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OBM Transplantation

Review

Chagas Disease, Leishmaniasis, and Malaria in Solid Organ Transplant Recipients

Spinello Antinori [1, 2, *], Laura Milazzo [2]

1. Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Via GB Grassi 74, Milan, Italy; E-Mail: spinello.antinori@unimi.it
2. III Division of Infectious Diseases, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, Via GB Grassi 74, Milan, Italy; E-Mail: laura.milazzo@unimi.it

* **Correspondence:** Spinello Antinori; E-Mail: spinello.antinori@unimi.it

Academic Editor: Maricar Malinis

Special Issue: Diagnosis and Management of Infections in Solid Organ Transplant Recipients

OBM Transplantation
2019, volume 3, issue 1
doi:10.21926/obm.transplant.1901039

Received: October 28, 2018
Accepted: January 02, 2019
Published: January 15, 2019

Abstract

Solid organ transplantation (SOT) is increasingly employed worldwide to treat several diseases causing both acute and chronic organ failure. Recipients of SOT are at an increased risk to develop infections as a consequence of immunosuppressive therapy. Sometimes such infections may be acquired by the transplanted organ or by reactivation of a previously acquired latent infection. The globalization and the increase of international travel poses a risk for exposure to infections such as Chagas disease (CD), leishmaniasis, and malaria endemic in tropical and subtropical areas of the world. We have reviewed the literature regarding risk factors, clinical presentation, diagnosis, and treatment of CD, leishmaniasis, and malaria in the setting of SOT.

Keywords

Chagas disease; leishmaniasis; malaria; solid organ transplantation; *Trypanosoma cruzi*; *Leishmania infantum*; *Plasmodium falciparum*; *Plasmodium vivax* ; review

1. Introduction

The role of protozoan infections among solid organ transplant (SOT) patients is becoming increasingly recognised in both endemic and non-endemic countries, although these infections are generally considered rare [1-3].

Diagnosis and treatment of infections such as Chagas disease, malaria, and leishmaniasis in the setting of SOT is challenging due to multiple factors; to help clinicians to properly manage them, several guidelines and recommendations have been published in recent years [4-9]. The use of immunosuppressive drugs in transplant patients means that such protozoan infections not only can be acquired *de-novo* (by vectors, transfusion, and the organ transplanted), but can also undergo reactivation in those with latent infection due to the induced immunosuppression.

In the present review, we consider risk factors, clinical presentations, diagnosis, and treatment regarding Chagas disease (American trypanosomiasis), leishmaniasis, and malaria in the setting of SOT recipients with perspectives of how to screen and follow-up latent infections.

2. Chagas Disease

2.1 Introduction

Chagas disease (CD), or American trypanosomiasis, is a protozoan infection caused by *Trypanosoma cruzi*. Initially described by Carlos Chagas in Brazil at the beginning of 20th century, it is widespread and endemic in Mexico as well as Central and South America, where 6 million people are infected and 65 million people at risk of contracting the infection [10]. However, the huge migration from Latin America to the United States and Europe has driven the emergence of CD in these countries with an estimated 68,000-122,000 cases in Europe and 300,000 in the United States [11-13]. A recent systematic review and meta-analysis showed a pooled prevalence of CD of 4.2% in five European countries, with the highest one (18.1%) found among Bolivian immigrants [14].

Although CD has been considered a vector-borne disease transmitted to humans by hematophagous triatomine bugs (known as “kissing bugs”), the parasite can also be transmitted from a mother to her newborn, by transfusion of infected blood, the oral route, and by organ transplantation [15]. The first evidence of possible CD transmission by organ transplantation was during the early 1980s in Brazil and Chile [16, 17]. In the United States, the first reported case of donor-derived CD was in 2001 [18]. Since then, CD has been reported in kidney, liver, heart, and lung recipients [19-22].

CD in SOT recipients can occur through three possible mechanisms: 1) transmission from chronically infected donors, 2) reactivation of latent infection in the recipient, or 3) infection acquired after transplant due to endemic exposure or possibly from transfusion of infected blood product.

2.2 Risk of Transmission by Infected Donor

The assessment of the risk of transmission of CD by organ transplantation from seropositive donor (D+) to seronegative recipient (R-) is based on a limited number of studies, which are generally retrospective and with short follow-up, as seen in Table 1 [21-30]. The average

prevalence was 19.3%, ranging from 9.6% for kidney transplant, 17.1% for liver transplant, to 75% for heart transplant [24, 27-30]. It is worth noting that in Argentina, the prevalence of *T. cruzi* infection among effective donors doubled (from 2.46% to 4.6%) from 2005 to 2009 [31]. A risk that is not negligible was also observed in Brazil, where among 2,822 potential organ donors, 1.3% had a positive *T. cruzi* serology, and the prevalence rate increased from 1.0% in 2010 to 1.6% in 2015 [32].

