Clinical Features and Outcomes in Patients With Disseminated Toxoplasmosis Admitted to Intensive Care: A Multicenter Study

Matthieu Schmidt,[1] Romain Sonneville,[2] David Schnell,[3] Naike Bigé,[4] Rebecca Hamidfar,[5] Nicolas Mongardon,[6] Vincent Castelain,[7] Keyvan Razazi,[8] Antoine Marty,[9] François Vincent,[10] Martin Dres,[11] Stephane Gaudry,[12] Charles Edouard Luyt,[13] Vincent Das,[14] Jean-Baptiste Micol,[15] Alexandre Demoule,[1] and Julien Mayaux[1]

[1]Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale, [2]Université Paris Diderot, Sorbonne Paris Cité, Assistance Publique–Hôpitaux de Paris, Hôpital Bichat–Claude-Bernard, Service de Réanimation Médicale et des Maladies Infectieuses, [3]Hôpital Saint-Louis, Service de Réanimation Médicale, and [4]Hôpital Saint Antoine, Service de Réanimation Médicale, Paris; [5]Hôpital Albert Michalon, Service de Réanimation Médicale, Grenoble; [6]Hôpital Cochin, Service de Réanimation Médicale, Paris; [7]Hôpital de Hautepierre, Service de Réanimation Médicale, Strasbourg; [8]Hôpital Henri Mondor, Service de Réanimation Médicale, Créteil; [9]Institut Gustave Roussy, Service de Réanimation Médico-Chirurgicale, Villejuif; [10]Hôpital Avicenne, Service de Réanimation Médico-Chirurgicale, Bobigny; [11]Hôpital Kremlin Bicêtre, Service de Réanimation Médicale, Bicêtre; [12]Hôpital Louis Mourier, Service de Réanimation Médico-Chirurgicale, Colombes; [13]Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Réanimation Médicale, Paris; [14]Centre Hospitalier Intercommunal André Grégoire, Service de Réanimation Médico-Chirurgicale, Montreuil; and [15]Hôpital Gustave Roussy, Service d'Hématologie, Villejuif, France

Background. Characteristics and outcomes of adult patients with disseminated toxoplasmosis admitted to the intensive care unit (ICU) have rarely been described.

Methods. We performed a retrospective study on consecutive adult patients with disseminated toxoplasmosis who were admitted from January 2002 through December 2012 to the ICUs of 14 university-affiliated hospitals in France. Disseminated toxoplasmosis was defined as microbiological or histological evidence of disease affecting >1 organ in immunosuppressed patients. Isolated cases of cerebral toxoplasmosis were excluded. Clinical data on admission and risk factors for 60-day mortality were collected.

Results. Thirty-eight patients were identified during the study period. Twenty-two (58%) had received an allogeneic hematopoietic stem cell transplant (median, 61 [interquartile range {IQR}, 43–175] days before ICU admission), 4 (10%) were solid organ transplant recipients, and 10 (27%) were infected with human immunodeficiency virus (median CD4 cell count, 14 [IQR, 6–33] cells/μL). The main indications for ICU admission were acute respiratory failure (89%) and shock (53%). The 60-day mortality rate was 82%. Allogeneic hematopoietic stem cell transplant (hazard ratio [HR] = 2.28; 95% confidence interval [CI], 1.05–5.35; $P = .04$) and systolic cardiac dysfunction (HR = 3.54; 95% CI, 1.60–8.10; $P < .01$) within 48 hours of ICU admission were associated with mortality.

Conclusions. Severe disseminated toxoplasmosis leading to ICU admission has a poor prognosis. Recipients of allogeneic hematopoietic stem cell transplant appear to have the highest risk of mortality. We identified systolic cardiac dysfunction as a major determinant of outcome. Strategies aimed at preventing this fatal opportunistic infection may improve outcomes.

Keywords. disseminated toxoplasmosis; multiorgan failure; immunosuppression; allogeneic stem cell transplant; outcome assessment.

Received 12 May 2013; accepted 16 August 2013; electronically published 30 August 2013.

Correspondence: Matthieu Schmidt, MD, Service de Pneumologie et de Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital, 75651 Paris Cedex 13, France (matthieuschmidt@yahoo.fr).

