

Tuberculosis and Chronic Renal Failure; Therapy Patterns

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ABSTRACT Summary Patients with chronic renal failure have a high incidence of tuberculosis, possibly due to a decrease in cellular immunity. Treatment of tuberculosis in these patients may be complicated by an increased risk of toxicity from tuberculosis drugs and careful monitoring for side-effects is essential in this group.

KEY WORDS keywords tuberculosis, chronic renal failure, treatment

Introduction

Text Tuberculosis is an important health threat for all dialyzed patients with final stage of chronic renal failure, the prognostic of this disease being severely worsened in these patients.

The chronic renal failure is associated with important deficiencies of the immune mechanisms.

Generally, the febrile reaction to infections in these patients is diminished, often absent.

Uremia is accompanied frequently by lymphopenia.

The response of T cells to mitogens, the delayed hypersensitivity as well as phagocytic activity of mononuclear cells are depressed in the presence of uremia.

The morphologic alterations of the parenchyma and of the airways that appear because of the uremia toxicity, are affecting the mucociliary clearance and the integrity of endothelial and epithelial barriers.

In addition, the associated chronic infections affinity is decreasing even more the capacity of local defense through nonspecific defense mechanisms.

The patients with chronic renal failure have a higher incidence of tuberculosis, this being estimated of 10 to 15 fold times more than the general population.

The mortality in dialyzed patients that are infected with the tuberculosis bacilli is twice more than the general population and 3,3 fold more than in dialyzed patients without this infection. Survival in these patients is small: 5 of 13 patients die in the first 3 months from the diagnosis of tuberculosis, before the completion of antituberculosis treatment.

Quick diagnosis of tuberculosis in dialyzed patients is delayed by the increased frequency of

extrapulmonary localizations and the nonspecific clinical symptoms that imply the debut of tuberculosis. Usually, more than 50% of these patients have been diagnosed with tuberculosis 12 months after the beginning of dialysis.

The extrapulmonary tuberculosis is more often seen in dialyzed patients, in about 50% more of these cases than in general population.

The peritoneal tuberculosis, a rare localization in immunocompetent hosts, represents an important form of manifestation in dialyzed patients.

There is no controlled randomized trial that might offer a baseline for treatment guidance in renal failure, the actual guides being based on series of reported cases, the knowledge of pharmaceutical characteristics of the medication in use as well as the experts recommendations in this domain, including the international agencies involved in the tuberculosis control.

The known factors that can influence tuberculosis treatment in renal failure are:

1. Drugs pharmacokinetics, especially drugs proportion excreted by the kidneys and their clearance by dialysis (haemodialysis and peritoneal dialysis). These factors may affect the serum levels of drugs therefore their toxicity.
2. The severity of toxicity anticipated by an escalation of serum drug levels and the possibility of alternative efficient drugs for the healing of tuberculosis patients.
3. Coexistence of diverse pathologies with the possibility of an interaction between various drugs that may affect antituberculous therapy.

The standard regimens are of 6 or 9 months duration.

The prolonged treatment is an individual decision based on specific clinical circumstances like the immunosuppressed cases or multiple organ extended tuberculosis.

Generally, when a reduced frequency of therapy administration is indicated, standard dosages are used, intermittent administration being preferred to a lower dosage, without compromising the regimens of treatment by the under dosed drugs serum therapeutic levels.

Multi drug resistance tuberculosis is treated with specific drugs according to drugs sensitivity.

Hemodialysis leads frequently to the elimination of the majority of antituberculous drugs and, therefore, antituberculous drugs are administered after dialysis. There are few data in literature regarding the drugs elimination by peritoneal dialysis.

Careful monitoring is essential, the adverse effects (mostly neuropsychic, hepatic or optic neuropathy) being highly encountered in renal failure patients, especially dialyzed ones.

Studies showed that 46% of the renal failure patients present adverse reactions to the antituberculosis drugs used, a percentage even higher in dialyzed patients with the same pathology.

These percentages are very high, knowing the fact that only 26% of normal renal function patients manifest adverse reactions to the antituberculosis drugs and only 5% of these reactions are important enough to determine the modification of the antituberculosis treatment scheme.

The antituberculosis treatment in moderate impaired renal function patients, with a rate of glomerular filtrate of 30-60ml, must be adapted by using standard medication in low doses, comparative with normal renal function patients.

If multi drug resistant tuberculosis is not an issue, then ethambutol must be avoided.