Table 1 Transmission from *Trypanosoma cruzi* seropositive donors to seronegative recipients (case studies and cohort studies).

Organ	Author/Reference	Country of transplant	N (%)	Prophylaxis	Parasitaemia after transplant	Time onset, median (range)	Outcome N° deaths/N° patients (%)
Kidney	Riarte/[23]	Argentine	3/16 (18.7)	No	3/3	60 (37-165) days	1/16 (6.2) unrelated to CD
	Sousa/[24]	Brazil	0/9 (0)	Yes	0/9	Nihl	0/10
	Huprikar/[21]	USA	2/16 (12.5)	No	2/2	11 weeks (5-17)	3/16 (18.7)
	Cicora/[25]	Argentine	0/6 (0)	No	0/6	Nihl	NR
	Cura/[26]	Argentine	1/15 (6.7)	No	NR	NR	NR
Liver	Barcan/[19]	Argentine	1/1 (100)	No	1/1	84 days	1/1 (100) unrelated to CD
	D'Albuquerque/[27]	Brazil	0/6 (0)	Yes	0/6	Nihl	2/6 (33.3) unrelated to CD
	Salvador/[28]	Spain	0/2 (0)	Yes	0/2	Nihl	1/2 (50) unrelated to CD
	McCormack/[29]	Argentine	2/9 (22.2)	Yes	2/9	3 months	2/9 (22.2) unrelated to CD
	Cura/[26]	Argentine	5/10 (50)	No	2/2	39,5 days	NR
	Huprikar/[21]	USA	2/9 (22.2)	No	1/1	10 weeks	3/11 (27.3)
	Balderramo/[30]	Argentine	0/4 (0)	Yes	0/4	Nihl	1/4 (25)
Heart	Huprikar/[21]	USA	3/4 (75)	No	1/1	7 weeks (3-9)	2/4 (50)
Lung	Huprikar/[21]	USA	1/1 (100)	No	1/1	NR	0/1
	Cura/[26]	Argentine	1/1 (100)	No	1/1	73 days	0/1
Total			21/109 (19.3)	5/11 (45.5) studies*	14/48 (29.2)		16/81 (19.7)

*References [21] and [26] are counted once; NR, not reported

2.3 Risk of Reactivation in Infected Recipients

Risk of reactivation of *T. cruzi* infection varies according to the organ transplanted and the degree of drug immunosuppression, with the highest risk associated with heart transplantation (mean average of 44.9%) and similar risk for kidney (21.7%) and liver (33.3%) transplantation, as shown in Table 2 [30, 33-47]. The majority of the studies regarding reactivation came from Brazil and are related to patients who undergo heart transplantation, with a prevalence rate ranging from 23% to 90% [33-41, 44]. In Brazil, end-stage Chagas cardiomyopathy (CHC) is currently the third most common determinant for heart transplants (HTx), but it is also associated with a better outcome, with a 12-year survival rate of 46% [33, 47]. A recent study conducted in the United States between 2012-2016 showed a rate of reactivation of 61% among patients undergoing HTx [45]. In another study from the USA, the rate of reactivation after HTx was 45.5% [46].

Table 2 Risk of reactivation of Chagas disease in seropositive transplant recipients.

Organ	Author/Reference	Country of transplant	N (%)	Prophylaxis	Median time of reactivation (range)	Outcome N° deaths/N° patients (%)
Kidney	Riarte/[23]	Argentine	5/23 (21.7)	No	63 days (35-730)	1/23 (4.3)
Liver	Balderramo/[30]	Argentine	3/9 (33.3)	No	NR	2/9 (22.2)
Heart	Stolf/[34]	Brazil	3/4(75)	No	81 days (59-420)	NR
	Bocchi/[35]	Brazil	6/12 (50)	Yes (only first period)	NR	NR
	de Carvalho/[36]	Brazil	3/10 (30)	Yes	17 months (2-23)	3/10 (30) unrelated to CD
	Bocchi/[37]	Brazil	15/22 (68)			9/22 (40.9) at 2 years
	De Souza/[38]	Brazil	5/18 (23)	No	NR	NR
	Couto/[39]	Brazil	16/24 (67)	NR	NR	NR
	Fiorelli/[40]	Brazil	17/59 (29)	Yes	NR	24/59 (40.7) 1 death CDr
	Bacal/[41]	Brazil	21/39 (53)	No	NR	5/39 (12.8) at 2 years

