REVIEW ARTICLE

How should we treat tuberculosis in adult patients with chronic kidney disease?

Key messages from the British Thoracic Society Guidelines

Heather J. Milburn

Department of Respiratory Medicine, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

KEY WORDS

chronic kidney disease, guidelines, tuberculosis

ABSTRACT

This review highlights the key messages from the 2010 British Thoracic Society Guidelines on the management of *Mycobacterium tuberculosis* infection and disease in adult patients with chronic kidney disease. These guidelines were developed in response to many requests for advice from respiratory and infectious diseases physicians who treat patients with tuberculosis, as there was very little information available to help clinicians manage the disease in this population of often very sick patients. Renal units in the United Kingdom were prescribing variable chemoprophylaxis regimens that frequently had no basis in evidence, and drug doses used to treat tuberculosis were often inappropriate because of clinicians' natural concern about poisoning a patient with little or no renal function. The guidelines address these issues together with when and how to screen for latent infection and the different needs of patients with renal impairment, those needing dialysis and those with a transplanted kidney. It became very clear in compiling these guidelines that there is a shortage of both background information on rates of tuberculosis in such patients in countries with low background prevalence, and good randomized controlled trials of treatment regimens. Wherever possible, the recommendations made are evidence-based, but this was not always available. This review gives a summary of those recommendations and reiterates some of the important messages; in particular, tuberculosis should be managed with the full involvement of the chest or infectious diseases physician who is the local lead for this important infection.

Introduction The aim of this review is to highlight the key messages from the 2010 British Thoracic Society (BTS) Guidelines for the prevention and management of *Mycobacterium tuberculosis* infection and disease in adult patients with chronic kidney disease (CKD),[1] and to give some information on the background leading to the recommendations. It is not intended as a substitute for the full guidelines, which can be accessed at www.brit-thoracic.org.uk/tuberculosis/tuberculosis-guidelines.aspx. It is strongly recommended that clinicians faced with tuberculosis (TB) in a patient with advanced kidney disease refer directly to the guidelines for advice. The recommendations are based on the best evidence available or, where evidence is lacking, the advantages and disadvantages of possible options for management are discussed. The advice given cannot be fully comprehensive and there will always be patients who do not fit into the categories used. Much of clinical practice has developed from experience over many years and is not based on concrete evidence from trials. This kind of information is also valuable, however, when discussing possible advice. As there is little or no evidence to inform when to screen for latent TB infection (LTBI), for example, we have discussed the merits and disadvantages of various options and have suggested a rational approach, but it is for the individual clinician to make a judgment based on the particular circumstances (s)he encounters.

Background It is likely that TB will be seen more frequently in patients with CKD as people from

Correspondence to:
Heather J. Milburn, MSc, MD, FRCP, Chest Clinic, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK, phone: +44-207-188-5847, fax: +44-207-188-1289, e-mail: heather.milburn@gstt.nhs.uk
Received: August 2, 2010.
Accepted: August 2, 2010.
Conflict of interests: none declared.
Pol Arch Med Wewn. 2010; 120 (10): 417-422

TABLE Grades of renal impairment

stage 1 CKD: normal creatinine clearance and function but urinary tract abnormality, e.g., polycystic kidney, structural abnormality
stage 2 CKD: creatinine clearance 60–90 ml/min
stage 3 CKD: creatinine clearance 30–60 ml/min
stage 4 CKD: creatinine clearance 15–30 ml/min
stage 5 CKD: creatinine clearance <15 ml/min with or without dialysis

Abbreviations: CKD – chronic kidney disease

the areas of the world with high background levels of TB are also at increased risk of CKD.[2] Although the management of uncomplicated pulmonary TB is well established in patients with intact renal function, evidence for management of this disease in patients with CKD, on dialysis or following renal transplantation, is sparse and often conflicting. This lack of clarity has led to increased requests for advice from respiratory and infectious diseases physicians who manage TB in these patients.

