

## Re-addressing the Problem of Tuberculosis in Renal Transplant Recipients

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Tuberculosis (TB) which remains one of deadliest communicable diseases, is an ancient in origin and has been reported from Egyptian tomb painting and examination of mummies as early as 4000 BC [1]. According to world health organization's recent global report, in 2013 estimated 9.0 million people developed TB (more than half were in the South-East Asia and Western Pacific Regions) and 1.5 million died from the disease, though number of dying patients decreasing every year from 2000-2013. HIV positive patients acquire TB infection 26-31 times more frequently than other people; this is because of their state of poor immune system [2].

Solid organ transplant recipients fall in category of immunocompromised community as they have to take variable amount of immune suppressants through their life. Reported incidence of TB in solid organ transplant recipients vary widely from 0.26 to 15% worldwide, with some countries known to have TB as endemic infection certainly report higher prevalence [3-12].

Although there is no central registry system to enumerate exact figures of organs transplanted every year in India and Pakistan, both countries have performed thousands of renal transplants over last two to three decades and there are many published reports on prevalence of TB in these recipients [9-11,13].

TB after renal transplant can occur as reactivation in recipients with past history or even in absence of definite history they may have acquired subclinical infection, as disease is endemic and chances of exposure are very high. Then it may get transmitted from donor through organ or may happen as freshly acquired air borne infection. During pre-transplant assessment of recipient use of tuberculin skin testing has limitation because of risk of energy in immune compromised population, which is true for end stage renal failure, due to impaired cell mediated immunity [14].

Not only that this population is at greater risk of developing TB, but it constitutes challenge in diagnosis of infection because of atypical presentation and extra pulmonary rare sites involvement with infection [3,4,9]. Patients may present with high grade spiking continuous fever along with associated symptoms originating from system which is actually not involved with infection and thus may misdirect pathway of clinical suspicion and investigations. Secondly involvement of rare sites with TB infection is also a challenge for treating physicians [15,16]. For example laryngeal TB was found in one of patients included in 54 [11], the only symptom this patient had was daily spiking fever and all radiology and microbiology investigations remain unresponsive, finally direct laryngoscopy and biopsy from a suspicious area on one of vocal cords revealed typical caseating granuloma with giant cells.

The standard diagnostic tools remain acid fast staining of body fluid samples to demonstrate bacilli or Auramine-rhodamine/auramine

**Received date:** 09 Sept 2015; **Accepted date:** 14 October 2015; **Published date:** 19 October 2015.

**Citation:** Naqvi R (2015) Re-addressing the Problem of Tuberculosis in Renal Transplant Recipients. *J Infect Pulm Dis* 1(1): doi <http://dx.doi.org/10.16966/2470-3176.102>

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O fluorescence staining which permits rapid scanning of the specimen. Cultures on Lowenstein Jensen media which is powerful tool, takes 6-8 weeks to confirm diagnosis and sensitivity. Earlier detection of growth, within two weeks can be achieved with BACTEC, method which utilizes radio labeled nutrient substrate, gas pressure monitoring and fluorescence emission. ELISA (Quantiferon Gold) and Elli spot, an immunospot assay, used for detection of interferon gamma but their use in patients from population of high exposure remains debatable. Though Quantiferon has advantages upon tuberculin skin test in ways that it is more specific, there could be no reader's biases, it is not affected by booster phenomenon, not affected by prior BCG vaccination and patients require only one visit. However; false negative test may occur in immune compromised patients. Then molecular techniques of nucleic acid amplification and identification of mycobacteria is another tool in use over last few decades. With nucleic acid amplification tests (NAAT) even patients with latent tuberculosis can be reported as positive, most likely because of the presence of very small number of live or dead bacteria that may be found in macrophages [17]. Although NAAT is rapid and have reasonable clinical performance, major problem with NAAT is technical staff and consumables cost which is a definite burden especially in countries where TB is endemic. Radiological studies including ultra sonography, computed tomography and positron emission tomography may also contribute to diagnosis of TB in remarkable number of patients. Another important tool is the tissue diagnosis but getting a tissue for histopathology not always a possibility.

Treatment with conventional anti tuberculous drugs directs towards another challenge as sharing the common metabolic pathway of p450 cytochrome enzyme leads to enhanced requirement of calcineurin inhibitors, the mainstay of immune suppression regimen. This result in many fold rise in cost of immune suppression and drug monitoring, as on one hand increase in dosage and on other repeated blood levels are required [18].

With reported high incidence and prevalence of TB in transplant recipients from developing world, efforts has been made to bring down the numbers and one most important is use of chemoprophylaxis in transplant recipients. From our own institution which is largest center for living related renal transplant in the region ([www.siu.org](http://www.siu.org)), we designed a randomized study where one arm received one year chemoprophylaxis with isoniazid after renal transplant and we observed significant decline in number of infected patients with TB in our population [19]. Later a review was published including observational studies and randomized trials, concluding that there is evidence that isoniazid should be used as prophylaxis for TB in renal transplant recipient especially in India and Pakistan where disease is endemic. But at the same time authors recommend multicenter blinded controlled trials for isoniazid, to deliver more confident verdict upon same [20].

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