Clinical Infectious Diseases 2013;57(11):1535–41

DOI: 10.1093/cid/cit557

Toxoplasma gondii is a ubiquitous parasite found worldwide. Reactivation of latent disease can cause infection, not only in patients with human immunodeficiency virus (HIV) infection, but also in patients who have undergone allogeneic hematopoietic stem cell transplant (HSCT) [1] and recipients of solid organ transplant [2]. Despite progress in prophylaxis and early diagnosis [3–5], toxoplasmosis is still a significant

Table 1. Patient Characteristics in Intensive Care Unit

Patient Characteristics (N = 38)	No. (%) or Median (IQR)
Hematological malignancies	24 (63)
Acute leukemia, myeloid or lymphoid	13 (34)
Lymphoma, Hodgkin or non-Hodgkin	6 (16)
Other disease	5 (16)
Time of hematological malignancy course, mo	40 (15–101)
Allogenic HSCT	22 (58)
Genoidentical stem cell transplant	5 (13)
Phenoidentical stem cell transplant	9 (24)
Cord blood transplant	8 (21)
Time between allogeneic HSCT and ICU admission, d	61 (43–175)
Grade II–IV graft-vs-host disease	9 (24)
D/R *Toxoplasma gondii* serostatus	
D^+/R^+	7 (18)
D^-/R^+	15 (39)
Solid organ transplant	4 (10)
Kidney	2 (5)
Liver	2 (5)
Time between solid organ transplant and ICU admission, d	760 (49–1734)
D/R *Toxoplasma gondii* serostatus	
D^+/R^-	2 (5)
D^-/R^+	1 (3)
D^-/R^-	1 (3)
HIV	10 (27)
CD4 cell count, cells/μL	14 (6–33)
HIV load, $\log_{10}$/mL	5.0 (5.0–5.1)
Duration of HIV infection, mo[a]	92 (37–184)
Reason for ICU admission	
Acute respiratory failure	34 (89)
Neurological impairment	16 (42)
Shock	20 (53)
Temperature, °C	38.5 (37.8–39.0)
Systolic cardiac dysfunction[b]	16 (42)
Hemophagocytic lymphohistiocytosis	12 (32)
Neutropenia	6 (18)
Biological value at ICU admission	
Leukocyte count, cells/μL	3830 (1900–10 800)
Lymphocyte count, cells/μL	230 (120–450)
Lactate dehydrogenase level, IU/L	2575 (1456–4703)
Lactate level, mmol/L	3.5 (1.6–8.0)
Ferritin maximum value, μg/L[c]	12 579 (5650–45 575)
Troponin maximum value, μg/L	0.58 (0.25–3.09)
Time between symptoms and ICU admission, d	2 (1–4)
Time between symptoms and specific treatment, d[d]	3.0 (1.0–5.5)
Time to specific treatment after ICU admission, d[d]	0 (0–1.5)
Specific treatment[d]	
Pyrimethamine-sulfadiazine	16 (44)
Pyrimethamine-clindamycin	8 (22)
Trimethoprim-sulfamethoxazole	11 (30)
Other treatment	
Invasive mechanical ventilation within first 48 hours	34 (89)
Duration of mechanical ventilation, d	4 (1–17)
Renal replacement therapy during ICU stay	24 (63)
Vasopressors within first 48 hours	33 (87)

Abbreviations: D, donor; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; IQR, interquartile range; R, recipient.

[a] Obtained from 6 of 10 HIV patients.

[b] Cardiac function evaluated by echocardiography was obtained on 34 patients within first 48 hours.

[c] Obtained from 17 patients.

[d] In 36 of 38 patients, 2 patients did not receive antitoxoplasmosis-specific treatment.

threat for immunosuppressed patients. In patients with a severe neurological form leading to intensive care unit (ICU) admission, hospital mortality averages 24% [6]. Although toxoplasmosis presents most often as a localized central nervous system infection, severely immunocompromised patients are also exposed to disseminated toxoplasmosis [1]. Disseminated toxoplasmosis mostly involves the lungs [7, 8], but may also cause myocarditis and hepatitis, which, although less frequent than cerebral forms, are associated with worse prognosis. [9–11]. It is noteworthy that severe forms necessitating ICU transfer have not been thoroughly described [12]. The purpose of the present study was to describe the clinical and biological features and the outcome of adults with disseminated toxoplasmosis admitted to ICU over a 10-year period.