In 2008, the Joint Tuberculosis Committee (JTC) of the BTS set up a working group to examine the available evidence and produce comprehensive guidance on screening for active TB disease and latent infection, together with management of these conditions in adult patients with CKD, on dialysis and following renal transplantation. In addition to several chest physicians with experience in both the management of TB and the production of guidelines, the group included renal physicians representing the Renal Association (United Kingdom [UK]), a microbiologist, infectious diseases physician, and pharmacologist. The JTC and BTS have been responsible for several other well-respected guidelines relating to the management of TB,[3-5] and we hope the current guidelines will be similarly useful. They are based on current practice in the UK but should be equally relevant to the rest of Europe. In the UK, the 1998 and 2000 BTS guidelines were largely superseded by the National Institute for Clinical Excellence (NICE) guidelines in 2006,[6] but these gave very little help on how to manage TB in patients with renal disease. The American Thoracic Society had a larger section on treatment of TB in renal disease in their 2003 TB guidelines,[7] and we referred to these and incorporated some of the recommendations, particularly those regarding drug dosage. The new BTS guidelines have also, however, given recommendations on screening and management of LTBI and prophylaxis for patients going on to transplantation.

Each recommendation in the guidelines is graded by the strength of the supporting evidence using the revised Scottish Intercollegiate Guidelines Network grading system. Levels of evidence are graded from 1++ ("high quality meta-analyses, systematic reviews of randomized controlled trials [RCTs] or RCTs with very low risk of bias") through to 4 ("expert opinion"), and recommendations graded from A through to D, where A indicates high levels of evidence and D low levels. The quality of evidence in this field is generally limited, with much based on case series rather than RCTs, and this is reflected in 13 of the 22 recommendations being graded D and only 6 graded A.

Levels of renal impairment in CKD have been graded according to the criteria used by the Renal Association (UK) and are shown in the **TABLE**.

What is the extent of the problem of tuberculosis in chronic kidney disease? Immunodeficiency is a feature of CKD and this is further compounded by immunosuppressive therapy, making these patients more susceptible to reactivation of LTBI or new infection. Identifying patients at risk of TB is not always straightforward, and diagnosing active disease can be delayed as the clinical presentation may be uncharacteristic. Extrapulmonary disease, particularly peritoneal disease, is relatively common and symptoms may be nonspecific.

Both CKD and TB are more common in Asians and black people than in the indigenous white population in the UK,[2] but there is little information on the prevalence of TB in CKD in countries with low background prevalence. Most of the published case series are from areas of the world with high background rates of TB, and reported case rates are enormously variable but always high. In attempting to quantify the risk of developing active TB, we have used the relative risks reported by NICE:[6] × 20 for patients with CKD or on dialysis, and × 37 for renal transplant recipients. These figures are, however, based on a small series from 1983,[8] and management of rejection following transplant has been refined considerably since then, leading to a rise in infective complications. It is likely, therefore, that this risk has increased over time, and new studies are needed from countries in Europe and North America with relatively low background rates of TB. There have been very few studies in patients on peritoneal dialysis and case rates are difficult to determine.

When and how should we screen for latent tuberculosis infection? Given the substantially increased risk of active TB in patients with CKD, on dialysis or awaiting transplant, there is clearly a need to try to reduce that risk. There are, however, conflicting data on when and how these patients should be screened for LTBI. Some groups recommend tuberculin skin testing (TST) for all with CKD or as evaluation of potential transplant recipients,[9,10] but, because of underlying immunodeficiency, this test lacks sensitivity in these patients, with reported anergy rates of up to 50%.[1] A positive test can be helpful but a negative result cannot be assumed to be a true negative. The interferon gamma release assays (IGRA) have not been fully evaluated in these patients, but the limited evidence to date suggests that both the QuantiFERON-Gold tests (Cellestis, Australia) and the T-SPOT.*TB* (Oxford Immunotec, UK) are probably more useful screening tools for LTBI in this patient group than the TST. Indeterminate

assays are, however, more likely in this population, and there is scant evidence on negative predictive values. It is therefore important to interpret them in the light of previous history of TB, foreign travel, ethnic and environmental background, and radiographic changes.

