

Tuberculosis in renal transplant recipients: Challenges in developing countries

Authors

João Egidio Romão Junior¹

¹ Beneficência Portuguesa Hospital.

The number of kidney transplanted patients has grown significantly in developing countries, primarily driven by an epidemic of chronic kidney disease.¹ In Brazil alone, over 100,000 patients are maintained on chronic dialysis program, and such prevalence is in constant growth.^{2,3}

Kidney transplant recipients are a risk group for primary infections and reactivation of latent *Mycobacterium tuberculosis* infection, with diagnostic and treatment challenges that are specific to this group of patients: difficulty in diagnosing tuberculosis (TB), not always with typical clinical features, high risk of spread, high mortality rate and low sensitivity of diagnostic techniques available in locations distant from major transplant centers, in addition to the high toxicity; and interactions between anti-TB drugs with anti-rejection immunosuppressive agents.^{4,7}

Most cases of tuberculosis in renal transplant patients (TBTxR) occur by reactivation of a latent infection in the first months after surgery and during the period of most intense immunosuppression. However, primary infections have been reported as well as exceptional cases of tuberculosis transmitted by the renal graft itself.⁵

The incidence of this serious complication after renal transplantation is related to global geographic areas, ranging from 0.35% to 15% - being more common in developing countries with high TB prevalence in the general population.^{6,7} In a recent meta-analysis, pooled TB prevalence in kidney

transplanted patient was 2.51%; and based on publications from the last 15 years, that is about 14 times higher than the reported prevalence in the general population; for countries with high TB prevalence, the meta-regression analysis reported a TBTxR prevalence 43 times higher than that for the general the population.⁶ Thus, TBTxR prevalence is very high in Asian patients (up 14.7%), falling to mean values near 2.5-3.0% in Central Europe, Northern Africa, and Latin America, being 0.5% in Western Europe and North America (Table 1).

Given these TBTxR prevalence rates in developing countries, it is mandatory that every kidney recipient and donor be submitted to a well-established routine concerning TB diagnosis (and latent TB infection). The physician should take a thorough medical history (occupation, travels, TB past and exposure and use of anti-TB drug), and imaging tests (chest radiograph). In specific cases, the use of tuberculin skin test (PPD) and interferon-gamma release tests - IGRA (QuantiFERON-TB Gold and T-SPOT.TB) may aid in the diagnosis of latent TB. However, a study analyzing the accuracy of these tests showed low sensitivity (31%, 53% and 50%, respectively) and specificity (63%, 69% and 67%, respectively), with PPD showing lower sensitivity and comparable specificity.⁸

In addition to the epidemiological risk of each region, TBTxR risk factors include: recipient characteristics (advanced age, diabetes, chronic

Submitted on: 10/05/2014.

Approved on: 10/08/2014.

Correspondence to:

João Egidio Romão Junior.
Clínica de Nefrologia e
Transplantes, Beneficência
Portuguesa Hospital.
Rua Maestro Cardim, nº 560, cj
172, SP, Brasil. CEP: 01323-001.
E-mail: joao.egidio@uol.com.br

DOI: 10.5935/0101-2800.20140060

TABLE 1 TUBERCULOSIS PREVALENCE IN KIDNEY TRANSPLANTED PATIENTS, ACCORDING TO GEOGRAPHIC REGIONS [REF 6,9^{MODIF}]

Regions	Countries	TbTxR Prevalence (var.)
Asia	China. Thailand. India. Pakistan. Sri Lanka	4.4 (1.3-14.7)
Northern Europe	Egypt. Tunisia	3.2 (1.4-3.8)
Central Europe	Slovenia. Serbia. Poland. Turkey	2.6 (1.2-5.8)
Latin America	Brazil. Mexico. Colombia	2.4 (1.7-4.5)
Western Europe	Belgium. Spain. France	0.5 (0.4-1.6)
North America	United States	0.4 (0.3-0.4)

liver disease, and previous transplantation), medical history (lung images compatible with TB, positive PPD, exposure to TB), post-transplant complications (CMV, pneumonia by *Pneumocystis jiroveci* and *Nocardia*) and use of more intensive immunosuppression.⁹

All TB high risk patients should be submitted to prophylaxis, taking into account that most cases of TBTxR are associated with reactivation of latent infections with immunosuppression and that there are difficulties with the correct diagnosis of this disease. The overall prophylaxis is not recommended due to the high incidence of drug complications.¹⁰ The drug of choice for this prophylaxis is isoniazid, used in the first months after the transplant.

