



Research Article

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Low seroprevalence and low incidence of infection with *Toxoplasma gondii* (Nicolle et Manceaux, 1908) in pediatric hematopoietic cell transplantation donors and recipients: Polish nationwide study

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Abstract: Toxoplasmosis is a potentially fatal complication after hematopoietic cell transplantation (HCT). Pre-transplant seropositivity of graft recipient to *Toxoplasma gondii* (Nicolle et Manceaux, 1908) is an important factor for disease reactivation after HCT. As toxoplasmosis epidemiology varies all over the world, we performed a Polish nationwide retrospective cohort study to determine the seroprevalence of toxoplasmosis in donors and pediatric allogeneic and autologous HCT recipients and the incidence of clinically evident toxoplasmosis in this patient group. Polish adult donors had higher anti-*T. gondii* seroprevalence than Polish pediatric donors (28% vs 8%; OR = 4.4; p = 0.02) and allo-HCT recipients (28% vs 17%; OR = 1.9; p = 0.01). Clinically apparent disease occurred in 1% of allo-HCT recipients: it was diagnosed by PCR as cerebral and/or ocular toxoplasmosis and successfully treated with antiprotozoal therapy. Regarding current practice, no prospective screening for infection of *T. gondii* in pediatric HCT centres is being performed, but, vast majority of HCT pediatric patients are receiving anti-*T. gondii* active prophylaxis. Since pre-HCT *T. gondii* serology was not assessed in all HCT; recipients, we propose this test should be a standard practice. Standardisation of management with infection of *T. gondii* in children after HCT is needed.

Keywords: bone marrow transplantation, children, prophylaxis, toxoplasmosis, treatment, trimethoprim, sulfamethoxazole

Toxoplasma gondii (Nicolle et Manceaux, 1908) is an intracellular parasite that causes infection in most mammals worldwide (Olariu et al. 2015). The infection is transmitted to humans by ingestion of food or water contaminated with oocysts shed by cats or by eating raw or undercooked meat containing tissue cysts (Martino et al. 2000, Olariu et al. 2015, Dard et al. 2018). Seroprevalence *T. gondii* of varies widely between countries (10–95%) (Olariu et al. 2015, Gatti-Mays et al. 2016, Isa et al. 2016, Berrett et al. 2018).

Although *T. gondii* causes asymptomatic infection in immunocompetent hosts and most newborns, it can severely affect congenitally infected infants and immunocompromised patients (Martino et al. 2000, Olariu et al. 2015). Toxoplasmosis was formerly considered a rare disease among hematopoietic cell transplantation (HCT)

recipients with reported incidences varying from 0.8 to 8%, depending on the seroprevalence of *T. gondii* in the studied population (Decembrino et al. 2017, Prestes et al. 2018). Recent data highlighted post-HCT toxoplasmosis as a potential life-threatening disease with a poor prognosis and reported mortality rates of 60–90% if the onset is early after transplantation (Decembrino et al. 2017, Prestes et al. 2018). An acute, fulminating, disseminated infection or single-organ disease (usually encephalitis) is usually seen in highly immunocompromised individuals, in whom these infections appear to result from reactivation of latent tissue parasites in seropositive individuals (Martino et al. 2000). The most frequently involved organs are the brain, lungs and heart (Hakko et al. 2013).

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Table 1. Definitions for toxoplasmosis after hematopoietic cell transplantation – modified from Martino et al. (2000)

Toxoplasmosis classification	Definition	
Toxoplasmosis disease	Definite toxoplasmosis	Histological or cytological demonstration of tachyzoites in tissue samples obtained either by biopsy, BAL or at autopsy. Isolation of the parasite by culture in these samples would be evidence of the disease.
	Probable toxoplasmosis (PCR-documented)	Clinical and radiological evidence suggestive of organ involvement plus at least one positive PCR test from blood, CSF and/or BAL, but no histologic confirmation and absence of another pathogen which may explain the findings.
	Possible toxoplasmosis (Imaging-documented)	CT or MRI highly suggestive of CNS toxoplasmosis (as considered by each hospital's neuroradiologists) and response to anti- <i>Toxoplasma</i> therapy, but no laboratory evidence of toxoplasmosis and absence of another pathogen which may explain the findings.
Toxoplasmosis infection	Positive PCR in blood in a patient without any evidence of organ involvement or seroconversion for <i>Toxoplasma gondii</i> after transplant in a previously sero-negative patient (with or without fever).	

