Tuberculosis in patients on Dialysis
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Approximately 1/3rd of the world population is infected with tuberculosis (1). Patients with end stage renal disease undergoing chronic dialysis are 6-25 times more likely to develop tuberculosis (TB) compared to the general population mainly due to impaired cell-mediated immunity (2).

Risk Factors of TB for Patients on Dialysis

In a retrospective analysis, age, Asian and Native American race, smoking, reduced body mass index, low serum albumin, ischemic heart disease and anemia were found as significant risk factors for dialysis patients to develop TB (3).

In a prospective multi-center clinical trial assessing the role of risk factors for TB in dialysis patients, Christopoulos et al. observed that history of TB, use of vitamin D supplements, dialysis efficiency, serum albumin and zinc levels were not proved to influence significantly the risk of TB. However, advanced age (>65 years), body mass index (underweight being more prone) diabetes mellitus, tuberculin reactivity, healed TB lesions on chest X-ray and time on dialysis were significant risk factors for development of TB. Those treated with dialysis less than 12 months presented significantly higher risk for TB (4).

The symptomatology of TB is often confused with that of chronic kidney disease leading to difficulty in early diagnosis and high mortality (5). Extra pulmonary TB in dialysis patients is more common (6) and may be seen up to 77% of cases compared to the general population occurrence of 11.5% (1).

Clinical presentation:

The most common forms of presentation are lymphadenitis, gastrointestinal, bone, genitourinary, peritonitis, pleural effusion, pericardial effusion, miliary TB and pyrexia of unknown origin (7-10).

In our study in Saudi Arabia over 11 years on 330 patients on maintenance dialysis (225 on hemodialysis and 125 on peritoneal dialysis) 48 (14.5%) patients developed TB. Thirty two (67%) presented with fever, cough (n=16), weight loss (n=9), anorexia (n=7). Twenty three of 48 cases had pulmonary TB (including 4 with miliary TB) and 25 (52%) had extra-pulmonary TB. The extra-pulmonary organs involved were peritoneal (n=15), lymphadenopathy (n=11), pericardial (n=4), bone (one each of dorsal spine, rib and metatarsal), cold abscess one infraclavicular and 1 infrascapular), bone marrow (n=2), epididymo-orchitis (n=1), renal mass (n=1). Two patients with fever and weight loss for 6 and 8 weeks and no definite organ involvement were treated empirically for TB and responded well. Thirty six patients (including two empirically treated had single system involvement, 10 had involvement of two systems and 2 had 3 systems involved (6).
**Diagnosis:**

The diagnosis of TB in dialysis patients is generally difficult because of frequent extra-pulmonary involvement and nonspecific symptoms: A high degree of suspicion is needed in patients on dialysis with symptoms of fever, weight loss and/or lymphadenopathy. The diagnosis is confirmed by the isolation of acid-fast bacilli, the finding of typical caseating granuloma on biopsy or the growth of tubercle bacilli from the culture of the biopsy material (11).

In our study of 48 patients already referred to (6) the diagnosis was based on chest x-ray (n=23), Ziehl-Neelsen stain and culture of sputum and fluid (n=15), ascitic fluid examination-exudate and increased adenine deaminase (ADA) levels (n=12), lymph node biopsy (n=11), pleural fluid examination-exudate and increased ADA levels (n=5), bone marrow aspiration with evidence of granuloma (n=2), nephrectomy and histology (n=1), surgery and dorsal spine biopsy, laparotomy and peritoneal biopsy (n=1).

**Tuberculin Skin Test (TST):**

Infection with Mycobacterium tuberculosis is followed by delayed type hypersensitivity (DTH). This reactivity is the basis of the TST which is used for the detection of TB infection in persons without symptoms. The previously sensitized CD4+ T lymphocytes are attracted to the skin test site where they proliferate and produce cytokines. Cases of active TB are often accompanied by strongly positive skin test reactions (12). The TST measures the DTH response to intradermal inoculation of tuberculin purified protein derivative (PPD), a crude mixture of >200 Mycobacterium tuberculosis proteins (13). A skin induration >10 mm in diameter is considered positive (14). However anergy to TST is prevalent in end stage renal disease (ESRD) patients and is significantly higher than in the general population (44% versus 16%) (15). TST was positive in only 35% of patients in our study (6). Because of its poor sensitivity a negative STS cannot be used to exclude the possibility of latent or active TB in dialysis patients. Booster TST (two consecutive tests within 7-14 days) with a higher dose of PPD (usually double) has been recommended in immunocompromised like dialysis patients to improve the sensitivity of TST. Dogan et al found a positive test in 11.3% of 124 chronic hemodialysis patients whereas the second test added 12.1% more (16). The importance of TST despite its low sensitivity cannot be underestimated since a positive test forms an indication for TB prophylaxis in dialysis patients. A 6 month course of prophylaxis with isoniazid as 15 mg/kg dose 2 or 3 times per week has been recommended and up to 90% of treated patients enjoy long term protection from TB (17,18).