Screening of all patients with CKD, or even just those on hemo- or peritoneal dialysis, would be time consuming and expensive and unlikely to be cost-effective. It is recommended that screening in this group should be by good clinical practice of detailing any history of prior TB and its treatment, TB contact, a clinical examination, and a chest radiograph in any patient at high risk (those of Asian or African ethnic origin and anyone born in an area of high background risk). An IGRA test, with or without a TST, can be used if there is concern, but routine assessment of these patients using these screening tests is not recommended. Any patient with an abnormal chest radiograph consistent with previous TB, but who has been adequately treated, should be monitored regularly, and renal physicians may wish to seek advice from the local respiratory or infectious diseases physician who is the lead for TB. Neither the TST nor IGRA tests are suitable for such patients with a positive history as none of them is able to distinguish between distant and recent infection.

The risk of developing active TB following renal transplantation is particularly high, and screening may be beneficial in this group. This can be achieved while the patient is on the waiting list for transplantation so that chemoprophylaxis may be given before transplantation, reducing the problematic drug interactions with posttransplant immunosuppression. The guidelines give tables for individual risk assessments. In general, these show that all black and Asian patients and those born overseas should be screened and considered for prophylaxis, either before or after transplant. In many renal units, the current practice is to give blanket chemoprophylaxis to all at-risk transplant recipients without assessment. Inevitably, this means that some patients will receive chemoprophylaxis without evidence of LTBI. Whether or not this has any advantages over screening and targeted treatment is, however, unknown.

How should we give chemoprophylaxis? Chemoprophylaxis for TB itself carries a risk, particularly of hepatitis, and the rates of drug-induced hepatitis from various regimens are given in the guidelines. These rates are, however, taken from studies in populations with intact renal function, and it is possible that they may be different in the renally impaired. In patients at low risk of LTBI and where there is no evidence from a positive TST or IGRA test, the risk of hepatitis from chemoprophylaxis often outweighs that of development of active TB, thus mitigating against routine chemoprophylaxis for all transplant recipients. Generally, it is recommended that the decision on a chemoprophylactic regimen should be taken with the involvement of a TB specialist. Some important recommendations are made on dosages to dispel myths about dose reductions. Isoniazid and rifampicin can generally be used in normal doses in CKD, during dialysis or following renal transplantation. Adequate regimens given are: 6 months isoniazid (300 mg) daily, or 15 mg/kg 3 × per week (max. 900 mg) in stages 4 and 5 CKD and dialysis, plus pyridoxine 10–25 mg daily; 3 months rifampicin plus isoniazid plus pyridoxine in normal daily doses for weight; 4–6 months rifampicin alone in normal daily doses for weight.

Long-term use of isoniazid is not recommended. There is no evidence to support use of lower doses as these are inadequate for treatment of LTBI and lead to lower peak levels and possible development of drug resistance. Vigilance should always be maintained for signs of toxic side effects or the possible development of active TB in these patients.

Making a diagnosis of active tuberculosis Extrapulmonary TB is common in renal patients, occurring in 30% to 50% of cases of TB, and classic symptoms are not always present. Peritoneal disease has been reported to occur in 57% of patients on dialysis.[11] The possibility of TB should always be considered in any patient with a chronic cough, unexplained weight loss or night sweats, a cloudy peritoneal dialysate, lymphadenopathy or chronic site-specific symptoms. Appearances on a chest radiograph should be compared with previous films and, if new abnormalities are present, advice should be sought from a respiratory physician. Every effort should be made to obtain a specimen for culture and sensitivity. Histological appearances of granulomata, with or without caseation or necrosis, are helpful, but a portion of all biopsy specimens should be sent in a plain pot (without formalin) to the microbiology laboratory for culture. Patients producing sputum should be asked for 3 consecutive early morning specimens for direct smear, culture, and sensitivity. New chest radiograph abnormalities should prompt additional investigations if sputum is not available, such as induced sputum or flexible bronchoscopy. Mediastinal lymph nodes can be assessed by endobronchial ultrasound-guided transbronchial needle aspiration or mediastinoscopy, depending on local availability.

