. [33].

Current guidelines: CG, treatments, the role of fluoroquinolones and MDR

Currently, the CDC-recommended preferred regimen for treatment of non-resistant TB includes 2 months of daily isoniazid, rifampin, pyrazinamide, and ethambutol followed by 4 months of only isoniazid and rifampin. After the initial 2 months of therapy, if cultures remain positive for TB, the 4-month continuation phase is extended by 3 months for a total continuation period of 7 months. For TB patients taking antiretroviral therapy (ART) for concurrent HIV infection, the treatment regimen and timeline is similar; however, drug interactions between rifampin and ART medications must be taken into consideration and the alternative rifabutin must be considered. If an HIV-positive patient is not receiving ART during their TB treatment regimen, the 4-month continuation phase must be extended by 3 months for a total continuation period of 7 months [28].

The CDC defines multi-drug resistant TB (MDR-TB) as TB that is resistant to at least isoniazid and rifampin. For treatment of MDR-TB, the CDC recommends an initial intensive phase of treatment which includes the use of at least 5 drugs for a duration of 5-7 months, followed by a continuation phase of at least ten months. During the intensive phase, the CDC strongly favors the inclusion of a later-generation fluoroquinolone, bedaquiline, and linezolid [29].

In the treatment of TB specifically resistant to isoniazid but not rifampin, a 6-month regimen of daily rifampin, ethambutol, pyrazinamide, and a later-generation fluoroquinolone is suggested [29].

The current CDC guidelines for treatment of latent tuberculosis have been developed to maximize efficacy and minimize toxicity of drug therapy. For non-resistant latent tuberculosis infections, the CDC has 3 preferred drug regimens. In adults and children > 2 years old with TB infection, regardless of HIV status, the CDC strongly recommends a regimen of 3 months of weekly isoniazid and rifapentine, with the potential disadvantage of cost of therapy. A regimen of four months of daily rifampin is recommended for children and adults with TB who are negative for HIV; the primary disadvantage to this regimen is the interactions that rifampin has with many other drugs. In HIV-positive individuals with TB, a regimen of daily isoniazid and rifampin is suggested. The potential disadvantages of this therapy are once again the interactions that rifampin has with many other drugs, as well as the increased risk of hepatotoxicity with both of these drugs being used together [30].

The BCG vaccine for TB is a live-attenuated vaccine. The WHO recommends that in countries with a high incidence of TB and/or leprosy, all healthy newborns should be given the vaccine [31]. The CDC states that in the USA which is a relatively low-incidence country, the vaccine should be given to children with unavoidable exposure to a person with infectious TB [32]. Contraindications for the BCG vaccine includes but are not limited to immunocompromised status, positive HIV status, and pregnant or lactating women [31,32].

Prevalence of TB, among HIV patients, Migrants, and Refugees

The number of international migrants globally in 2019 was 272 million which represented 3.5% of the world's population. There was a total of 1.5 million people who died from TB in 2018 251 000 of which had HIV. The United Nations High Commissioner for Refugees estimates the number of people around the world have been forced to flee their homes at close to 80 million. Among them are nearly 26 million refugees Worldwide, TB ranks in the top 10 causes of death and the leading cause from a single infectious agent. In a WHO report from 2018, an estimated 10 million people fell ill with tuberculosis (TB) worldwide. This is a considerable sum considering that TB is preventable and treatable. 44% of new cases occurred in the South-East Asian region, followed by 24% in the African region, and finally 18% in Western Pacific. In the world, eight countries accounted for two thirds of the new TB cases: India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh and South Africa. TB has a very high spreadability, which makes it especially potent in poorly isolated groups such as migrants and refugees. The prevalence can be attributed to many causes, such as limited access to diagnostic and treatment services, unhealthy conditions, and compromised immunity.

Quiz:

1. A 34 year old female nurse presents to your clinic with concerns that she may have been exposed to tuberculosis recently as she works in a nursing home, and there was a recent outbreak where several of the residents were diagnosed with active tuberculosis. She underwent a tuberculin skin testing which resulted in 12mm of induration, but she denies any symptoms including shortness of breath, fevers, night sweats and weight loss. Which of the following is the best next step in management of this patient?

