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Central nervous system infections in solid organ transplant recipients: Results from the Swiss Transplant Cohort Study

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SUMMARY

Objectives: To describe the epidemiology and clinical presentation of central nervous system (CNS) infections in solid organ transplant (SOT) recipients in the current era of transplantation.
Methods: Patients from the Swiss Transplant Cohort Study (STCS) transplanted between 2008 and 2018 were included with a median follow-up of 3.8 years. Epidemiological, microbiological, and clinical data were extracted from the STCS database and patients' medical records. We calculated incidence rates and 90-day survival of transplant recipients with CNS infection.
Results: Among 4762 patients, 42 episodes of CNS infection in 41 (0.8%) SOT recipients were identified, with an overall incidence rate of 2.06 per 1000 patient-years. Incidence of CNS infections was similar across all types of transplantations. Time to CNS infection onset ranged from 0.6 to 97 months after transplant. There were 22/42 (52.4%) cases of viral infections, 11/42 (26.2%) of fungal infections, 5/42 (11.9%) of bacterial infections and 4/42 (9.5%) of probable viral/bacterial etiology. Clinical presentation was meningitis/encephalitis in 25 cases (59.5%) and brain-space occupying lesions in 17 cases (40.5%). Twenty-three cases (60.5%) were considered opportunistic infections. Diagnosis were achieved mainly by brain biopsy/necropsy (15/42, 36%) or by cerebrospinal fluid analysis (20/42, 48%). Up to 40% of cases (17/42) had concurrent extra-neurological disease localizations. Overall, 90-day mortality rate was 29.0% (73.0% for fungal, 14.0% for viral and 11.0% for bacterial and probable infections, $p<0.0001$).
Conclusions: CNS infections were rare in the STCS, with viral meningoencephalitis being the most common disease. Fungal infections were associated with a high mortality.

Introduction

Neurologic complications occur in up to 40% of solid organ transplant (SOT) recipients and are caused by a wide range of etiologies, including infections, drug toxicity, cerebrovascular events, metabolic disorders, and cancer[1-4]. Non-infectious complications

Abbreviations: CI, Confidence interval; CMV, Cytomegalovirus; CNS, Central nervous system; CSF, Cerebrospinal fluid; EBV, Epstein-Barr virus; eCRF, Electronic case report; HSV, Herpes-simplex virus; ICU, Intensive care unit; IQR, Interquartile range; JCV, JC polyomavirus; PML, Progressive multifocal leukoencephalopathy; PTLD, Post-transplant lymphoproliferative disorders; SOT, Solid organ transplant; STCS, Swiss Transplant Cohort Study; TBE, Tick-borne encephalitis; TMP/SMX, Trimethoprim/sulfamethoxazole; VZV, Varicella-zoster virus.

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seem to be more frequent and tend to occur earlier than infections[2]. This is partially due to the introduction of effective antimicrobial preventive strategies such as vaccination, prophylaxis, and preemptive therapy, which have dramatically reduced the incidence of opportunistic infections in the current transplantation era[5]. Accordingly, the spectrum and burden of central nervous system (CNS) infections have changed, with a decreased incidence ranging from 24% in the 1970s[6] to 1.5% in more recent studies[2,7]. However, epidemiological data on CNS infections in SOT recipients are limited, as they mostly arise from single-center cohorts with few studies performed during the last two decades[2,6-16].

The diagnosis and management of CNS infections in immunocompromised patients remain challenging. First, CNS infections in the transplant setting may result from reactivation of latent infections, from donor-derived infections or by *de novo* infections caused by both opportunistic and "common" community-acquired pathogens[17,18], so that the differential diagnosis is broad. In addition, atypical clinical presentations of infection together with presence of non-infectious comorbidities (that may mimic or mask the neurological presentation of infection) may delay diagnosis[17]. Finally, high-quality evidence to guide the best therapeutic approach to CNS infections specifically in SOT recipients is lacking. Of note, management is often complicated by potential drug toxicities and drug-drug interactions between antimicrobial and immunosuppressive drugs[3]. Increasing our knowledge on the current epidemiology and clinical presentations of CNS infections in SOT recipients is essential to improve diagnostic, preventive, and therapeutic approaches in this specific group of patients.

In this study, we comprehensively describe the epidemiology, clinical presentation, management and outcomes associated with CNS infections within the Swiss Transplant Cohort Study (STCS), a prospective cohort of SOT recipients that collects high-quality data on infectious complications following transplantation[19].