Optimal management of tuberculosis in renal disease Patients found or suspected of having active pulmonary TB should be isolated, preferably in negative pressure facilities. Positive pressure rooms should never be used for these patients, particularly on renal units, as the infection could be disseminated to other vulnerable patients.

The pharmacological properties of the antituberculous drugs have been extensively reviewed, but clear guidance on dosing, dosage schedule,

therapeutic drug monitoring, timing of administration in relation to dialysis, and concomitant use of immunosuppressive drugs was lacking. In these guidelines, we have put forward suggestions for dosing and dosing schedules in patients with CKD, on dialysis and following renal transplantation, based on the evidence available and incorporating some of the recommendations made by the American Thoracic Society.[7]

All cases of active TB should be managed by either a chest or infectious diseases physician who is the local lead for TB. The management of TB should follow national guidelines, with 4 drugs for the first 2 months followed by 2 drugs for a further 4 months for most cases of fully sensitive disease. TB of the central nervous system is an exception to this general rule and treatment should be for 1 year. Symptoms and signs consistent with TB should stimulate initiation of treatment (once appropriate diagnostic samples have been taken) without waiting for culture results. If signs and symptoms are consistent with TB and/or there is a response to treatment, the drug regimen should be continued, even if culture results are negative.

Is drug toxicity a particular problem? Adverse effects of antituberculous treatment have been found to be more common in patients with renal disease than in those with normal renal function.[12] Rifampicin does not cause increased problems in patients with impaired renal function as it is metabolized by the liver and only about 10% is found unchanged in the urine. Isoniazid is also metabolized by the liver into less active compounds and most clearance occurs from hepatic metabolism. The half life is, however, increased by about 45% in slow acetylators and neuropsychiatric disturbance has been reported. Pyrazinamide is also metabolized by the liver but elimination of its metabolites may be delayed in patients with stages 4 and 5 CKD and in those on hemodialysis, leading to uric acid retention and gout. Around 80% of ethambutol is excreted unchanged by the kidneys so accumulation of this drug is inevitable in patients with impaired renal function. The same is true of the aminoglycosides.

Chronic kidney disease The reported increases in adverse effects of these drugs have led to manipulation of drug doses, which has not always been appropriate. It is clear that increasing the interval between doses of pyrazinamide, ethambutol, and the aminoglycosides in patients with stages 4 and 5 CKD or those on dialysis is definitely preferable to reducing the dose. These drugs exhibit concentration-dependent activity and lower doses may reduce drug efficacy. Evidence shows that the efficacy of both ethambutol and pyrazinamide improves when the drugs are administered in higher doses less often than in lower doses daily.[1] Rifampicin may be given in normal daily doses and isoniazid may be given in normal daily doses or as 15 mg/kg (max. 900 mg) 3 times per week in those with severely compromised renal function. Serum levels of ethambutol and the aminoglycosides should be monitored, or moxifloxacin may be used as an alternative to ethambutol, but this is only suitable for a daily dosing regimen. Isoniazid, rifampicin, pyrazinamide, ethambutol/moxifloxacin should be the first line of treatment used. Pyridoxine supplementation should be given with isoniazid to prevent the development of peripheral neuropathy. A fourth drug is needed because of the rising incidence of isoniazid resistance and the disproportionate number of ethnic minority cases with CKD.