1. Order a chest x-ray
2. Rifampin for 4 months
3. Isoniazid & rifampin once a week for 12 weeks
4. Isoniazid for 1 year

Answer:

Correct: This should be the first step in the diagnostic criteria to ascertain whether the patient has an active or a latent form of the disease regardless of the lack of current symptoms

Incorrect: While this regimen can be used in preventive therapy in patients with positive skin testing, further investigation takes precedent to rule out active tuberculosis

Incorrect: This is another alternative regimen can be used in preventive therapy in patients with positive skin testing, but further investigation takes precedent

Incorrect: This regimen can be used in patients with subclinical infection

2. A 3 year old patient is accompanied by his parents for a routine well child visit. His growth and development have been normal and has only had 1 bout of rhinosinusitis diagnosed when he was 23 months old. During the evaluation his mother mentions that she has been receiving treatment for several

months for an active tuberculosis that she was diagnosed with while overseas in the military. She also mentions that the drug regimens have not yet been successful and antibiotics have had to be changed several times. Due to this, the doctor decides that the patient should receive the BCG vaccine as he is at a high risk of contracting this disease. Before administration, which of these side effects of the BCG vaccine should be mentioned to the parents to avoid worry?

1. Blood in the stool
2. Difficulty walking
3. Parotid gland swelling
4. Skin ulceration

Answer:

Incorrect: Hematochezia is more commonly associated with the rotavirus vaccine rather than the BCG vaccine

Incorrect: Difficulty walking and neuropathies are not typical side effects of the BCG vaccine but are associated with other vaccines including MMR vaccine

Incorrect: Parotid gland swelling is a rare side effect from the MMR vaccine and is not typical of the BCG vaccine.

Correct: The patient is indicated to receive the BCG vaccine as he will be continuously exposed to persons with infectious pulmonary tuberculosis who have bacilli resistant to isoniazid and rifampin, and the child cannot be separated from the presence of the infectious patient. Parents of patients receiving the Bacille Calmette-Guérin vaccine must be told about possible side effects including fever, headaches, skin blistering and potential self-resolving skin ulceration at site of injection

3. A 55-year-old male presents to the clinic with recurring back pain and fevers for the past 3 months that have progressively worsened and have been non-responsive to NSAIDs which had previously helped. He is currently married and he has lived in England for the past 9 years after moving from Congo. He is up to date on all of his vaccinations including Hep B, MMRV and BCG but is unsure when he received the pneumococcal vaccine. He denies any past medical history but mentions that his mother passed away from metastatic melanoma at age 56 and his father from an MI at age 74. He denies any night sweats or malaise but he is quite pleased that he is able to fit into his wedding tuxedo once again. He also denies skin changes, nausea, vomiting, hemoptysis, urinary changes or bowel habit changes. Besides ordering PPD, chest and lumbar x-rays, which of the following is also indicated at this time?

1. Bone biopsy and culture
2. Spinal nerve conduction studies
3. Liver ultrasound
4. HIV ELISA

Answer:

Incorrect: Although a bone biopsy and culture could be used to confirm the most likely suspicion (Pott's Disease), screening measures should be used first before more invasive procedures are completed

Incorrect: Symptoms of Pott's Disease include fevers, back pain, paresthesias and weakness. Although this patient is complaining of back pain, the lack of neurological symptoms would make this test inappropriate at such a time

Incorrect: A liver US would not be useful in a suspected diagnosis of Pott's Disease unless hepatic involvement is suspected.

Correct: HIV testing is recommended as a part of the evaluation of all suspected or confirmed TB cases, especially in persons suspected of having Extra Pulmonary TB (EPTB) because of the increased frequency of extrapulmonary involvement in immunocompromised persons. As well, even in patients that have received the BCG vaccine, tuberculosis cannot be ruled out as the vaccine is only 70-80% effective at prevention

4. A 18-year-old male presents to the clinic with shortness of breath, fever and reddish-brown sputum for the past 2 months. He has a past medical history of hypertension, type 1 diabetes and ankylosing spondylitis. He states that he works as a physical therapist at the nearby hospital. He was recently diagnosed with active TB and has been started with the appropriate treatment. What is the most likely mechanism of his susceptibility to infection?

1. Dampening of the pro-inflammatory process
2. Inhibit the synthesis of DNA
3. Inhibit the synthesis of folic acid
4. Counteracting of the cyclooxygenase (COX) enzyme

Answer:

Correct: One of the first line treatments for the prevention of progression in ankylosing spondylitis are TNF- α antagonists. Tuberculosis (TB) & other opportunistic bacterial, viral & fungal infections have been observed in patients on TNF- α antagonists. TNF is produced by numerous cells in the immune system (dendritic cells, macrophages, TH1 cells) as well as fibroblasts & smooth muscle cells.

Incorrect: This is the mechanism of antibacterial fluoroquinolones and metronidazole, which has no such side effects.

Incorrect: This is the mechanism of antibacterial sulfonamides trimethoprim, which has no such side effects.