BAL – bronchoalveolar lavage; CNS – central nervous system; CSF – cerebro-spinal fluid; CT – computerised tomography; MRI – magnetic resonance imaging; PCR – polymerase chain reaction for *Toxoplasma gondii* (Nicolle et Manceaux, 1908).

There are conflicting data on primary prophylaxis against *T. gondii* after HCT (Gajurel et al. 2015, Ullmann et al. 2016). Moreover, myelosuppressive effect of trimethoprim/sulfamethoxazole (TMP/SMX), a commonly used prophylactic agent in varying dosing, can be problematic in this population (Gajurel et al. 2015). This has created a great deal of discrepancy regarding appropriate prophylaxis against *T. gondii* in the setting of HCT (Gajurel et al. 2015).

As epidemiology of toxoplasmosis varies all over the world, we performed a Polish nationwide retrospective cohort study to determine the seroprevalence of toxoplasmosis in donors and pediatric allogeneic HCT (allo-HCT) and autologous HCT (auto-HCT) recipients and the incidence of clinically evident toxoplasmosis in this patient group. We also analysed the clinical course of toxoplasmosis disease in pediatric HCT recipients. Additionally, we determined the current practices in prophylaxis, diagnostics and treatment of toxoplasmosis in all pediatric HCT centres in Poland.

MATERIALS AND METHODS

Design of the study. In this retrospective, multicentre, nationwide cohort study all Polish pediatric HCT centres (Bydgoszcz, Krakow, Lublin, Poznan, Wroclaw) participated over a period of two years (2015–2016). The information on all recipients and donors was collected in the centres and analysed centrally by two independent researchers. Apart from basic data on donors, recipients, and type of transplants, the data also included information on the *Toxoplasma gondii* immunological serostatus (anti-*T. gondii*-IgG) in of donors and recipients, screening for *T. gondii* infection/reactivation and anti-*T. gondii* prophylaxis. The centres also reported cases of clinically overt toxoplasmosis. The diagnostics of toxoplasmosis in suspected cases included magnetic resonance imaging (MRI) and commercially available real-time PCR, which was performed on peripheral blood, cerebrospinal or vitreous fluid. This study was approved by the Ethics Committee of Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun.

Anti-infective prophylaxis. Uniform, standard prophylaxis was applied for all patients undergoing HCT (Ljungman et al. 2008, Styczynski and Gil 2008, Styczynski et al. 2009) in the peri-transplantation period and in the post-HCT period. TMP 6 mg/kg/day + SMX 30 mg/kg/day three times a week was used as *Pneumocystis jiroveci* Frenkel, 1976 pneumonia (*PjP*) prophylaxis active against

T. gondii or aerolised pentamidine was used for anti-*PjP* prophylaxis with no additional prophylaxis against *T. gondii*.

Definitions. Infection of *T. gondii* and toxoplasmosis disease were defined according to European Group for Blood and Marrow Transplantation Infectious Diseases Working Party guidelines (Martino et al. 2000) (Table 1).

Statistical analysis. The chi-square test with odds ratio (OR) and confidence intervals (95% CI) were used to calculate the difference in occurrences of categorical variables between groups. All reported p-values are two-sided; $p < 0.05$ was considered as statistically significant.

RESULTS

Demographics. A total of 664 individuals were included in the study: 287 allo-HCT recipients (including 7 from Ukraine), 90 auto-HCT pediatric recipients, and 287 donors of hematopoietic stem cells. Allo-HCT recipients included 181 males and 106 females at median age of eight years (range, 0.1–26), while auto-HCT recipients included 48 males and 42 females with median age of 4.7 years (range, 0.6–21). Among 287 donors, Poland was country of origin in 212 (74%) cases (including 49 siblings <18 years), Germany in 56 (20%), other countries (USA (n = 6), Israel (n = 4), Italy (n = 3), Spain (n = 2), Australia (n = 1), France (n = 1), Sweden (n = 1), Taiwan (n = 1) for 19 (6.6%) transplants. Of 212 Polish donors 124 were male and 88 female with median age of 25 years (range, 1–49).