	Bestetti/[42]	Brazil	9/10 (90)	No	NR	1/10 (10)
	Diez/[43]	Argentine	5/10 (50)	No	75 days (32-92) for clinical manifestation; 21 days (7-21) for kDNA-PCR	2/10 (20) unrelated to CD
	Campos/[44]	Brazil	17/64 (26)	No	NR	NR
	Kransdorf/[45]	USA	5/11 (45.5)	No	23 days	2/11 (18.2)
	Gray/[46]	USA	19/31 (61)	No	3 weeks (<1-89 weeks)	1/31 (3.2) unrelated to CD
Sub-total*			141/314 (44.9)			
Total			149/346(43.1)			50/224 (22.3)

NR, not reported; CD, Chagas disease; CDr, Chagas disease reactivation; KDNA PCR, polymerase chain reaction targeted to minicircle variable region; * referred to heart transplant

The 10-year survival rate of patients with HTx for CHC in the USA study was 57% and did not differ from the reported survival rate of patients with idiopathic dilated cardiomyopathy [48].

The use of mycophenolate mofetil (MMF) compared to azathioprine has been associated with a 6-fold higher risk of *T. cruzi* reactivation in a Brazilian retrospective study of HTx patients [41]. Another small study from Brazil reported a 90% reactivation rate among HTx patients treated with MMF, although the incidences of other post-transplant morbidities were similar in Chagas and non-Chagas disease patients [42].

2.4 De Novo *Post-Transplant Infection*

De novo acquisition of CD in a seronegative recipient who had received an organ from a seronegative donor has been very rarely described but can occur from travel or residence in an endemic area as well as through blood transfusions [23, 49]. Riarte et al. reported two kidney transplant patients who were infected through the vector route and were diagnosed by seroconversion in the absence of any clinical manifestations [23].

2.5 Clinical Presentation

Acute CD has been diagnosed following kidney, heart, liver, and lung transplantation from *T. cruzi* seropositive donors; the clinical picture ranges from asymptomatic parasitaemia detected only by polymerase chain reaction (PCR) performed on peripheral blood samples to an acute disease presenting with daily high fever or with involvement and dysfunction of the kidney, heart, and brain [19, 20, 22, 23, 50, 51]. Besides fever in patients experiencing post-transplant acute infection several clinical pictures have been reported: acute chagasic myocarditis, cerebral

trypanosomiasis with space-occupying brain lesions or kidney failure [18, 20, 51, 52]. In the above cited cases, trypomastigotes were identified in the bloodstream, peritoneal fluid, and cerebrospinal fluid, and *T. cruzi* amastigotes were found in endomyocardial biopsies [20, 51, 52]. In an autopsied kidney transplant recipient, disseminated CD was demonstrated with intense *T. cruzi* parasitism involving the heart, liver, spleen, kidney, bladder, and pancreas [51]. The median interval from transplantation to diagnosis of acute infection in a US study was 8 weeks, with a range of 3-29 weeks [21].

Reactivation of CD among seropositive recipients is currently diagnosed by detection of blood parasitaemia by polymerase chain reaction (PCR) or by endomyocardial biopsy (among HTx patients) which allows early preemptive therapy and improved survival [36, 43]. The Chagas reactivation rate in patients who underwent HTx is reported on average to be 41%, ranging from 23% to 90%, depending on the study [32, 34, 36-46]. Multiple episodes of reactivation (up to eight) have been described among patients who underwent heart transplantation [40]. A parasitological response is generally rapidly achieved as documented by the absence of parasites by Strout analysis after one week of treatment, although using more sensitive methods such as kDNA PCR a negative results is observed between 1 and 2 weeks after treatment [26, 43]. Clinical manifestations include febrile illness, new onset of painful wine-colored nodules (metastatic chagomas) which can ulcerate, erythematous plaque or panniculitis, acute myocarditis, or tumor-like brain lesions mimicking toxoplasmosis or neoplastic processes [53-59]. Myocarditis and meningoencephalitis can run an aggressive course, rapidly leading to the death of the patients [58-60]. Nevertheless, the outcome and survival rate of SOT recipients who develop acute CD or reactivation of the disease, especially among heart transplant recipients monitored and treated promptly, is similar to patients not affected by CD and in some instances even better [23, 30, 33, 36, 37, 46]. Among liver transplant recipients in Argentina, the median stay in intensive care, median hospital stay, rate of acute graft rejection, rate of infection, and rate of graft survival was similar in patients at risk of CD compared to the controls, with no deaths attributable to acute CD [30]. Mortality related to CD reactivation among HTx recipients has been reported in 0.3% to 0.7% of patients in Brazil and in 0% of patients in a recent study in the USA [33, 40, 46].