PATIENTS AND METHODS

The study was conducted in 14 adult ICUs located in university-affiliated hospitals in France, between 1 January 2002 and 1 January 2012. The study was approved by the Institutional Review Board of the Pitié-Salpêtrière University Hospital (CCP Ile de France VI).

Selection of Patients

A search of all retrospective cases of toxoplasmosis was conducted on the ICUs' databases. After the analysis of each

patient's record by 2 investigators, only the patients who met the criteria of disseminated toxoplasmosis according to the following criteria were included in the study: (1) immunosuppression and (2) evidence of infection by *Toxoplasma gondii* defined by either (a) microbiological evidence of a positive real-time polymerase chain reaction (PCR) by amplification of its B1 gene [13–15] result in peripheral blood and in either bronchoalveolar lavage (BAL) or in a bone marrow aspirate, or (b) the demonstration in >1 organ of parasites by direct histopathology examination from tissue biopsy specimens (May-Grünwald-Giemsa staining [16]). Patients with isolated cerebral toxoplasmosis were excluded from the present study. Trimethoprim-sulfamethoxazole (TMP-SMZ) or pyrimethamine prophylaxis at the time of ICU admission was recorded for all patients.

Data Collection

The following data were collected for each patient: any history of immunosuppression (ie, hematological malignancies, solid organ transplant, or HIV infection) and pretransplant toxoplasmosis serostatus of the donor and the recipient for patients with allogeneic HSCT or solid organ transplant. Time of HIV diagnosis, ongoing treatment, CD4 cell count, and HIV RNA were collected as well.

Physiological variables and laboratory data were collected on admission. Simplified Acute Physiology Score (SAPS) II [17] and Sequential Organ Failure Assessment (SOFA) [18] were calculated at ICU admission. Reasons for ICU admission were classified as acute respiratory failure (ie, oxygen therapy >5 L/min required to obtain saturation of peripheral oxygen >95%), neurological impairment (ie, seizures, motor deficit, coma, or delirium), and shock (ie, evidence of tissue hypoxia with sustained hypotension and vasopressors infusion). Neutropenia was defined as a neutrophil count <500 cells/μL, whereas hemophagocytic lymphohistiocytosis was defined according to the diagnostic guidelines [19]. Systolic cardiac dysfunction was defined as an ejection fraction ≤40% within 48 hours of ICU admission (Table 1).

Advanced life support measures taken during the ICU stay (mechanical ventilation, vasopressors, and renal replacement therapy), therapeutic regimens, and time between ICU admission

Table 2. Univariate Analysis of Risk Factors Associated With Mortality

Patient Characteristics (n = 36)[a]	Alive 60 Days After ICU Admission (n = 7)	Dead 60 Days After ICU Admission (n = 29)	60-Day Mortality		
			HR	95% CI	*P* Value
Sex, male	5 (71)	18 (63)	0.96	.46–2.11	.93
Age, y	42 (39–57)	47 (36–56)	0.99	.96–1.02	.54
Underlying disease					
Hematological malignancy	1 (14)	22 (76)	2.80	1.22–7.25	.01
HIV	4 (57)	5 (17)	0.41	.14–1.01	.05
Solid organ transplant	2 (29)	2 (7)	0.51	.08–1.72	.32
Underlying risk factor					
Neutropenia	1 (14)	5 (17)	0.85	.28–2.06	.73
Allogeneic HSCT	1 (14)	20 (69)	2.28	1.05–5.35	.04
Reason for ICU admission					
Acute respiratory failure	5 (71)	27 (93)	2.43	.72–15.07	.17
Neurological impairment	3 (43)	11 (38)	1.00	.45–2.10	.99
Shock	3 (43)	15 (52)	1.50	.72–3.18	.28
Systolic cardiac dysfunction[b]	0 (0)	16 (55)	3.54	1.60–8.10	<.01
Invasive mechanical ventilation[c]	4 (57)	28 (96)	6.01	1.26–107.6	.02
Hemophagocytic lymphohistiocytosis	2 (29)	10 (34)	0.96	.43–2.03	.91
Lactate level at ICU admission, mmol/L	1.7 (1.3–2.3)	3.8 (1.7–8.0)	1.16	1.05–1.27	<.01
Time between symptoms and ICU admission, d	1 (0–6)	2 (1–4)	1.02	.93–1.09	.69
Time between symptoms and specific treatment, d	3 (1–6)	3.0 (1.5–6.0)	0.99	.03–1.05	.97
SAPS II	50 (32–67)	63 (48–82)	1.03	1.00–1.05	<.01
SOFA score day 1	8 (7–10)	13 (10–18)	1.15	1.06–1.25	<.01

Categorical variables are expressed as No. (%) and continuous variables as median (interquartile range).