TB diagnosis in kidney transplanted patients is usually difficult, challenging and almost always late.^{4,7} Extrapulmonary and disseminated manifestations are not uncommon, with nonspecific symptoms which are different from those seen in the general population. In this context, TB should be part of the differential diagnosis of febrile conditions in renal transplant patients. Diagnosis is confirmed by finding the acid-fast bacilli (AFB) in material collected from the patient, its growth in specific culture media, or characteristic histological diagnosis of TB and the use of PCR (polymerase chain reaction).

Recommendations for TB treatment in kidney transplanted patients follow the traditional regimens proposed,^{4,5,7,9} and early treatment is

critical to good patient outcome. Another concern is the interaction between anti-TB drugs with immunosuppressive agents. Rifampicin is an inducer of P450 cytochrome enzymes, reducing serum levels of calcineurin inhibitors (cyclosporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus) and corticosteroids, which may result in renal allograft rejection and loss.⁷ TBTxR patient mortality is also high in relation to TB in the general population, with rates up to 34.9% being described.^{7,9,10}

In this issue of the Journal of Nephrology, Higuera *et al.* show tuberculosis data in kidney transplant patients from Colombia.¹¹ The authors analyzed 641 transplant patients, with 12 confirmed cases of TB (gross incidence of 1.87%) in eight years of monitoring. As described, extrapulmonary presentation was observed in one third of the cases, a high incidence of hepatotoxicity associated with anti-TB drugs, TBTxR related to acute rejection and renal allograft dysfunction, and high mortality (16.7%).

Recently in Brazil, transplant centers of excellence have described their experiences with TBTxR. Guida *et al.* reported 23 cases of TBTxR among 1,342 transplants performed (1984-2007), an incidence of 1.71%, with 3 deaths caused by TB.¹² In another retrospective analysis, Matuck *et al.* analyzed 982 transplants (1981-2002); of these, 44 developed TB after transplantation and the overall mortality was 34.9%.¹³ Already with data from the last decade (2000-2010), Marques *et al.* reported 43 (2.8%) TBTxR cases among 1,549 transplant recipients, with an incidence of 803 cases/100,000 patients.¹⁴ Only 7% of the cases had a history of TB, and TB prophylaxis was not routinely employed. The incidence of rejection was high and mortality was 12%, all attributed to TB.

More recently, de Lemos *et al.* reported 535 kidney transplant patients, with 274 considered of high risk for TB.¹⁵ The overall cumulative incidence was 2.1%. Among patients at low risk for TB, the incidence of TBTxR was 1%, while among those at high risk, the incidence of TBTxR was only 0.7% for those treated prophylactically, and 7% among 75 high risk patients who did not receive isoniazid prophylaxis. Thus, the authors concluded on the importance of chemoprophylaxis in patients at high risk for TB.

In conclusion, several studies show increased risk of TBTxR in developing countries, with no concrete evidence of the effectiveness of strategies for prevention, early diagnosis and reducing rates of morbidity and mortality in these patients.⁶ Clinical monitoring of renal transplant recipients in developing countries should consider constant monitoring, maintaining a high index of clinical suspicion for TB, following the particularities of this patient population.