2.6 Diagnosis

Diagnosis of chronic *T. cruzi* infection is achieved by two positive serology methods employing different antigens as recommended by the World Health Organization (WHO). A third test, such as immunoblotting with trypomastigote excreted-secreted antigen (TESA), is indicated when serology is inconclusive (one positive and one negative test) and to rule out cross-reactions (with *Leishmania*). PCR shows a low sensitivity due to low parasitaemia during chronic infection and should not be used as a screening test [61]. On the contrary, PCR for *T. cruzi* performed on blood is currently considered the gold standard for post-transplant monitoring and early diagnosis of acute infection or reactivation [26, 30, 43]. Quantitative real-time PCR monitoring during the first 6 to 24 months post-transplant is actually recommended and employed in the centers transplanting the organs of Chagas disease patients [1, 5, 9, 31, 45]. Direct parasitological examination (Strout method or blood smear) on peripheral blood, cerebrospinal fluid, or pericardial fluid as well as histopathology are less sensitive, although usually employed [20, 51, 52]. Blood culture and xenodiagnosis are also less sensitive and time-consuming methods. Interestingly, serological

response in acute post-transplant CD can be completely abrogated or can be delayed, and in patients with reactivated disease, a decrease of IgG1 and IgG3 titres has been shown [19, 23].

2.7 Indication, Screening, and Management of Chagas Disease in SOT

Recommendations regarding different aspects of CD and SOT (i.e., who should be transplanted, what organs from seropositive *T. cruzi* donors should be used or discarded, how to screen patients before and after transplantation, how to treat CD, etc.) have been released from Argentine, Brazil, Spain, the USA, and from a working group from Latin America, as shown in Table 3 [5, 6, 9, 31, 62].

Table 3 Chagas disease recommendations for Solid Organ Transplant recipients.

Country, year, reference	**Argentine, 2010, [31]**	**USA, 2011, [9]**	**Spain, 2011, [6]**	**Latin America, 2018, [5]**	**Brazil,2016, [62]**
Pre-transplant screening of putative recipients	* All native from Latin-American * born to Latin American mothers *recipients of unscreened blood or blood products * resident or traveller to high risk areas for > 6 months	* Universal testing for those born in endemic areas	*Native population from endemic areas * Population who have received a blood transfusion in endemic countries * Offspring of mothers who are native from an endemic country and have a positive or unknown serology for Chagas * Population who have lived in an endemic area fro more than 1 month	* Systematic screening is required for all recipients at risk for *T. cruzi* infection before transplant	* Screening mandatory
Pre-transplant screening of putative donors	Same as for putative recipients	Targeted screening for donors born in Latin America	Same as for putative recipients	* Systematic screening is required for all donors at risk for *T. cruzi* infection before transplant	* Screening mandatory for all donations (use the same algorithm for blood donations)
Which tests should be used for screening Chagas disease	Two serological tests using different methodologies	Ortho EIA and Abbott Prism Chagas tests	Rapid serologic test with high sensitivity; confirmation by 2 specific serological techniques required	Two different serologic tests	Two different serologic tests
Acceptan	Infected	Transplant	The heart and the	The decision to	Law restriction

ce of organs from donor with CD	deceased donors are unacceptable for heart transplantation. The allocation of other organs, with appropriate informed consent, could be acceptable for infected recipients; for uninfected kidney recipients and, eventually, for uninfected lung and liver recipients in emergency situations	centers can consider transplanting kidneys and livers from *T. cruzi* infected donors. Rejection of hearts from *T. cruzi*-infected donors. Lung, pancreas and intestine can be considered with caution. All patients should provide appropriate informed consent concerning risk and benefits	intestines should be excluded for transplantation. For the remaining organs, transplantation will be possible subject to the informed consent of the recipient (without other options and for urgency cases)	accept an organ from an infected donor is a balance between urgency of need for the organ and the acceptance of the risk of possible infection in the recipient, both by the medical team and the recipient through informed consent, along with the ability to diagnose and treat infection if it occurs	on the use of organs from CD patients. The team will decide whether the organ is acceptable for use or not regarding kidney, kidney/pancreas, liver and lung donations
Criteria for microbiologic diagnosis of reactivation	Not reported	Not reported	* Positive Strout method * Positive PCR in patients with previous negative PCR	* Direct detection of *T. cruzi* in blood, fluids and tissues * High levels of quantitative PCR	* Direct microscopic detection of *T. cruzi* in blood, fluids and tissues
Post-transplant monitoring of patients receiving	Monitoring weekly or every 2 weeks for the first 6 months, monthly thereafter,	Monitoring with *T. cruzi* PCR and microscopy of blood specimens	Parasitologic studies (quantitative PCR, Strout method, direct parasitologic test according to the possibilities of	Monitoring weekly during the first 2 months, every 2 weeks through months 3 to 6,	Sequential parasitologic monitoring in the peripheral blood, every week for up to 60 days and