Hemodialysis Dose intervals should be increased to 3 times per week to coincide with dialysis sessions and reduce the risk of drug accumulation and toxicity. There are arguments for both giving the drugs 4 to 6 hours before dialysis or immediately after dialysis. The advantage of giving the drugs 4 to 6 hours before dialysis is that the possibility of ethambutol or pyrazinamide toxicity is reduced. However, the drug may be prematurely removed, leading to suboptimal levels, and it also raises practical issues for morning shift patients. The advantages of giving the medication immediately after dialysis include avoiding premature drug removal, offering the opportunity for directly observed therapy, together with it being practically easier, especially for morning shift patients. There is, however, the possible risk of raised drug levels of ethambutol and pyrazinamide between dialysis sessions, and therapeutic drug monitoring is useful if this is a concern. The choice of strategy may be influenced by a need to ensure adherence, practical issues, and expected pharmacokinetics or drug interactions.

Peritoneal dialysis Mechanisms for drug removal during peritoneal dialysis differ from those in hemodialysis, so it cannot be assumed that the same recommendations apply to both modes of dialysis. Patients may require careful monitoring, although one study has shown that no dose adjustment was necessary for isoniazid, rifampicin, or pyrazinamide.[13] Rifampicin, however, because of its high molecular weight and lipid solubility, is less dialyzable through the peritoneal membrane, with only minimal amounts recovered in the dialysate, implying that oral administration of rifampicin may not be adequate for the treatment of peritoneal TB.[13] There is very little published work on this topic and multicenter studies are needed to give us a greater understanding of the best dosing schedules to use in these patients.

The introduction of continuous renal replacement therapy in critically ill patients has raised questions on how to manage TB in these patients. As yet there are no studies on which to base any guidance.

Renal transplantation The main difficulty encountered when treating TB after renal transplantation

is the interaction of particularly rifampicin with immunosuppressive regimens, increasing the risk of graft rejection. Doses of mycophenylate mophetil, tacrolimus, and ciclosporin may need adjustment and levels of these drugs should be monitored. As a general rule, corticosteroid doses should be doubled in patients taking rifampicin. Once rifampicin has been stopped, liver enzyme induction usually takes 2 weeks to return to normal. Although renal function usually returns to normal after transplantation, this may vary and modifications to the antituberculous regimen may be necessary depending on the level of transplant function.

Drug-resistant disease There is an appendix to the guidelines dealing with second-line drugs used in the management of drug-resistant disease. These drugs must only be used with the full involvement of a specialist with experience in the management of drug-resistant TB to reduce the risk of development of further resistance. Experience with these drugs in patients with impaired renal function is limited. A dosing table is given but drug levels should be monitored wherever possible.

Summary The new BTS guidelines represent a major synthesis of the available evidence to support the investigation and management of LTBI and active TB in patients with various levels of renal impairment. The quality of evidence is, however, surprisingly patchy, often necessitating a discussion of alternative management strategies. There is clearly a need for well designed RCTs in some areas.

REFERENCES

1 Milburn HJ, Ashman N, Davies P, et al.; British Thoracic Society Standards of Care Committee and Joint Tuberculosis Committee Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. Thorax. 2010; 65: 557-570.

2 Lightstone L. Preventing renal disease: the ethnic challenge in the United Kingdom. Kidney Int. 2003; 63: S135-138.

3 Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax. 1998; 53: 7: 536-548.

4 Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Joint Tuberculosis Committee of the British Thoracic Society. Thorax. 2000; 55: 11: 887-901.

5 British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-a treatment. Thorax. 2005; 60: 800-805.

6 The National Collaborating Centre for Chronic Conditions. Tuberculosis. Clinical diagnosis and management of tuberculosis and measures for its prevention and control March 2006. http://www.nice.org.uk/nicemedia/pdf/CG033FullGuideline.pdf. Accessed July 28, 2010.

7 Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med. 2003; 167: 603-662.