Elderly patients require special attention.

First line drugs for the treatment of tuberculosis must be used only after consultation with a specialist in tuberculosis treatment that will be able to supervise the drugs administration throughout the prescribed period of time.

The recommendations of the American Thoracic Society and European Respiratory Society regarding the use of antituberculosis treatment are:

Rifampicine

It is excreted especially over hepatobiliary path. 30% the most can be excreted unmodified in urine.

In younger patients, elevated concentrations do not achieve toxic levels. Thus, rifampicine can be administered to renal failure patients without dosage modification: 10 mg/kgc/day until a maximum of 600 mg/day in patients over 50 kg bodyweight and 450 mg/day in patients under 50 kg bodyweight.

Isoniazid

It is excreted especially over hepatobiliary path, that's why it can be used as normal dose of 5mg/kgc/day until a maximum dose of 300mg/day. Some studies have shown an elevated level of neurotoxicity attributed to isoniazid, including confusion and psychosis, especially in dialyzed patients. Thus, supplementary pyridoxine is essential when isoniazide is used in this type of patients.

Pyrazinamide

Its excretion is primary hepatic, but its metabolites can be partially excreted through the renal path. Hyperuricemia is also a problem in chronic renal failure patients.

Therefore, it is recommended that the dosage should be lowered proportional to the severity of the renal failure and that hepatic parameters should be carefully monitored.

Thus, it is recommended a dose of 25-35 mg/kgc in intermittent administration 3 times per week, with a maximum of 2 grams for patients over 50 kg bodyweight and 1,5 grams for those patients under 50 kg bodyweight, these doses being administered after dialysis.

Ethambutol

This drug is excreted especially by the kidneys, therefore its administration must be avoided. Ocular toxicity represents one of the dangers that are frequently encountered with this drug. Regular ophthalmologic exams are highly recommended. Ethambutol must be used only in special cases like the one of multi drug resistant tuberculosis. In these cases the frequency of ethambutol administration will be reduced to 3 times per week after dialysis.

For those patients with creatinine clearance of 50-100ml/min must be administered one dose of 25 mg/kgc/day 3 times per week.

If creatinine clearance is 30-50ml/min, the dose should be given twice per week.

If the creatinine clearance is 10-30ml/min, it has been suggested a dose of 15 mg/kgc/day every 36-48 hours.

Ethambutol will be avoided if the glomerular filtrate rate is below 10ml/min.

Ciprofloxacin

It is excreted by hepatic and renal paths. The adverse effects will be carefully monitored.

Also, the dose will be lowered to 500mg daily, after dialysis.

Moxifloxacin

It can be administered without dosage modification 400mg daily, after dialysis.

Prothionamide

It is excreted especially by hepatic path; it can be used in dose of 7,5-15 mg/kgc/day after dialysis, without exceeding 250-500mg/12 hours. It is recommended close monitoring of adverse reactions like hepatotoxic effects and neuropathy.

Streptomycin, amikacin, capreomycin

These drugs will be used only if their serum levels can be monitored. Recommended doses are 12-15 mg/kgc/day three times per week, after dialysis.

Cycloserine

This drug has a high risk of neurotoxicity especially in renal patients, therefore it must be avoided as much as possible. In special cases (multi drug resistance tuberculosis), it can be administered in lowered doses of 250mg/day or 500mg three times per week.

Clofazimine

It can be used only in patients with multi drug resistant tuberculosis in doses of 200-300mg daily.

Paraaminosalicylic acid (PAS)

It is excreted unmodified in urine, being able to cause acidosis. For this reason, it must be avoided the standard drug and it must be replaced by PASER granules, that are less toxic because they don't determine sodium retention. Doses will be unmodified, no more than 4 grams per day.

CONCLUSIONS

1. Isoniazid, rifampicine and pyrazinamide are metabolized especially by the liver and can be administered in renal failure.
2. Streptomycin as well as other aminoglycosides are excreted predominantly by the kidneys and therefore must be used with caution in renal failure.

3. Renal function must be measured before the initiation of antituberculous treatment. Streptomycin levels must be closely monitored in renal failure and for avoiding its toxicity serum levels must not exceed 4mg/l. If the patient is under dialysis, streptomycin must be given 4-6 hours before dialysis, or after dialysis.
4. The administration of ethambutol must be restricted in renal impairment. Its usage will be avoided if the glomerular filtrate rate is below 10 ml/min.

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