Should Tuberculosis Prophylaxis Be Given for the Chronically Dialyzed Patients?

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Until the middle of this century, tuberculosis was, in Dickens' words, 'a disease which medicine never cured, wealth warded off, or poverty could boast exemption from – which sometimes moves in giant strides, and sometimes at a tardy sluggish pace, but, slow or quick, is ever sure and certain' [1]. *Mycobacterium tuberculosis* is an extremely successful pathogen that continues to thrive in developing countries and is re-emerging in the industrialized world. Globally, it remains a more frequent cause of death than any other infectious agent [2]. Approximately a third of the world's population is infected with *M. tuberculosis*, and the World Health Organization estimated that in 1996 there were 8 million new cases of tuberculosis and 3 million deaths from the disease [2]. The sinister synergy between this disease of antiquity and the newer pathogen human immunodeficiency virus is responsible for the death of about a third of all patients with AIDS in Africa [3].

Yet progression to disease and death is far from an inevitable consequence of exposure. There is dramatic variability in the rates of infection among persons exposed to different sources of infection, and of those infected, approximately 90% never become ill. The inability to predict whose patients are most likely to transmit infection and who among those infected will have the disease and infect others remains a major barrier to optimal public health and patient care.

Host resistance to *M. tuberculosis* is mediated by cellular immunity as this is impaired in patients with chronic renal failure [4], the incidence of tuberculosis in dialyzed patients should be high. Cellular and humoral immune responses are suppressed in uremic subjects [5]. The increase in sister chromatid exchange (SCE), chromosomal aberrations, tumor markers and the impaired cell function have been reported [6–8]. Uremia thus induces a remarkable suppression of the immune status. In addition, patients receiving hemodialysis spend prolonged periods of time together in health-care facilities, thereby increasing the potential for tuberculosis transmission if a patient has active disease. For these reasons, routine tuberculosis screening of hemodialysis patients has been recommended [9]. Although the Mantoux tuberculin skin test remains the most useful screening tool, cutaneous anergy decreases the accuracy of the test.

End-stage renal failure patients on chronic dialysis are prone to tuberculous infection due to a defect in cellular immunity. The incidence is reported to be 10–16 times higher than that in the general population [10–14]. One in every 3 people in the world is infected with *M. tuberculosis*, and observed rates of new tuberculosis infection are on the increase, especially in the third world [15–18]. In the 'rich' countries, latent tuberculosis can be reactivated in a number of 'high-risk' patient populations such as AIDS, silicosis, immunosuppression, malnutrition and end-stage renal failure [15–17]. Worldwide tuberculosis

infection in dialysis patients ranges from 5 to 25% [18]. Over 40% of dialyzed patients with tuberculosis have extrapulmonary manifestations of the disease, and this makes the disease difficult to diagnose, causing delay in commencing curative therapy [18]. For these reasons, tuberculosis prophylaxis in chronically dialyzed patients is worthy of consideration, especially as isoniazid (INH) prophylaxis effectively reduces reactivation of latent tuberculosis for prolonged periods of time [19]. Unfortunately, only one study has addressed this issue in dialyzed patients [20]. In that study, conducted in southern India, 184 hemodialysis patients entered a double-blind, randomized trial of INH prophylaxis. A trend towards protection from tuberculosis was demonstrated [19]. Therefore, a number of questions still need to be answered. What drug should be given for prophylaxis? What are the possible benefits and complications of such therapy? And finally, which dialysis patients should receive tuberculosis prophylaxis?

What Drug Should Be Given for Prophylaxis?

The drug of choice is INH. It has excellent oral absorption. It is bactericidal and can be given once every 2–3 days. There is no need for dose reduction in patients with impaired renal function and it is very cheap [21]. The effectiveness of INH in preventing tuberculosis is unquestionable. At least 50–60% of treated patients will enjoy long-term protection from tuberculosis after a 6-month period of therapy, and in some conditions protection rises to 90% [22, 23]. Salpeter et al. [24] also argue that INH prophylaxis, for all low-risk tuberculin skin test reactors older than 35 years of age, will prevent thousands of tuberculosis-related deaths. INH prophylaxis is successful, if the drug is taken under supervision, on a two or three times weekly basis (15 mg/kg/dose), a perfect solution for hemodialysis patients [16].