an organ from an infected donor	and weekly for 2 months after intensification of immunosuppr ession	weekly for the first two months, every 2 weeks during the third month, then monthly until at least 6 months post-transplant ation	the laboratory. Weekly for 2 months, bimonthly between the second and sixth months post-transplant, annually thereafter	and annually thereafter or at any time after an intensification of immunosuppr ession	indirect parasitologic and serology examination on days 30 and 60 after transplantation. Thereafter , clinical, serologic and parasitologic (direct/indirect/ PCR)examinatio ns should be performed every two months for up to one year of follow-up; then every 6 months for as long as immunosuppres sion persists
Prophyla xis for recipients of infected organs	The risk of toxicity among patients with end-stage renal disease and liver insufficiency, seems to outweight its potential benefit	Prophylaxi s not recommen ded	Consider use of post-transplant prophylaxis or early treatment of reactivation	Monitoring preferred over the use of prophylaxis	Monitoring preferred over the use of prophylaxis. Prophylaxis indicated if the sequence monitoring is not indicated

Chagas cardiomyopathy is not an absolute contraindication to heart transplantation, although some centers have adopted strict clinical and laboratory monitoring protocol to diagnose early, asymptomatic reactivation and early institution of treatment [45]. Similarly, patients with chronic indeterminate CD are considered suitable candidates for other solid organ transplants. Spanish guidelines specifically contraindicate any type of transplant for patients with advanced megaesophagus or megacolon [6]. Serologic screening is recommended both for candidate donor and recipients who share epidemiologic risk factors for CD, such as those born in Latin America, those born in non-endemic countries by Latin American mothers, recipients of blood transfusions in endemic countries, and those who have resided or travelled in Latin America [5, 6, 9, 31].

All guidelines indicate the use of two serological techniques for confirming the diagnosis of *T. cruzi* infection, whereas US guidelines specifically recommend the use of an FDA-cleared test

(Ortho EIA and Abbott Prism Chagas test) with additional testing by the Center for Disease Control (CDC) if a donor is found positive [9]. The use of organs from CD-infected donors is a matter of debate with absolute and relative contraindications; all guidelines absolutely contraindicate the use of the heart from a positive donor in positive or negative recipients [5, 6, 9, 31]. This is the consequence of the high rate of CD transmission with heart transplantation observed in a series of patients in which the CD diagnosis was discovered "*a posteriori*" [21]. This statement is in agreement with a recent autopsy study demonstrating the persistence of *T. cruzi* in 57.1% of heart samples [63].

In the same study, no samples from the lung, liver, kidney, pancreas, esophagus, or gastrointestinal tract were found to have the parasite as detected by histology, immunohistochemistry, or PCR. However, Spanish guidelines also recommend against the use of small bowel from infected donors [6]. In general, all guidelines indicate that liver and kidney transplants from positive donors can be made in cases of urgency, having obtained an appropriate informed consent concerning risk and benefits from the patient [6, 9, 31].

All guidelines advise to monitor post-transplant patients with laboratory tests (quantitative PCR, Strout method) that are able to identify parasites in the bloodstream responsible for *de novo* acute infection or reactivation among infected recipients [5, 6, 9, 31]. Indications about timing are similar among the recommendations, with close monitoring during the first 6 months after transplantation and when an intensification of immunosuppressive drug regimen is needed (Table 3). Heart transplant patients are recommended closer and more prolonged parasitologic monitoring, including evaluation of endomyocardial biopsies [5, 6, 9, 31, 64].

As far prophylaxis, among recipients of infected organs and in patients with chronic CD, guidelines favour an approach based on careful monitoring over the use of prophylactic treatment because of lack of evidence and the potential of drug toxicity [5, 6, 9].

In regard to immunosuppressive drug regimens, mycophenolate mofetil (MMF) should be avoided, especially in heart transplant recipients, and replaced by azathioprine or cyclosporine; when possible, antithymocyte globulin should also be avoided for rejection prevention [5, 6]. Basiliximab and daclizumab have been suggested as possible alternatives to MMF during the induction phase [6]. Moreover, based on an *in vitro* study showing activity against *T. cruzi* growth, rapamycin is indicated as another possible alternative to the use of MMF [5, 6]. Finally, it is recommended to maintain the immunosuppression at the lowest possible level, and a single retrospective study conducted in heart transplant recipients found patients receiving lower doses of cyclosporine (3-5 mg/kg versus 5-10 mg/kg) had significantly lower reactivation rates than those receiving higher doses of cyclosporine [5, 6, 60].