**The Interferon (IFN)-γ Release Assays (IGRAs):**

Recently, two in vitro assays that measure T cell release of IFN-γ in response to stimulation with the highly tuberculosis specific antigens ESAT-6 and CFP-10 have become commercially available. These are Quantiferon TB Gold, a whole blood enzyme linked immunosorbent assay (ELISA) for measurement of IFN-γ and T-SPOT TB, an enzyme linked immune spot (ELI spot) assay. These are more specific than the TST as a result of less cross reactivity due to BCG vaccination and sensitization to non-tuberculosis mycobacteria.
For the diagnosis of active TB in dialysis patients the sensitivity and specificity of IGRAs using QFT-G were found to be 100% and 89.7% respectively (19). The authors conclude that QFT test is a useful supplementary tool for the diagnosis of active tuberculosis even in dialysis patients. Negative and indeterminate test may be used to exclude for the presence of active TB. TST, the classic diagnostic tool for the diagnosis of latent TB has several drawbacks including poor sensitivity (because of high prevalence of anergy in dialysis patients and specificity with false positive tests in vaccinated with Bacillus Calmette Guerin (BCG). So IGRAs should be used instead of TST for latent TB screening in dialysis patients (21).

**Treatment**

After 1993 the short course therapy consisting of Isoniazid (INH), Rifampicin (Rif), Pyrazinamide (PZA) and Ethambutol (Eth) or streptomycin for 2 months followed by only INH and Rif for another 4 months to complete a total 6 month therapy has been recommended for pulmonary as well as extra pulmonary TB except TB meningitis and children with military or bone/joint TB. Such cases require a therapy for 12 months (22). This short course therapy was used in 32 (66%) of patients in our study (6) with satisfactory response. In an earlier study also short course chemotherapy with 4 drugs was used in 6 patients and all of them recovered (23).

**Isoniazid (INH):** is metabolized in the liver through acetylation which is a genetic characteristic and varies from patient to patient. Despite there being individuals with fast and slow acetylation isoniazid in daily doses of 300 mg or 5-6 mg/kg body weight can be given in patients on dialysis (24,25). In slow acetylators the renal excretion is 30% whereas in rapid acetylators renal excretion is 7%. Some authors recommend a dose of 200 mg/day in patients on dialysis with slow acetylation. Isoniazid is removed well by dialysis and so the dose should be given after dialysis on the dialysis days (26). Side effects of Isoniazid include hepatitis and central and peripheral neurotoxicity. In our study three (6.2%) patients developed neurotoxicity. Symptoms of central nervous system toxicity like dysarthria, irritability, seizures and euphoria have been noted in different studies (27).

**Rifampicin:** The drug is primarily metabolized in liver (24). Renal excretion of Rifampicin is only 7% in non-uremic patients and dose need not be adjusted in dialysis patients (26).

**Ethambutol:** Largely excreted by kidneys. In dialysis patients or in chronic kidney disease patients with creatinine clearance less than 30 ml/min, a dose of 15-20 mg/kg should be given 3 times/week (24). Ethambutol is removed by peritoneal and to a lesser extent by hemodialysis (24,29). Toxicity on optic nerve warrants monitoring of visual activity and color vision while on Ethambutol.

**Pyrazinamide:** The metabolites are eliminated by kidney and can accumulate in renal failure patients. So the dose needs to be reduced in dialysis patients. The daily dose needs to be reduced to half in patients with creatinine clearance of less than 10ml/min. Pyrazinamide is significantly reduced by dialysis. So the dose should be given after dialysis.
at a dose of 25-35mg/kg three times a week. Hyperuricemia increases in patients with renal failure while using Pyrazinamide (4,30).

**Streptomycin**: If needed, Streptomycin may be used in a dose of 750 mg 3 times/week 6-8 hours before dialysis (31).

**Mortality:**

The mortality rate of TB in dialysis patients is high ranging from 17-75% (8). In the USRDS analysis TB was independently associated with a 42% increased mortality (3). However, many studies have reported no or low mortality, possibly related to early diagnosis and treatment. In our study out of 48 patients 13(27%) died. However in none death could be attributed directly to TB (6). Similar results have been observed in other studies (23,32,33).

**References:**


Conflict of Interest: None
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