8 Lichtenstein IH, MacGregor RR. Mycobacterial infections in renal transplant recipients: report of five cases and review of the literature. Rev Infect Dis. 1983; 5: 216-226.

9 CDC and MMWR. Targeted tuberculin testing and treatment of latent tuberculosis infection 9 June 2000/Vol. 49/No. RR-6. http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf. Accessed July 28, 2010.

10 Aguado HM, Torre-Cisneros J, Fortun J, et al. Tuberculosis in solid-organ transplant recipients: Consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. Clin Infect Dis. 2009; 48: 1276-1284.

11 Quantrill SJ, Woodhead MA, Bell CE, et al. Peritoneal tuberculosis in patients receiving continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant. 2001; 16: 1024-1027.

12 Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. Tuberc Lung Dis. 1996; 77: 37-42.

13 Ahn C, Oh KH, Kim K, et al. Effect of peritoneal dialysis on plasma and peritoneal fluid concentrations of isoniazid, pyrazinamide, and rifampicin. Perit Dial Int. 2003; 23: 362-367.

ARTYKUŁ POGLĄDOWY

Jak leczyć gruźlicę u dorosłych z przewlekłą chorobą nerek?

Główne przesłania z wytycznych British Thoracic Society

Heather J. Milburn

Department of Respiratory Medicine, Guy's and St Thomas' NHS Foundation Trust, Londyn, Wielka Brytania

SŁOWA KLUCZOWE

gruźlica, przewlekła choroba nerek, wytyczne

STRESZCZENIE

W niniejszej pracy poglądowej przedstawiono zasady postępowania w przypadku zakażeń wywołanych przez *Mycobacterium tuberculosis* u dorosłych z przewlekłą chorobą nerek wg wytycznych British Thoracic Society. Wytyczne te opracowano z powodu licznych próśb o poradę skierowanych do pulmonologów i lekarzy chorób zakaźnych, którzy opiekują się chorymi na gruźlicę, oraz z uwagi na brak informacji skierowanych do lekarzy leczących gruźlicę w tej populacji chorych. W ośrodkach nefrologicznych w Wielkiej Brytanii często stosowano bardzo zróżnicowane schematy leczenia, które nie były oparte na dowodach naukowych, oraz podawano nieodpowiednie dawki leków (ze względu na obawy przed „zatruciem" pacjentów ze znacznie upośledzoną czynnością nerek). Niniejsze wytyczne odnoszą się do tych zagadnień, a także precyzują, kiedy i jakie badania przesiewowe należy wykonywać w celu wykrycia zakażenia utajonego oraz jakie są różnice w leczeniu pacjentów z upośledzeniem czynności nerek, wymagających leczenia dializami i chorych po przeszczepieniu nerki. Podczas opracowywania zaleceń w pełni ujawnił się niedostatek informacji, zarówno na temat częstości występowania gruźlicy u osób w krajach z małą ogólną chorobowością, jak i brak danych pochodzących z dobrze przeprowadzonych kontrolowanych badań z randomizacją, oceniających różne schematy leczenia. Tam gdzie było to możliwe, zalecenia oparto na danych naukowych, jednak nie zawsze były one dostępne. Niniejsza praca poglądowa jest podsumowaniem tych zaleceń. Szczególnie istotny jest wniosek o konieczności leczenia gruźlicy przy pełnej współpracy pulmonologa lub specjalisty chorób zakaźnych, który kieruje zwalczaniem tej infekcji w danym regionie.

Adres do korespondencji:
Heather J. Milburn, MSc, MD, FRCP, Chest Clinic, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK, tel.: +44-207-188-5847, fax: +44-207-188-1289, e-mail: heather.milburn@gstt.nhs.uk
Praca wpłynęła: 02.08.2010.
Przyjęta do druku: 02.08.2010.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2010; 120 (10): 417-422
Tłumaczył dr med. Robert Drabczyk