Seroprevalence of toxoplasmosis of in adult and pediatric donors and pediatric recipients. Among allo-HCT recipients, pre-transplant *Toxoplasma gondii* serology was available for 87% (250/287) patients: 19% (47/250) were IgG-positive and 81% (203/250) naive for the infection (Table 2). In auto-HCT recipients, *T. gondii* serology was available for 47% (42/90) patients, including 14% (6/42) IgG-positive before transplantation and 86% (36/42) IgG-negative. *T. gondii* serostatus was available in 78% (166/212) Polish donors: 24% (39/166) were IgG-positive and 77% (127/166) were IgG-negative.

In comparison to donors from Poland and Germany, we found a high rate (58%) of untested donors from other countries. In comparison to allo-HCT recipients we found also high number of untested auto-HCT recipients (13% vs 53%). However, among those who were tested, no difference was found in seropositivity between allo- and auto-HCT recipients found (19% vs 14%; $p > 0.05$).

Table 2. Characteristics of donors and recipients and *T. gondii* seroprevalence

	Donors (country of origin)			Recipients	
	Poland	Germany	Other*	Allo	Auto
Number of individuals	212	56	19	287	90
Age (median, range)	25 (1–49) yrs	31 (18–58) yrs	27.5 (18–44) yrs	8 yrs (1 mo–26 yrs)	4.7 yrs (7 mo–21 yrs)
Sex (male/female)	124/88	37/19	8/11	181/106	48/42
Anti-Toxo-IgG (+)	39 (23%)	10 (22%)	1 (13%)	47 (19%)	6 (14%)
Anti-Toxo-IgG (-)	127 (77%)	35 (78%)	7 (88%)	203 (81%)	36 (86%)
not tested	46	11	11	37	48

*Country of other donors origin: USA (n = 6), Israel (n = 4), Italy (n = 3), Spain (n = 2), Australia (n = 1), France (n = 1), Sweden (n = 1), Taiwan (n = 1); mo – months; yrs – years.

There was no significant difference between Polish donors and allo-recipients in anti-*T. gondii*-IgG seropositivity (23% vs 19%; $p > 0.05$). When patients from Ukraine (seven IgG+; two IgG-) were excluded from the analysis, the sub-group of Polish allo-HCT recipients included 17% (40/241) IgG+ and 83% (201/241) IgG- patients (37 of Polish allo-HCT recipients were untested). Donors from Poland included 23% (49/212 donors) pediatric and 77% (163/212) adults. In the Polish pediatric donors group *T. gondii* serology was available for 76% (37/49) donors. Anti-*T. gondii*-IgG antibodies were present just in 8.1% (3/37), whereas 92% (34/37) donors were seronegative.

Among Polish adult donors the serology was available for 79% (129/163). *T. gondii* seropositivity rate was 28% (36/129), while 72% (93/129) donors were seronegative. The seroprevalence of Polish adult donors was higher than in Polish pediatric allo-HCT recipients (28% vs 17%, OR 1.94; 95% CI 1.16–3.24; $p = 0.01$). There was also significantly higher *T. gondii* seroprevalence among Polish adult donors than Polish pediatric donors (28% vs 8%, OR 4.38; 95% CI 1.27–15.18; $p = 0.02$). No difference in seropositivity between Polish pediatric donors and allo-HCT recipients group was observed. There were no differences in seropositivity between adult donors with respect to country of origin (Table 2).

In 74% (212/287) of donor-recipient pairs anti-*T. gondii*-IgG status was available, so we could assess donor-recipient serology combinations. In 63% (133/212) of cases both donor and recipient were seronegative (D-/R-), 19% (40/212) were D-/R+, 15% (32/212) were D+/R- and 3.3% (7/212) were D+/R+.

Current practice in management of toxoplasmosis.

In all Polish pediatric HCT centres post-transplant prophylaxis against *PjP* was performed. In 87% (327/377) recipients, including 87% (250/287) allo-HCT and 86% (77/90) auto-HCT, TMP 6 mg/kg/day + SMX 30 mg/kg/day three times a week was used as anti-*PjP* prophylaxis active against *T. gondii*. Because of TMP/SMX adverse events or contraindications, in nine patients (allo-HCT only) aerosolised pentamidine was used for *PjP* prophylaxis with no additional prophylaxis against *T. gondii*. Prospective PCR screening for infection/reactivation of *T. gondii* was done only one (0.3%) patient.