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

[a] Performed on 36 of 38 patients. Two patients did not receive antitoxoplasmosis specific treatment and were excluded for survival analysis.

[b] Cardiac function evaluated by echocardiography was obtained on 34 patients within the first 48 hours.

[c] Within the first 48 hours.

and commencement of antitoxoplasmosis therapy were determined for each patient.

We also recorded ICU and 60-day mortality, which were extracted from the patient's file or by contacting the patient's treating physician.

Statistics

Qualitative variables are expressed as number and percentage and the quantitative variables as median and interquartile range (IQR). Comparisons between groups were performed using the χ^2 tests for categorical variables and with the Mann-Whitney *U* test for the quantitative variables. The α error was set at .05. A Cox regression was performed to identify baseline variables associated with outcome, and unadjusted hazard ratios for death with their 95% confidence intervals were calculated (Table 2). Kaplan-Meier survival curves were computed for clinically relevant parameters associated with 60-day mortality, and comparisons were made using the Mantel-Cox log-rank test. The statistical analysis was performed with Prism 4.01 software (GraphPad Software, San Diego, California) and JMP 9.0.0 software for Windows (SAS Institute, Cary, North Carolina).

RESULTS

Patient Selection and Criteria for Disseminated Toxoplasmosis

During the 10-year study period, 38 patients (median age, 47 years [IQR, 38–56 years]; 63% male) fulfilled our inclusion criteria (Figure 1). The main characteristics of these patients at ICU admission are presented in Table 1.

Hematological malignancy was the most common cause of immunosuppression, accounting for 63% (n = 24) of cases. Among them, 22 of 24 (92%) patients had allogeneic HSCT, of whom one-third received a cord blood transplant. Two patients with non-Hodgkin lymphoma (B-cell and T-cell, respectively) did not receive allogeneic HSCT. HIV infection was the second most common cause of immunosuppression (n = 10 [27%]). Solid organ transplant accounted for 10% of cases (Figure 1). A negative *Toxoplasma* serostatus prior to transplant was noted in 3 patients who received a solid organ transplant (Table 1). None of the patients received TMP-SMZ or pyrimethamine prophylaxis.

Blood PCR results were positive for all patients tested (34/34), and were positive in the cerebrospinal fluid in 8 of 10 cases, in the BAL fluid in 30 of 31 cases, and in bone marrow in 10 of 13 cases. Histopathological examination was positive in BAL fluid in 28 of 31 cases and in bone marrow in 8 of 13 cases. Autopsy confirmed diagnosis in 5 cases. Pneumonitis (83%), brain abscesses (25%), bone marrow (28%), and meningitis (22%) were the most common manifestations of *Toxoplasma* infection. In 1 patient, autopsy confirmed bowel, adrenal gland, and pancreas *Toxoplasma* involvement.

Patient Features and Management

Reasons for ICU admission were mostly acute respiratory failure (89%), followed by shock (53%) and neurological