REFERENCES

1. Medina-Pestana JO, Duro-Garcia V. Strategies for establishing organ transplant programs in developing countries: the Latin America and Caribbean experience. *Artif Organs* 2006;30:498-500. DOI: <http://dx.doi.org/10.1111/j.1525-1594.2006.00250.x>
2. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Watanabe Y, dos Santos DR. Report of the Brazilian Chronic Dialysis Census 2012. *J Bras Nefrol* 2014;36:48-53. DOI: <http://dx.doi.org/10.5935/0101-2800.20140009>
3. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Watanabe Y, dos Santos DR. Brazilian Chronic Dialysis Survey 2013 - Trend analysis between 2011 and 2013. *J Bras Nefrol* 2014;36:476-84
4. British Thoracic Society Standards of Care Committee and Joint Tuberculosis Committee; Milburn H, Ashman N, Davies P, Doffman S, Drobniewski F, Khoo S, et al. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. *Thorax* 2010;65:557-70. PMID: 20522863
5. Morris MI, Daly JS, Blumberg E, Kumar D, Sester M, Schluger N, et al. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. *Am J Transplant* 2012;12:2288-300. DOI: <http://dx.doi.org/10.1111/j.1600-6143.2012.04205.x>
6. Reis-Santos B, Gomes T, Horta BL, Maciel EL. Tuberculosis prevalence in renal transplant recipients: systematic review and meta-analysis. *J Bras Nefrol* 2013;35:206-13. DOI: <http://dx.doi.org/10.5935/0101-2800.20130033>
7. Hsu MS, Wang JL, Ko WJ, Lee PH, Chou NK, Wang SS, et al. Clinical features and outcome of tuberculosis in solid organ transplant recipients. *Am J Med Sci* 2007;334:106-10. PMID: 17700199 DOI: <http://dx.doi.org/10.1097/MAJ.0b013e31812f5a4e>
8. Ferguson TW, Tangri N, Macdonald K, Hiebert B, Rigatto C, Sood MM, et al. The Diagnostic Accuracy of Tests for Latent Tuberculosis Infection in Hemodialysis Patients: A Systematic Review and Meta-Analysis. *Transplantation* 2014 Oct 3. [Epub ahead of print] DOI: <http://dx.doi.org/10.1097/TP.0000000000000451>
9. Muñoz P, Rodríguez C, Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. *Clin Infect Dis* 2005;40:581-7. PMID: 15712081 DOI: <http://dx.doi.org/10.1086/427692>
10. Currie AC, Knight SR, Morris PJ. Tuberculosis in renal transplant recipients: the evidence for prophylaxis. *Transplantation* 2010;90:695-704. DOI: <http://dx.doi.org/10.1097/TP.0b013e3181ecea8d>
11. Higuaita LMS, Nieto-Ríos JF, Daguer-Gonzalez S, Ocampo-Kohn C, Aristizabal-Alzate A, Velez-Echeverri C, et al. Tuberculosis in renal transplant patients: The experience of a single center in Medellín-Colombia, 2005-2013. *J Bras Nefrol* 2014;36:512-8.
12. Guida JP, Bignotto Rosane D, Urbini-Santos C, Alves-Filho G, Ribeiro Resende M, Mazzali M. Tuberculosis in renal transplant recipients: a Brazilian center registry. *Transplant Proc* 2009;41:883-4. DOI: <http://dx.doi.org/10.1016/j.transproceed.2009.01.075>
13. Matuck TA, Brasil P, Alvarenga Mde F, Morgado L, Rels MD, da Costa AC, et al. Tuberculosis in renal transplants in Rio de Janeiro. *Transplant Proc* 2004;36:905-6. DOI: <http://dx.doi.org/10.1016/j.transproceed.2004.03.093>
14. Marques ID, Azevedo LS, Pierrotti LC, Caires RA, Sato VA, Carmo LP, et al. Clinical features and outcomes of tuberculosis in kidney transplant recipients in Brazil: a report of the last decade. *Clin Transplant* 2013;27:E169-76. DOI: <http://dx.doi.org/10.1111/ctr.12077>
15. de Lemos AS, Vieira MA, Halpern M, Quaresma RG, Borchardt AC, Santos MA, et al. Results of implementation of preventive recommendations for tuberculosis after renal transplantation in an endemic area. *Am J Transplant* 2013;13:3230-5. DOI: <http://dx.doi.org/10.1111/ajt.12470>