Benznidazole (5 mg/kg/day) is generally recommended as a first line drug for treatment of acute infection and reactivation for 30 or 60 days [5, 6, 31]. The choice of benznidazole is dictated by its better tolerability, although studies evaluating drug interactions with immunosuppressive drugs are lacking. In patients with renal or hepatic failure, no dose adjustment is needed. Nifurtimox (8-10 mg/kg/day) is considered a second choice that requires a more prolonged administration (90 days). Both drugs are metabolised by cytochrome P450, thus, with possible increase of cyclosporine, tacrolimus, sirolimus, and everolimus blood levels [5]. A frequent monitoring of blood cell count is needed for both drugs because of potential myelosuppression [5,6]. Skin rash, peripheral neuropathy, insomnia, and gastrointestinal intolerance are other possible adverse effects associated with anti-trypanosomal drugs [5, 6].

3. Leishmaniasis

3.1 Introduction

Leishmaniasis refers to a group of vector-borne diseases caused by more than 20 *Leishmania* species belonging to the family Trypanosomatidae [65-67]. The natural reservoir of the parasite can be animal (zoonotic leishmaniasis) or human (anthroponotic leishmaniasis). The disease can present in four main forms: cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), visceral leishmaniasis (VL), and post-kala-azar dermal leishmaniasis (PKDL). In 2015, according to the WHO, 87 and 75 countries were considered endemic for CL and VL, respectively, with almost 200,000 new cases of CL and 25,000 new cases of VL [65].

SOT recipients can develop *de novo Leishmania* infection through vector transmission, reactivation of a latent infection, or acquire the infection by donated organ or blood transfusion, although this occurs less frequently [68, 69].

VL is the picture observed more frequently among SOT recipients whereas CL and MCL are only occasionally reported [68, 70-72]. Leishmaniasis is described predominantly among kidney transplant recipients in comparison with other SOT recipients, but it is presently unknown if this is due to an increased risk related to renal failure or dialysis or due to the fact that kidney transplants comprise the great majority of SOTs [65, 68, 73-75].

3.2 Risk Factors

Only few studies have evaluated seroprevalence of *Leishmania* infection among candidates for organ transplantation or recipients of SOT [74, 76-78]. A study from northeastern Brazil conducted among 310 haemodialysed patients showed a 22.3% reactivity to *Leishmania* by indirect fluorescence antibody test [74]. Another study from Brazil evaluating 50 liver recipients and 17 liver donors found a 1.5% seroprevalence, but when polymerase chain reaction (PCR) was applied, 23.5% of donors and 8% of recipients resulted positive for PCR-specific *Leishmania infantum* either in blood, liver, or spleen samples [76]. In the USA, five out 48 (10.6%) Hispanic transplant candidates had positive *Leishmania* antibody titres [77]. Finally, a study from southern Spain found a 4.8% prevalence of positive *Leishmania* antibodies from 625 asymptomatic renal transplant recipients [78]. A multicenter case-controlled study performed in Brazil and Spain found a 5.7-fold higher incidence of VL in the former country that has been explained by the higher incidence of VL in Brazil (1.8 cases per 100,000 inhabitants) in comparison with Spain (0.4 cases per 100,000 inhabitants) and by an earlier onset of the disease as a consequence of reactivation [79]. In the above cited study, high-dose prednisone in the preceding 6 months was the only independent risk factor significantly associated with development of VL (OR 2.5) [79].

Interestingly, a study conducted in Madrid during an outbreak of leishmaniasis found an annual risk of developing VL among SOT recipients 136 times higher compared to immunocompetent subjects living in the same area [80]. Three risk factors emerged as associated with the diagnosis of VL: 1) living in close proximity to the area affected by the outbreak (relative risk 11.74%), explained by a higher chance to be bitten by the infected phlebotomous; 2) receiving a SOT during the outbreak; and 3) being black from sub-Saharan Africa, with a relative risk of 6.40% [80]. The role of ethnicity and its possible association with VL needs to be explored in future studies, as black people emerged as the most affected in another study from Brazil [81].

3.3 Clinical Presentation

VL is by far the most frequently encountered clinical presentation of leishmaniasis among SOT recipients described in kidney, liver, heart, lung, and pancreas transplantation [7, 68, 79-81]. Fever is the most common symptom of VL, but in the study by Clemente et al., 14% of patients were afebrile [68, 79]. Visceromegaly (either hepatomegaly or splenomegaly) has been variably reported in the literature but is generally high (75-81%), although only one-third of patients present with the classic triad of fever, visceromegaly, and pancytopenia [68, 79, 81]. The median time to diagnosis of VL after transplantation ranges from 11 months to 28 months, although in one study, one-third of patients were diagnosed within the first 6 months following transplantation [79, 81]. Active bleeding from the digestive tract was observed in 23% of patients and can be the mode of onset of the disease [81, 85]. Septic shock has been reported in 8% of patients in one study [79]. Concurrent cutaneous and visceral leishmaniasis has been observed among kidney and liver transplant recipients and both typical and atypical presentation of CL are reported in the literature [86-90]. Mucosal leishmaniasis localised on the tongue, lip, labial commissure, and nose has been described among SOT patients almost exclusively in the Mediterranean basin where the species responsible is *L. infantum* [68, 91-95]. Relapse of VL was reported in 26% to 28% of SOT patients and in one of these studies, more frequently among patients not receiving prophylaxis (34.8%) than those receiving prophylaxis (8.3%), with a p value of 0.19 [79, 81]. Relapse of VL has been reported to occur among kidney transplant recipients in a period ranging from 1 month to 5 years after the initial diagnosis [95]. Multiple episodes of relapse, as observed in HIV-positive patients, can be diagnosed also among SOT recipients, although for those living in endemic areas it is difficult to rule out reactivation from reinfection [95].