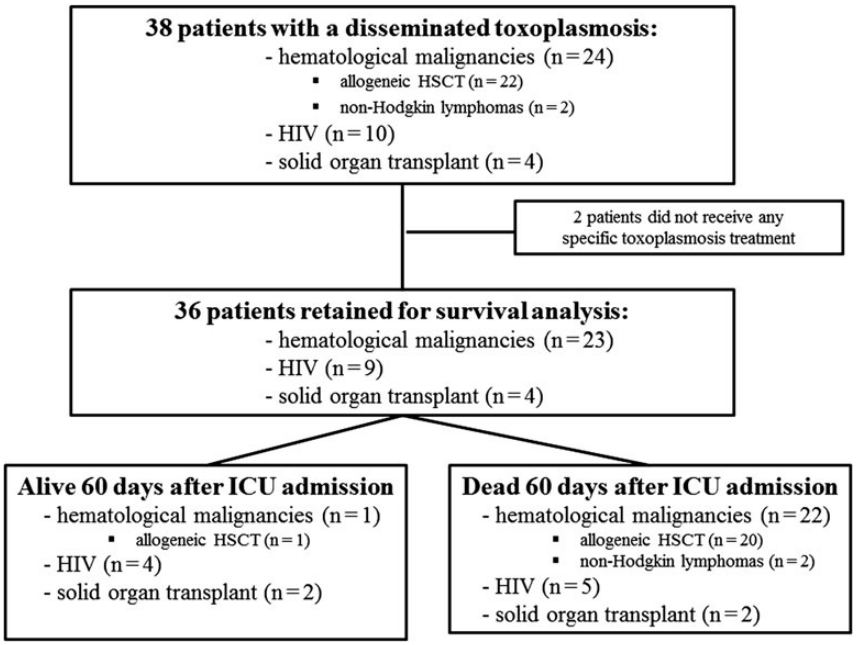

Figure 1. Patient flow chart. Abbreviations: HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit.

impairment (42%). Of note, the median lactate dehydrogenase and serum lactate levels were 2575 IU/L (IQR, 1456–4703 IU/L) and 3.5 mmol/L (IQR, 1.6–8.0 mmol/L), respectively. Additionally, a severe systolic cardiac dysfunction was found in 40% of the patients within 48 hours of ICU admission, whereas 32% had an additional diagnosis of hemophagocytic lymphohistiocytosis.

Mechanical ventilation was instituted in 35 (92%) patients within 48 hours of ICU admission (n = 34); the duration of mechanical ventilation was 4 (1–17) days. One other patient had mechanical ventilation commenced within 5 days. Vasopressive drugs were required in 33 (87%) patients, and 24 (63%) required renal replacement therapy. All but 2 patients received specific antitoxoplasmosis treatment, which was initiated a median of 0 days (IQR, 0–1.5 days) after ICU admission. The 2 patients not receiving specific antitoxoplasmosis treatment were excluded from survival analysis.

Outcomes

The median ICU stay was 4 days (IQR, 1–18 days). Overall ICU mortality was 78% (30/38 patients), and 60-day mortality was 82% (31/38). Survival analysis was performed on 36 patients who received specific antitoxoplasmosis treatment. Factors significantly associated with mortality included hematological malignancies as the underlying cause of immunosuppression, allogeneic HSCT, SAPS II score, SOFA at admission, elevated lactate levels, and systolic cardiac dysfunction (Table 2). All patients with systolic cardiac dysfunction died within 60 days of ICU admission. Survival was also significantly lower in patients who received mechanical ventilation within 48 hours of ICU admission (Figure 2).

DISCUSSION

Our major findings can be summarized as follows: (1) Among the immunocompromised patients in this cohort, most had received an allogeneic HSCT and had not been receiving prophylaxis at the time of diagnosis; (2) the main indications for ICU admissions were acute respiratory failure and shock; (3) overall ICU mortality and 60-day mortality were very high; and (4) hematological malignancies, cardiac dysfunction within first 48 hours, high SAPS II, and high SOFA at ICU admission were associated with high 60-day mortality.

Risk Factors of Disseminated Toxoplasmosis

To date, only 1 study, performed in the 1990s, reported presentation and outcome of patients with disseminated toxoplasmosis requiring ICU admission [12]. This monocentric cohort was of small size (9 patients) and focused on patients with HIV infection in the pre–highly active antiretroviral therapy (HAART) era [12]. We report a more contemporary, large, multicenter cohort in which disseminated toxoplasmosis was mostly observed in patients with hematological malignancies and absence of prophylaxis. As previously reported [1, 9, 20], we confirmed that pretransplant seropositivity of the recipients (22/22) was a risk factor for toxoplasmosis in patients with HSCT, suggesting reactivation of latent infection following high doses of immunosuppressive agents. As opposed to the low rate of cord blood transplant (6%) in a recent international report of HSCT [21], our cohort had an unexpectedly higher rate (21%). In response to severe impairment of cellular immunity and absence of specific immunity in the donor [22–24], our data suggest that cord blood transplant recipients could be at higher risk to develop a fatal disseminated toxoplasmosis than recipients of other types of allogeneic HSCT [25].