Toxoplasmosis. During the period of present study, three cases of clinically overt toxoplasmosis were reported; all of them in allo-HCT recipients (3/287, i.e. 1.04% of

allo-HCT; or 3/377, i.e. 0.8% of all HCTs). One of the cases was previously reported (patient 3) (see Zaucha-Prazmo et al. 2017). Toxoplasmosis was diagnosed at the probable level in two patients and possible level in one patient. Respective clinical data are presented in Table 3.

DISCUSSION

The geographical seroprevalence of toxoplasmosis in humans varies from less than ten to over 90 percent, depending on the country, due to regional differences of climate and life habits (Dard et al. 2018). For the Polish population the presence of anti-*Toxoplasma gondii* antibodies varies between 36% and 63%, depending on region and population studied (Nowakowska et al. 2006, Salamon and Bulanda 2014, Milewska-Bobula et al. 2015, Samojlowicz et al. 2017).

There are no studies on toxoplasmosis seroprevalence in Polish HCT donors and recipients. In our study we found lower percentages of *T. gondii* seroprevalence in pediatric allo- and auto-HCT recipients (17% and 14%, respectively) in comparison to national data. Relatively low seroprevalence of Polish donors (23%) could be explained by the high number of young donors (23% were under 18 years, and only 8% of them had positive anti-*T. gondii* serostatus). This can be explained by increase in seroprevalence with age, which was observed both in Poland and other countries (Nowakowska et al. 2006, Olariu et al. 2015). In our study we observed 22% of Polish donors, 13% of allo-HCT and 53% of auto-HCT recipients were untested for *T. gondii* seroprevalence. These data correspond to those presented by Gajurel et al. (2015) where 19% of pre-transplant allo-HCT recipients and 41% of auto-HCT recipients were not tested for infection of *T. gondii*. Therefore, performing pre-transplant serology is strongly recommended, irrespective of the expected rate of seropositivity (Ullmann et al. 2016, Decembrino et al. 2017).

We observed that prophylaxis with TMP/SMX against *PjP* which was active against *T. gondii* was conducted in all transplant centres (87% allo- and 86% of auto-HCT recipients). In 9 patients (all allo-HCT) pentamidine inhalation was used as a prophylaxis against *PjP* with no additional prophylaxis against *T. gondii*. TMP/SMX seems to be the most common agent in toxoplasmosis prophylaxis (Gajurel et al. 2015, Ullmann et al. 2016) and its protective effect in prophylaxis is suggested (Martino et al. 2005, Gajurel et al. 2015).

Table 3. Characteristics of three patients with toxoplasmosis.

Patient/ Variable	1	2	3
Gender/age (years)	F/17	M/9	M/17
Diagnosis	acute lymphoblastic leukemia	acute myeloblastic leukemia	Fanconi anemia
Type of donor	MUD-PBSCT (10/10)	MUD-BMT (10/10)	MUD-BMT (10/10)
Conditioning regimen	RIC (FLUD+TREO)	MAC (BU+CY+MEL)	RIC (FLUD+CY)
GVHD prophylaxis	ATG, CSA, MTX switched to TAC after second PBSCT	ATG, CSA, MTX	ATG, CSA, MTX
Engraftment day	+15	+19	+12
GVHD before toxoplasmosis	No	Yes, cGVHD, II° GI	No
Anti- <i>T.gondii</i> IgG donor/recipient	D?/R+	D+/R+	D-/R?
Post-transplant anti- <i>PjP</i> prophylaxis active against <i>T. gondii</i>	TMP 6 mg/kg/day + SMX 30 mg/kg/day three times a week	TMP 6 mg/kg/day + SMX 30 mg/kg/day three times a week	TMP 6 mg/kg/day + SMX 30 mg/kg/day three times a week
Post-transplant complications	graft loss, +57 second PBSCT	EBV-DNA-emia treated with rituximab, hypogammaglobulinemia	None
Toxoplasmosis symptoms onset (day post HCT)	+58 after first PBSCT/+1 after second PBSCT	+352	+90
Symptoms of toxoplasmosis	fever, headache, vomiting	visual impairment, retinochorioiditis	visual impairment, chorioiditis, fever, concussions disorders, sensory aphasia, headache
Changes in CNS MRI	yes	yes	yes
CSF general examination	pleocytosis 11/ μ L (100% lymphocytes), protein-raised, glucose-normal	pleocytosis 10/ μ L (98% lymphocytes), protein-normal, glucose-normal	pleocytosis 10/ μ L (95% lymphocytes), protein-raised, glucose-normal
Microbiological results	PCR DNA positive for <i>T. gondii</i> in blood and CSF	PCR DNA positive for <i>T. gondii</i> in vitreous, negative in blood and CSF	PCR DNA negative for <i>T. gondii</i> in blood and CSF, high levels and avidity of anti- <i>T. gondii</i> - IgM and IgG in blood and CSF
Treatment of toxoplasmosis	TMP/SMX+CLIN+DX	SULFADI+PYR+CLIN+DX followed by SULFADO+PYR+MP+DX	TMP+CLIN followed by TMP+DX
Outcome of toxoplasmosis	Cured	Cured	Cured
Toxoplasmosis level of diagnosis	Probable (CNS)	Probable (CNS+eye)	Possible (CNS+eye)