Incorrect: This describes the mechanism of nonsteroidal anti-inflammatory drugs (NSAIDs), which has no such side effects.

5. A 45-year-old Senegalese male presents to the clinic complaining of severe shortness of breath, a week-long hacking cough, and pyrexia. He stated that he has been dealing with this issue for a while, which has since worsened over the past month. He was diagnosed with TB 6 months ago but stopped the treatment early as he had attempted to take his medications but it did not improve his condition. Given his history of illness and lack of proper treatment regimen, which of the following would be the best choice for the treatment of his resistant TB?

1. Isoniazid & pyridoxine for 9 months
2. Close follow up, and referral to infectious disease
3. 2 months of rifampin, isoniazid & pyrazinamide and 4 months of rifampin & isoniazid
4. Rifampin & ethambutol for 12 months \pm pyrazinamide

Answer:

Incorrect: This course is for preventive Therapy in Patients with Positive Skin Test

Correct: One needs to first identify the extent of the resistance before prescribing any medication, that may worsen the situation, a multidrug resistant infection usually requires a combination of at least 3 drugs to which organisms are susceptible

Incorrect: This course is for a Conventional Therapy for susceptible organisms of active TB

Incorrect: While this can treat drug resistant TB, it is specifically tailored for those with Tuberculosis resistant to Isoniazid

6. A 49 year old patient presents to the clinic for a routine physical and PPD screen for their new role in a new hospital as a nurse technician. He has been feeling well and has been compliant for his medications for his hypertension and diabetes. Physical exam uncovers no abnormalities other than a scar on his left knee from when he was a teenager. Routine blood work was also completed at the previous visit and shows no abnormalities, including an HbA1C of 6.2%. Results from the PPD are read 48 hours later and the size of the induration measures 11mm, which leads the physician to order a chest x-ray. Results from the x-ray display no abnormalities so the physician decides to initiate him on a multi-drug treatment. Which of these options is most important when considering the treatment for this patient's latent condition?

1. Previous adverse reaction to clofazimine
2. Medication interactions
3. Family history of similar condition
4. Duration of illness

Answer:

Incorrect: Adverse reactions to medication are important but in the case of the treatment for latent TB the primary drugs of choice are isoniazid, rifampin, pyrazinamide, and ethambutol; none of which are similar to clofazimine. As well, clofazimine is used for the treatment of multibacillary mycobacterial leprosy rather than tuberculosis.

Correct: Medication interactions are of much importance during the treatment of latent tuberculosis as one of the most commonly used TB drugs, rifampin, can induce pathways that metabolize other drugs by activation of CYP450 and thereby reduce their concentrations and effects. Some of the affected drugs include hormone therapies (levothyroxine and tamoxifen), warfarin, anticonvulsants and digoxin.

Incorrect: Although family history of TB could help indicate exposure it would not affect the treatment for this patient's latent TB.

Incorrect: Duration of illness would not affect neither the treatment modality nor the antibiotic choice for the treatment of latent TB. On the other hand, resistance or previous treatment as potential for resistance should be considered.

7. A 45 year old male presented to the clinic in search of treatment for his leprosy which was diagnosed back in his

home country of Lebanon. He was unable to afford treatment at that time so it has slowly progressed over the past 2 years. Physical examination shows several hypo-pigmented skin lesions, with thickened surrounding skin, and central loss of sensation of his legs. His past medical history is unremarkable otherwise. He is told that the treatment for his condition will include dapsone, rifampicin, and clofazimine for 24 months. Of the following choices, which is the most appropriate for the physician to mention to the patient regarding his condition?

1. Slow resolution of lesions indicates treatment ineffectiveness
2. Avoidance of long-term close contact with others until lesions resolve
3. Loss of sensation will most likely not resolve
4. The risk of transmission is near zero once treatment begins

Answer:

Incorrect: The erythema and induration of skin lesions may decrease within months of initiating therapy but it may take years for cutaneous lesions to fully resolve, depending both on the initial number of lesions and severity of infection when starting treatment.

Incorrect: As soon as patients start treatment, they are no longer able to spread the disease and are not a risk to others including close contacts

Incorrect: Although many patients never regain complete resolution of neurological symptoms, many will regain back partial function of the nerves

Correct: Research has shown that the transmission is not immediate and requires prolonged, close contact with someone with untreated leprosy over many months. As soon as patients start treatment, they are no longer able to spread the disease and are not a risk to others including close contacts

8. A 50-year-old woman presented to her physician with a 1-month history of generalized weakness, 5kg unintentional weight loss, and night sweats. She has a history of hypothyroidism, and vitamin D deficiency. She is currently a physician in her first year of residency and denies sick contacts, exposure to tuberculosis, smoking, or the use of illicit substances. Her previous employment PPD skin test came as indeterminate, and there was no evidence of pulmonary tuberculosis on a chest radiograph. She began a treatment regimen of isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). A month later but reports back to the clinic with worsening fatigue, salt craving, vomiting, and loss of libido. What is the most likely reasoning for her current presentation of symptoms?