3.4 Diagnosis

A direct diagnosis of leishmaniasis (VL, CL, MCL) requires the demonstration of protozoa in biopsy samples from bone marrow or the spleen (VL) or from skin ulcer or mucosal lesions. This task can be achieved by microscopy, culture, or molecular diagnosis. In the study by Clemente et al., the sensitivity of bone marrow microscopy for the diagnosis of VL was 80.6%, better than the 75% achieved by polymerase chain reaction and the 56% achieved by culture [79]. However, in the same study, combining the three methods yielded a sensitivity of 89% [79]. Polymerase chain reaction (PCR) is considered the best available method for the diagnosis of VL, combining high sensitivity and specificity, rapid species identification, and the advantage of using peripheral blood samples (rather than bone marrow) with identical sensitivity and specificity [96]. However, the utilization of PCR in SOT is limited to few reported cases [79, 95, 97, 100]. Moreover, the problem of asymptomatic patients with positive PCR results needs to be considered because a threshold value capable of distinguishing this condition (asymptomatic parasitaemia) from the disease is presently unknown. It should be highlighted that in a recent case report of VL in a lung transplant recipient using real-time PCR which targets the kinetoplastic DNA, the authors were able to retrospectively detect the DNA of the parasite months before the diagnosis, suggesting the possibility to adopt a preemptive approach [97]. *Leishmania* serology has been reported to be positive in 76% of SOT patients with VL, but it is unable to distinguish between prior exposure and

active disease; additionally, in areas where Chagas disease coexists, cross-reactivity can be a problem because both parasites share antigens [7, 98].

3.5 Screening and Management of Leishmaniasis

Since there is not a clear demonstration of the utility of screening either among candidate organ transplant recipients or organ donors, available guidelines do not recommend this practice [7, 99, 100]. It is generally recommended that transplant recipients visiting endemic countries use insect repellent and avoid outdoor activities during the hours when sand flies are more active [7]. Liposomal amphotericin B (L-AMB) is considered the drug of choice for the treatment of leishmaniasis in SOT with a cumulative dose of 40 mg/kg administered over 10 infusions (days 1-5 followed by one week administration for 5 times) [100]. The liposomal formulation of amphotericin B is generally well tolerated and is preferred over amphotericin B deoxycholate among SOT recipients [79, 81]. In a review of the literature, the initial cure rate of VL among transplant recipients has been documented as 84% [68]. A Brazilian study conducted among kidney transplant recipients reported an 80% VL remission and return to dialysis in 33% of patients achieving VL remission [81]. Finally, in a Spanish–Brazilian study involving kidney, liver, heart, and lung transplant recipients, the cure rate at the one month follow-up was reported to be 94.2% [79].

Experience with miltefosine (the only available oral therapy for VL) in the setting of SOT is limited to 6 patients in whom the drug was used as salvage treatment after first-line therapy with L-AMB [101]. Patients were treated with 2.5 mg/kg/day of miltefosine for 28 days but 50% relapsed after an initial clinical improvement. As commonly used in HIV-infected patients, a secondary prophylaxis seems to also be warranted among SOT recipients, although the interval and means of administration are presently unknown [7, 79]. As far as the treatment of CL in SOT recipients, it is recommended to use the same systemic treatment (i.e. L-AMB) as for VL [7].

4. Malaria

4.1 Introduction

Malaria is the most common human protozoan disease worldwide caused by six different species of *Plasmodium*: *Plasmodium falciparum*, *P. vivax*, *P. ovale wallikeri*, *P. ovale curtisi*, *P. malariae,* and *P. knowlesi*, the latter being a zoonotic parasite emerging in East Asia [102]. The disease is usually transmitted by the bite of infected *Anopheles* mosquitoes, but transmission by blood (via transfusion or sharing of contaminated needles), by mother to child, or following organ transplantation is also possible [103-106]. Post-transplant malaria may be the consequence of a donor-derived infection, transmission by blood transfusion, recrudescence, or relapse of a previous infection in the transplant recipient [107-109].