ATG – antithymocyte globulin; BMT – bone marrow transplantation; BU – busulfan; cGVHD – chronic graft-versus-host disease; CLIN – clindamycin; CNS – central nervous system; CSA – cyclosporine; CSF – cerebro-spinal fluid; CY – cyclophosphamide; D – donor; DX – dexamethasone; F – female; FLUD – fludarabine; HCT – hematopoietic cell transplantation; GI – gastrointestinal; GVHD – graft-versus-host disease; M – male; MAC – myeloablative conditioning regimen; MEL – melphalan; MP – methylprednisolone; MRI – magnetic resonance imaging; MTX – methotrexate; MUD – matched unrelated donor; PBSCT – peripheral blood stem cell transplantation; *PjP* – *Pneumocystis jiroveci* pneumonia; PCR – polymerase chain reaction; PYR – pyrimethamine; R – recipient; RIC – reduced intensity conditioning; SULFADI – sulfadiazine; SULFADO – sulfadoxine; SMX – sulfamethoxazole; TMP – trimethoprim; TAC – tacrolimus; TREO – treosulfan; tw – three times in week; “-” – negative; “+” – positive; “?” – unknown

There are also some data about atovaquone, dapson, pyrimethamine/sulfadoxine, azithromycin and clindamycin use as prophylactic agents in HCT recipients, but there are no randomised controlled trials evaluating the efficacy of *T. gondii* prophylaxis (Gajurel et al. 2015). According to guidelines (Ullmann et al. 2016) TMP/SMX prophylaxis, administered to most transplant patients to prevent *PjP*, is also efficacious in preventing toxoplasmosis, but no primary prophylaxis against *T. gondii* is recommended. Secondary prophylaxis should be administered for at least three months after a successful therapy of toxoplasmosis to prevent relapse of CNS toxoplasmosis (Ullmann et al. 2016). Pyrimethamine+sulfadiazine, pyrimethamine+clindamycin or atovaquone are proposed for secondary prophylaxis (Ullmann et al. 2016).

As in other studies (e.g., Hakko et al. 2013, Gajurel et al. 2015, Helton et al. 2016, Decembrino et al. 2017, Prestes et al. 2018), we also observed toxoplasmosis during TMP/SMX prophylaxis in two of three patients. Suboptimal dosing, inadequate oral absorption and poor compliance may be reasons for this phenomenon (Gajurel et al. 2015).

Regular toxoplasmosis DNA PCR screening in HCT recipients is not recommended except for patients with clinical symptoms (Ullmann et al. 2016). In Polish pediatric HCT centres PCR screening for toxoplasmosis is not rou-

tinely provided. In contrast, PCR follow-up of allo-HCT patients was implemented in France in half of centres (Robert-Gangneux et al. 2015). Some authors suggest to perform real-time PCR screening of peripheral blood for all positive recipients with a seronegative donor, starting on the day of hematopoietic cell infusion, every 15 days during the engraftment period and subsequently every three months until CD4+ cell recovery occurs (Decembrino et al. 2017). Regular PCR follow-up of allo-HCT patients could guide pre-emptive treatment and improve outcome (Robert-Gangneux et al. 2015).