Outcome

This study highlights the fact that disseminated toxoplasmosis is a devastating opportunistic infection with very high ICU and 60-day mortality rates. The high mortality rate was consistent with a previous finding in 41 patients with HSCT, and 9 patients with HIV described in the 1990s [9, 12]. We also observed that 60-day survival was lower in patients with hematological malignancies than in patients with HIV infection or solid organ transplant. To illustrate, only 1 of 23 patients with hematological malignancies was alive 60 days after ICU admission (Table 2; Figure 2). A recent multicenter study focused on 22 patients with solid organ transplant reported a lower hospital mortality rate (14%) [26], but this cohort included less disseminated toxoplasmosis (22.7%) and more patients with isolated neurological localization (27%) (ie, patients who were excluded from our cohort) [26]. As previously reported in the pre-HAART era [12], disseminated toxoplasmosis in HIV patients still occurred with a high level of immunosuppression. The mortality that we observed in this population remained very high despite advanced life support measures (Table 1).

Clinical Features

The high mortality in our cohort could be partially explained by delays in diagnosis: 7 of 38 patients of our cohort died before a microbiological or histological diagnosis of toxoplasmosis was confirmed, and 2 of 38 died without having received any specific antitoxoplasmosis treatment (Figure 1). However, in our analysis, time between first symptoms and instigation of specific therapy was not associated with outcome. Disseminated toxoplasmosis may have various clinical presentations, which makes its diagnosis difficult. However, a very high level of immunosuppression, septic shock with a rapid multiorgan failure, a high serum lactate dehydrogenase level, and an absence of prophylaxis were common clinical features [12]. This was even

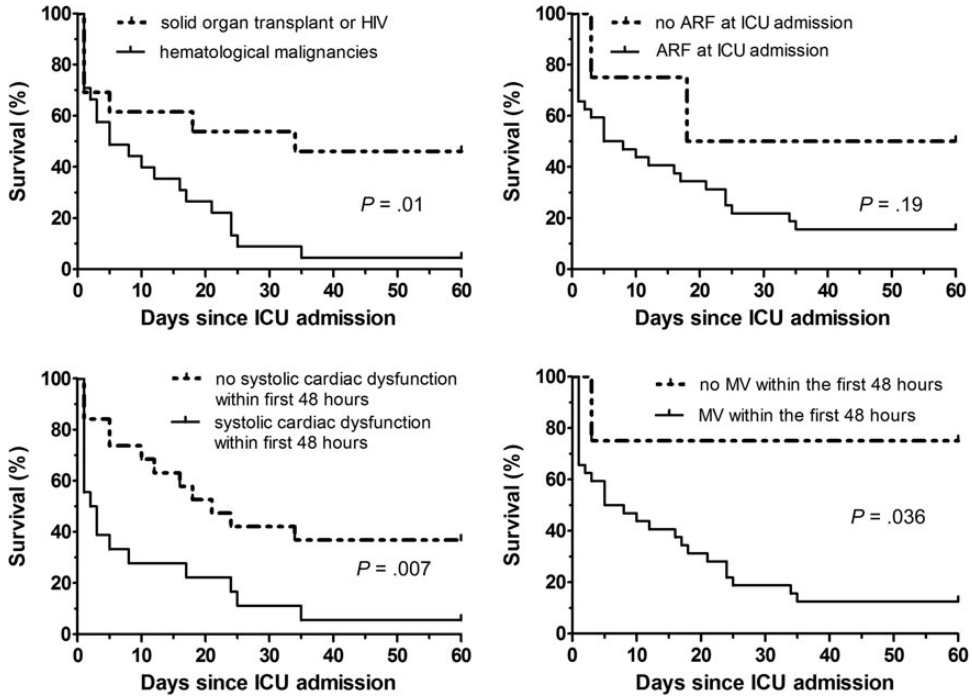

Figure 2. Effect of hematological malignancies, acute respiratory failure at intensive care unit admission, systolic cardiac dysfunction, or mechanical ventilation on survival in patients with disseminated toxoplasmosis. Abbreviations: ARF, acute respiratory failure; HIV, human immunodeficiency virus; ICU, intensive care unit; MV, mechanical ventilation.

more apparent in those patients with acute myocarditis, defined as severe left ventricular systolic dysfunction [26]. It is remarkable that cardiac dysfunction was also strongly associated with mortality in our cohort.