4.2 Donor Deferral and Screening

There are no uniform recommendations about deferral of candidate donors who have resided or travelled in endemic areas for malaria. In general, most recommendations refer to adopted policies for exclusion of blood donors [110]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommendations indicate screening with nucleic acid tests (NATs) in

all donors and recipients who have resided or travelled to areas of malaria endemicity in the 3 preceding years [111]. If the donor's death is secondary to malaria, organs should be rejected [111]. Brazilian guidelines and the recently published guidelines from Latin America recommend routine screening for donors coming from endemic regions, based on annual parasite incidence (API), and excluding those with a diagnosis of malaria in the previous 12 months, with fever in the previous 30 days, or having returned from a city with a high API in the previous 30 days [2, 8]. Candidate donors who had a history of *P. malariae* are permanently deferred from donation because this parasite probably persists for life, posing a risk even decades after a previous episode of apparently cured malaria, as observed in cases of transfusion-transmitted malaria [8, 103]. Moreover, potential donors with a diagnosis of active infection should be deferred from organ donation until the malaria is diagnosed and treated. All guidelines recommend the use of molecular screening with NATs which are able to detect low parasitaemia, a condition which can be missed by thick blood smears and rapid antigen tests that are considered insensitive [2, 8, 111]. Serology testing can be considered as a marker of previous exposure in the case of unclear donor travel history.

Even with the use of the most sensitive diagnostic test on blood, liver transplantation has been associated with the transmission of *P. vivax* due to the persistence of hepatic hypnozoites, which is also possible for *P. ovale* [112, 113]. Several cases of multi-organ transmission of malaria from a single donor have been described [107, 114, 115].

4.3 Post-Transplant Management

Malaria also carries a possible risk of recrudescence or reactivation among recipients with asymptomatic infection following immunosuppression [116]. For this reason, it has been suggested to prospectively monitor high risk patients (i.e., those coming from malaria-endemic areas) with PCR for a period of two months [117].

4.4 Clinical Presentation

Post-transplant malaria presents with high fever and chills that do not respond to empirical antibiotic therapy [107, 114, 115, 118-121]; thrombocytopenia and anemia are commonly observed as in the case of vector-borne malaria [114, 115, 118-121]. Mental impairment, coma, or acute renal failure may be observed as complications of *P. falciparum* malaria when the diagnosis is delayed [115, 118, 119]. Patients with a diagnosis of malaria after a liver transplant can display liver function deterioration with important increases of transaminases and bilirubin [107, 112, 115]. Malaria diagnosis in cases occurring through infected grafts is entertained after a median of 29.5 days [8]. Death of the patient was reported in 12% of cases recently reviewed, with the worst outcome among liver and heart transplant patients, although the overall low number of malaria cases prevent any definite conclusion [8].

4.5 Diagnosis

In all the reported cases of post-transplant malaria, the correct diagnosis was always achieved by conventional thick and thin smears of peripheral blood [8, 107, 112-115, 118-121]. Few cases of mixed infections caused by *P. falciparum* and *P. vivax* as well as by *P. malariae* and *P. ovale* were

reported in the literature [114, 121]. To the best of our knowledge, a very sensitive quantitative PCR for malaria has been used only in a single case of an allogenic haematopoietic stem cell transplant patient; it showed a long-term persistence of a positive PCR result (> 30 days) after therapy-induced resolution of symptoms and parasite disappearance detected by microscopy [109].

4.6 Treatment

Patients were treated according to the species of *Plasmodium* identified and the severity of the malaria picture observed [107-109, 112-115, 119-121]. There is an anecdotal report of two patients who underwent a pre-emptive treatment for malaria after the recognition of the disease in a recipient from the same organ donor [122]. Artesunate, the drug of choice for severe malaria, has been employed in a single case of malaria in a heart transplant patient [115].

The recommendations for treatment of malaria in SOT recipients are essentially the same as for the population of non-transplant patients [8].

5. Conclusion

In conclusion, although rarely observed, CD, leishmaniasis, and malaria pose a risk that is not negligible among SOT recipients, especially in the present era of globalisation. The awareness of this risk in recent years has led to the introduction of molecular tests in the clinical practice to screen both donors and recipients (especially for CD), and to promulgate recommendations and guidelines. The risk of reactivation is particularly important for CD, requiring PCR monitoring of the blood in order to make an early diagnosis and preemptive therapy. High quality studies are needed to accurately identify risk factors for CD reactivation.

Author Contributions

Spinello Antinori conceived the paper, made the bibliography search, wrote the paper; Laura Milazzo made the bibliography search, wrote the paper.

Funding

No funding for this research.

Competing Interests

The authors have declared that no competing interests exist.

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