1. Lack of treatment adherence
2. Her past medical history
3. The rifampin dosage
4. The isoniazid dosage

Answer:

Incorrect: While this can cause many future problems such as dissemination of the disease, and increase likelihood of

antitubercular resistance, the timeline is far too short for such symptoms to develop.

Incorrect: Her past medical history of hypothyroidism and gender, does increase her risk for autoimmune diseases, there is no indication that is the case, given the history of present illness and presentation.

Correct: Deterioration of her status following antitubercular treatment could be attributed to accelerated cortisol metabolism by induction of CYP 3A4 by rifampin.

Incorrect: The use of isoniazid without vitamin B6 does increase the risk of peripheral neuropathy not adrenalitis.

9. A 56 year old handyman presents with confusion, nonproductive cough, poor appetite, and a 14kg unintentional weight loss over this time. He was previously diagnosed with HIV in Liberia, but was never adequately treated. Vitals; blood pressure 90/70 mm Hg, heart rate 115 beats/minute, respiratory rate 20 breaths/minute, and temperature 38 °C. He appears disheveled, is awake and responsive, but he is disoriented to time and place. There are no neurological findings evident. Physical exam is normal with the exception of splenomegaly, multiple, non-tender, cervical lymph nodes bilaterally.

Labs:

Purified protein derivative (PPD): 17-mm induration,

White blood cell count: 13000/mm³ with no shift of neutrophils

Serum transaminase: 85 U/L

Serum sodium: 120 mEq/L

X-ray findings reveal many 3-mm micronodular lesions throughout both of his lungs. What is the most likely explanation for the low serum sodium level in this patient?

1. Psychogenic water drinking
2. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
3. Adrenal insufficiency
4. Excessive sweating

Answer:

Incorrect: It can be another explanation for hyponatremia, but, it would not explain the lymphoid hyperplasia, splenomegaly and lymphadenopathy.

Correct: The patient has miliary tuberculosis (TB), most commonly seen in the elderly and patients with HIV infection. HIV infection is associated with a higher frequency of extrapulmonary TB including disseminated (miliary) infection. Systemic features of weight loss, low-grade fever, and progressive weakness are common. Hyponatremia due to SIADH is also a common feature as is proposed to occur due to various mechanisms

Incorrect: While, adrenal insufficiency could explain some of the patient's symptoms and signs, but the presence of abnormal liver function tests, lymphadenopathy, and splenomegaly essentially rule out this disease.

Incorrect: Sweat is hypotonic, so the serum sodium level would increase in patients with severe sweating.

10. During morning rounds a team of physicians and medical students arrive in a patient's room who has been here at the hospital's inpatient medical floor for the past 2 weeks receiving medical treatment for tuberculosis. The patient has developed hemoptysis, fever and malaise after having spent his summer in India working at a local homeless shelter. Upon arrival to the hospital he was diagnosed promptly with active tuberculosis where treatment was started and clinical improvement was noted. The patient was also placed on airborne infection isolation(AII) precautions which included a negative pressure room and N95 respirators to all persons entering the room. The medical student asks the physician caring for the patient when the AII precautions can be lifted. Which of the following would be a correct response by the physician?

1. When there are two negative sputum smears at least 4 hours apart and at least one is collected during early morning.
2. When there are three negative sputum smears at least 8 hours apart and at least one is collected during the evening.
3. When there are three negative sputum smears at least 8 hours apart and at least one is collected during early morning.
4. When there are two negative sputum smears at least 4 hours apart and at least one is collected during the evening.

Answer:

Incorrect: That is an incorrect criteria as having 2 negative smears that are 4 hours apart are not sufficient.

Incorrect: While 3 negative smears at least 8 hours apart would be sufficient, it is crucial that one is during the early morning.

Correct: The criteria for discontinuing AII precautions include: Infectious TB is unlikely and another diagnosis is made that explains the syndrome OR Patient has 3 consecutive negative AFB sputum smear results(at least 8 hours apart and at least one is collected during early morning), patient has received standard antituberculosis treatment (minimum of 2 weeks), and patient has demonstrated clinical improvement

Incorrect: That is an incorrect criterion as having 2 negative smears that are 4 hours apart are not sufficient.

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