Patient Management

Negative *Toxoplasma* serostatus prior to transplant was found to be an independent risk factor for toxoplasmosis in solid organ transplant recipients [26]. In contrast, positive *Toxoplasma* serostatus seems to be a risk factor for patients with HIV and hematological malignancies [9, 12]. In addition, the rapid fatal evolution of the disease and difficult diagnosis should encourage physicians to consider routine toxoplasmosis PCR detection, at least in blood specimens in at-risk patients [4, 5, 20, 27]. Chemoprophylaxis could also be an alternative. However, the low incidence of disseminated toxoplasmosis should be weighed against the potential hematological toxicity of TMP-SMZ in patients with hematological disease, particularly during the close period after allogeneic HSCT. In our cohort, poor or delayed engraftment was the major reason for absence or discontinuation of prophylaxis during the period surrounding HSCT. Nevertheless, patients with allogeneic HSCT, in particular, those with cord blood transplant, are a challenging target group for prompt prophylaxis [5, 25, 28]. In these patients, chemoprophylaxis with atovaquone [29] or azithromycin [25, 30, 31] could be an interesting alternative before the transplant engraftment.

Limitations of the Study

There are several limitations to this study. First, although we have reported one of the largest populations of disseminated toxoplasmosis in ICUs to date, this is a retrospective study performed in multiple centers caring for patients with hematological malignancies or solid organ transplant. Second, we studied a mixed population of HIV-infected patients and HSCT and solid organ transplant recipients who had their own specificities (ie, management of toxoplasmosis diagnosis, prophylaxis, and treatment), and a detailed analysis of factors associated with 60-day mortality in each patient subgroup was not performed. Third, we cannot exclude the fact that the diagnosis, management, and prevention of toxoplasmosis before ICU and in ICU have changed during the study's period of 10 years.

In conclusion, disseminated toxoplasmosis in immunocompromised patients was essentially observed in allogenic HSCT and in absence of prophylaxis. The poor prognosis following ICU admission suggests that early detection and prompt preemptive treatment before ICU admission represent essential management strategies to improve outcomes. Early initiation of prophylaxis for patients with high-risk allogeneic HSCT

(ie, cord blood transplant) and with positive *Toxoplasma* serostatus pre-HSCT should be advocated.

Notes

Acknowledgments. The authors thank the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (GRRR-OH). They also thank Dr Aidan Burrell and Tony Trapani for editing assistance, and Nathalie Gault for her statistical advice.