Hepatotoxicity remains the major problem associated with INH administration, especially in the elderly, the malnourished and in the alcoholic [16, 25]. It generally occurs within the first 4–8 weeks of therapy, but in 20% of patients minor and asymptomatic elevation of hepatic enzymes occur, which is transient and does not necessitate cessation of INH treatment [16]. When transaminase levels increase to 2–3 times above normal, then INH must be stopped. But what of fetal INH-induced hepatitis? In 1996, after monthly liver function monitoring had become the accepted norm, Millard et al. [26] showed that, irrespective of age, the rate of fatal hepatitis is 1–2/

100,000 treated patients. Also, McGlynn et al. [27] failed to show a greater degree of INH hepatotoxicity in hepatitis B carriers. This observation may be relevant for dialysis patients who are infected with the hepatitis B virus.

Nervous system side effects have been documented in dialysis patients treated with INH [28]. INH inhibits phosphorylation of pyridoxine, and this leads to a reduced production of pyridoxal-5-phosphate, a co-enzyme essential in neurotransmission. In dialysis patients, serum pyridoxine levels are normal, but pyridoxine metabolism is not, and the addition of INH therapy makes these patients vulnerable to neurological toxicity. Fortunately, this problem is completely and easily avoidable by concurrent administration of INH and vitamin B₆ (100 mg/day) [28].

For persons possibly infected with tuberculous resistant to INH, various alternative therapies have been used [16]. Monotherapy with rifampin is effective, and if maintained for 6 months has a low incidence of side effects [29]. Another drug protocol currently under investigation is combined rifampin and pyrazinamide, with a duration of therapy lasting only 2 months [25].

Which Dialysis Patients Should Receive Tuberculosis Prophylaxis?

According to our current knowledge, any patients with a positive Mantoux skin test (5 U purified protein derivative of tuberculin – a sterile-killed concentrate obtained from human tubercle bacilli), should be considered to be infected with *M. tuberculosis*, even if they have previously received BCG vaccine [22, 30]. An indurated area of at least 10 mm, 48–72 h after intradermal injection, is positive in non-AIDS-infected, dialyzed patients; while in persons with x-ray findings consistent with healed tuberculosis or who have been in close contact with patients known to be infected with pulmonary tuberculosis, then an indurated area of 5 mm is regarded as positive [22]. If chronically dialyzed patients are regarded as ‘high risk’ for reactivation of latent tuberculosis, then one may be tempted to treat all dialysis patients with a positive tuberculin skin test. At the very least, any dialyzed patient with a positive tuberculin skin test and who lives or has migrated from an endemic area, has had close contact with any patient with active pulmonary tuberculosis, is a recent tuberculin test converter or has a x-ray suggestive of old tuberculosis, should receive prophylaxis. Woeltje et al. [17] advised regular tuberculin skin testing and encouraged INH prophylaxis in hemodialyzed patients.

Uremia impairs cell-mediated immunity and is known to cause anergy. When a high index of suspicion for tuberculosis exists, but the skin test is negative, then it should be repeated with 250 U dose. If this high-dose skin test is negative, then skin tests with other antigens should be performed. A negative reaction to these tests indicate anergic state [22]. Furthermore, false negative results on tuberculin skin testing can be caused by faulty test administration or interpretation, corticosteroid therapy, malnutrition, acute viral disease, candida infection or overwhelming tuberculosis. But recent studies have demonstrated that properly performed, multiple skin tests will be positive in over 60% of dialyzed patients [17]. If dialysis patients have a 'true negative' tuberculin skin test and no other risk factors associated with reactivation of tuberculosis, than they, most probably, should not be treated.

In conclusion, particularly in the developing countries tuberculosis incidence and mortality are higher than expected and found in the patients undergoing hemodialysis. Diagnosis of tuberculosis is obscured because the symptoms are nonspecific and attributable to uremia. INH prophylaxis is cost-effective in 'high-risk' populations for tuberculosis. INH prevents hospitalizations, eliminates a possible need for multidrug therapy for active tuberculosis at a later date, and reduces mortality [16]. Therefore, there are good reasons for tuberculosis prophylaxis to be given to chronically dialyzed patients. This policy was recommended by the Advisory Council for the elimination of tuberculosis [31]. Prospective, double-blind, randomized studies will clarify the need of tuberculosis prophylaxis for dialyzed patients, particularly in areas highly endemic for tuberculosis.

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