We observed that the TMP/SMX prophylaxis was routinely used in most patients after HCT, with a low percentage of clinically apparent toxoplasmosis in the Polish children after allo-HCT and no cases of toxoplasmosis in patients after auto-HCT. These facts question the use of routine prospective PCR monitoring of all patients after HCT. For this reason and due to high costs, a prospective screening is probably not necessary at all in auto-HCT children, and at least should be a matter of analysis in children after allo-HCT.

There is a logical relationship between global seroprevalence in the general population and the risk of reactivation in allo-HCT: the higher the pre-graft seroprevalence in the allo-HCT recipient population, the higher the incidence of

toxoplasmosis reactivation (Dard et al. 2018). In our study we observed just three cases of clinically apparent toxoplasmosis, all in allo-HCT recipients (one percent) with no toxoplasmosis in auto-HCT recipients. Previous data on the incidence of toxoplasmosis in seropositive allo-HCT recipients vary from 0% in China to 20% in Japan, whereas it is 6–16% in European countries (France, Germany, Spain) (Gajurel et al. 2015). These data come mainly from adult transplant centres and suggest that incidence is lower in pediatric allo-recipients toxoplasmosis than in adult populations, which corresponds with lower *T. gondii* seroprevalence in younger age.

In just one patient with toxoplasmosis both donor and recipient *T. gondii* serostatus were known, whereas in full information was not available two cases. One of three patients received myeloablative conditioning regimen (MAC) and in all cases antithymocyte globulin (ATG) was used. In one case mild chronic graft-versus-host disease (GVHD) was seen before toxoplasmosis diagnosis. Meers et al. (2010) found that out of 208 monitored patients, 18 developed clinical toxoplasmosis (Meers et al. 2010). Out of 18, 17 were seropositive and 14 received HCT from seronegative donors, suggesting that *T. gondii* negative serological status of donor is a risk factor of reactivation in seropositive patients (Meers et al. 2010). In addition, the main risk factors for toxoplasmosis reactivation are cord blood, haploidentical and mismatched unrelated donor HCT, low CD4⁺ cell count, MAC, total body irradiation, ATG use and severe GVHD (Gajurel et al. 2015, Decembrino et al. 2017, Dard et al. 2018). GVHD was seen in 59% of seropositive allo-HCT recipients, but has not been consistently associated with *T. gondii* reactivation (Gajurel et al. 2015).

We observed cerebral toxoplasmosis in three patients (two possible and one probable) with coexistence of ocular toxoplasmosis in two of them. The first symptoms were observed at day +58, +90 and +352 after HCT. All

the patients responded to differential treatment with no fatal outcome. Gajurel et al. (2015) reported distribution of toxoplasmosis organ involvement 46% for CNS, 41% for disseminated disease, 8% for pulmonary involvement and 2% for simultaneous CNS and ocular involvement, while toxoplasmosis-related deaths were observed in 51% of patients.

Clinical manifestation of toxoplasmosis in allo-HCT recipients mainly occurs within the first six months after transplantation (Hakko et al. 2013, Dard et al. 2018, Prestes et al. 2018). There is no optimal treatment of toxoplasmosis in HCT patients contrary to HIV-patients (Dard et al. 2018). Pyrimethamine, sulfadiazine, TMP/SMX, clindamycin, atovaquone, doxycycline, dapsone, azitromycin in various doses, combinations and different times were used in *T. gondii* infection treatment (Hakko et al. 2013, Gatti-Mays et al. 2016, Dard et al. 2018).

In conclusion, we observed higher anti-*T. gondii*-IgG seroprevalence in Polish adult donors in comparison to pediatric allo-HCT recipients and pediatric allo-HCT donors, thus its prevalence increases with age. We also observed that most of HCT patients received prophylaxis against *PjP* with TMP/SMX, which is active against *T. gondii*. However, its use depends on transplant centre practice. No prospective PCR screening for *T. gondii* infection is provided in Polish pediatric transplant centres. Finally, we have shown that toxoplasmosis in our country was rare and occurred only in the group of allo-HCT recipients. Current diagnostics and different treatment in each patient with antiprotozoal treatment was effective and resulted in full recovery. Since pre-HCT *T. gondii* serology was not assessed in all HCT recipients, we suggest this test should be standard practice but standardisation of management of infection of *T. gondii* in children after HCT is needed.

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