Financial support. M. S. was supported by the French Intensive Care Society; the Fonds de dotation Recherche en Santé Respiratoire, 2012; the Collège des Enseignants de Réanimation Médicale; and the Fonds d'Etudes et de Recherche du Corps Médical, Assistance publique-Hôpitaux de Paris.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Slavin MA, Meyers JD, Remington JS, Hackman RC. *Toxoplasma gondii* infection in marrow transplant recipients: a 20 year experience. Bone Marrow Transplant **1994**; 13:549–57.
2. Montoya JG, Liesenfeld O. Toxoplasmosis. Lancet **2004**; 363:1965–76.
3. Bretagne S, Costa JM, Fleury-Feith J, Poron F, Dubreuil-Lemaire ML, Vidaud M. Quantitative competitive PCR with bronchoalveolar lavage fluid for diagnosis of toxoplasmosis in AIDS patients. J Clin Microbiol **1995**; 33:1662–4.
4. Bretagne S, Costa JM, Kuentz M, et al. Late toxoplasmosis evidenced by PCR in a marrow transplant recipient. Bone Marrow Transplant **1995**; 15:809–11.
5. Martino R, Bretagne S, Einsele H, et al. Early detection of *Toxoplasma* infection by molecular monitoring of *Toxoplasma gondii* in peripheral blood samples after allogeneic stem cell transplantation. Clin Infect Dis **2005**; 40:67–78.
6. Sonneville R, Schmidt M, Messika J, et al. Neurologic outcomes and adjunctive steroids in HIV patients with severe cerebral toxoplasmosis. Neurology **2012**; 79:1762–6.
7. Mendelson MH, Finkel LJ, Meyers BR, Lieberman JP, Hirschman SZ. Pulmonary toxoplasmosis in AIDS. Scand J Infect Dis **1987**; 19:703–6.
8. Pomeroy C, Filice GA. Pulmonary toxoplasmosis: a review. Clin Infect Dis **1992**; 14:863–70.
9. Martino R, Maertens J, Bretagne S, et al. Toxoplasmosis after hematopoietic stem cell transplantation. Clin Infect Dis **2000**; 31:1188–95.
10. Sing A, Leitritz L, Roggenkamp A, et al. Pulmonary toxoplasmosis in bone marrow transplant recipients: report of two cases and review. Clin Infect Dis **1999**; 29:429–33.
11. Busemann C, Ribback S, Zimmermann K, et al. Toxoplasmosis after allogeneic stem cell transplantation—a single centre experience. Ann Hematol **2012**; 91:1081–9.
12. Lucet JC, Bailly MP, Bedos JP, Wolff M, Gachot B, Vachon F. Septic shock due to toxoplasmosis in patients infected with the human immunodeficiency virus. Chest **1993**; 104:1054–8.
13. Reischl U, Bretagne S, Krüger D, Ernault P, Costa J-M. Comparison of two DNA targets for the diagnosis of toxoplasmosis by real-time PCR using fluorescence resonance energy transfer hybridization probes. BMC Infect Dis **2003**; 3:7.
14. Menotti J, Vilela G, Romand S, et al. Comparison of PCR-enzyme-linked immunosorbent assay and real-time PCR assay for diagnosis of an unusual case of cerebral toxoplasmosis in a stem cell transplant recipient. J Clin Microbiol **2003**; 41:5313–6.
15. Costa JM, Pautas C, Ernault P, Foulet F, Cordonnier C, Bretagne S. Real-time PCR for diagnosis and follow-up of *Toxoplasma* reactivation after allogeneic stem cell transplantation using fluorescence resonance energy transfer hybridization probes. J Clin Microbiol **2000**; 38:2929–32.
16. Derouin F, Sarfati C, Beauvais B, Iliou MC, Dehen L, Lariviere M. Laboratory diagnosis of pulmonary toxoplasmosis in patients with acquired immunodeficiency syndrome. J Clin Microbiol **1989**; 27:1661–3.
17. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA **1993**; 270:2957–63.
18. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med **1996**; 22:707–10.
19. Janka GE. Hemophagocytic syndromes. Blood Rev **2007**; 21:245–53.
20. Chandrasekar PH, Momin F. Disseminated toxoplasmosis in marrow recipients: a report of three cases and a review of the literature. Bone Marrow Transplant Team. Bone Marrow Transplant **1997**; 19: 685–9.
21. Passweg JR, Baldomero H, Gratwohl A, et al. The EBMT activity survey: 1990–2010. Bone Marrow Transplant **2012**; 47:906–23.
22. Duband S, Cornillon J, Tavernier E, Dumollard J-M, Guyotat D, Péoc'h M. Toxoplasmosis with hemophagocytic syndrome after bone marrow transplantation: diagnosis at autopsy. Transpl Infect Dis **2008**; 10:372–4.
23. Delhaes L, Mraz J-C, Fréalle E, et al. Severe pulmonary toxoplasmosis after allo-SCT in two patients: from *Toxoplasma* genotyping to clinical management. Bone Marrow Transplant **2010**; 45:580–3.
24. Fricker-Hidalgo H, Bulabois C-E, Brenier-Pinchart M-P, et al. Diagnosis of toxoplasmosis after allogeneic stem cell transplantation: results of DNA detection and serological techniques. Clin Infect Dis **2009**; 48: e9–15.
25. Bautista G, Ramos A, Forés R, et al. Toxoplasmosis in cord blood transplantation recipients. Transpl Infect Dis **2012**; 14:496–501.
26. Fernàndez-Sabé N, Cervera C, Fariñas MC, et al. Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: a matched case-control study. Clin Infect Dis **2012**; 54:355–61.
27. Aoun M, Georgala A, Mboumi K, et al. Changing the outcome of toxoplasmosis in bone marrow transplant recipients. Int J Antimicrob Agents **2006**; 27:570–2.
28. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant **2009**; 15:1143–238.
29. Katlama C, Mouthon B, Gourdon D, Lapierre D, Rousseau F. Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. Atovaquone Expanded Access Group. AIDS **1996**; 10:1107–12.
30. Tabbara KF, Hammouda E, Tawfik A, Al-Omar OM, Abu El-Asrar AM. Azithromycin prophylaxis and treatment of murine toxoplasmosis. Saudi Med J **2005**; 26:393–7.
31. Godofsky EW. Treatment of presumed cerebral toxoplasmosis with azithromycin. N Engl J Med **1994**; 330:575–6.