Patients and methods

Study design and patient's population

The STCS is a multicenter nationwide cohort, involving six Swiss transplantation centers, where comprehensive and structured data of all SOT recipients in Switzerland are prospectively collected since May 2008. Patient- and organ-specific data, including infections, are collected at the time of transplantation, at 6 and 12 months, and yearly thereafter. Data are entered into a central database system through a standardized electronic case report (eCRF). The present study included all SOT recipients enrolled in the STCS since May 2008 until December 2018. Patients without informed consent to participate in the STCS at enrollment or with subsequent consent withdrawal were excluded. The local Ethics Committees at each center approved the STCS. The local Ethics Committee at the Lausanne University Hospital approved the protocol of the present study (Protocol number 2019–01698).

Data collection

We used the STCS database for available data regarding the occurrence of infection, demographic and clinical data, as well as patient and graft survival. Clinical data includes the characteristics of transplantation, immunosuppressive therapy, diagnosis and therapy of rejection and use and duration of antimicrobial prophylaxis. Infectious disease events, including CNS infections, are collected by transplant infectious diseases specialists according to the definitions developed by the STCS Infectious Diseases Working Group[20,21]. Infections are diagnosed and managed at each center according to local guidelines as part of routine clinical practice. For all identified cases of CNS infection, a specific CRF was filled out to retrieve detailed data not routinely collected in the STCS database, including clinical characteristics, microbiological data, radiologic imaging, and diagnosis and management of CNS infections, as well as the net state of immunosuppression at time of infection.

Definitions of CNS infection

Definitions of infection followed the STCS Infectious Diseases guidelines developed by the STCS infectious-disease working group[22]. Proven CNS infections were defined by pathogen isolation and the presence of signs and symptoms or clinical evidence of CNS infection [radiographic evidence and/or pleocytosis, elevated protein and/or decreased glucose at cerebrospinal fluid (CSF) analysis]. In the absence of microbiological documentation, CNS infections were considered probable if clinical response to specific antimicrobial treatment was observed. Fungal CNS infection required host, clinical (focal lesions or meningeal enhancement on imaging), and microbiological criteria (histopathologic, culture or PCR-based detection of a mold or yeast from CSF or brain tissue, cryptococcal antigen or galactomannan in CSF). We classified CNS infections into meningitis/encephalitis and brain-space occupying lesions according to the clinical presentation, and into opportunistic and non-opportunistic diseases according to the type of pathogen. CNS infections due to fungi, Epstein-Barr virus (EBV), cytomegalovirus (CMV), JC polyomavirus (JCV), *Listeria* and *Nocardia* were considered opportunistic infections. Although herpes-simplex virus (HSV) and varicella-zoster virus (VZV) infections are more common in SOT recipients, we classified them as non-opportunistic as they can also occur in immunocompetent patients. Although post-transplant lymphoproliferative disorder (PTLD) is not considered to be an infection, we decided to include it among the cerebral brain-space occupying lesions because of the strong association with EBV infection and because CNS PTLD is included in the differential diagnosis of brain abscess in transplant recipients. Of note, we only included EBV-related PTLD in this series. Regarding the CSF characteristics, pleocytosis was defined as a CSF cell count greater than 5 cells/mm^3, hyperproteinorrachia as a CSF protein concentration higher than 450 mg/L, and hypoglycorrachia as a CSF glucose concentration lower than 50 mg/dL. Glasgow Coma Scale and Glasgow Outcome Scale were used to define level of consciousness at presentation and degree of recovery, respectively.

Statistical considerations

Descriptive statistics were used to summarize the characteristics of study population and to illustrate the clinical presentation of CNS infections, according to type of infection, organ transplant, and time of onset after transplantation. Categorical variables were reported as counts and percentages, whilst continuous variables as median and interquartile ranges (IQR). Incidence rate of CNS infection was calculated per 1000 person-years. In case of sequential transplantations, the last transplantation before the occurrence of a CNS infection was considered as starting-point. Ninety-day survival following a CNS infection was estimated using the Kaplan–Meier method. The log-rank test was used to compare survival distribution between groups. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using R version 3.6.1 (R foundation for statistical computing, Vienna, Austria) and Graphpad Prism version 8.0.1 (La Jolla, California).

Results

Study population

Among the 5137 transplanted patients, 4762 (93%) were included in the study with a median follow-up of 3.86 years (IQR

Table 1
Baseline characteristics of the study population.

	SOT recipients with CNS infection (n = 41)	SOT recipients without CNS infection (n = 4721)
Sex, female n (%)	18 (43.9)	1694 (35.9)
Age at enrollment, years, median (IQR)	54.36 [37.77, 61.77]	54.16 [42.16, 62.10]
Type of transplantation, n (%)		
Kidney	23 (56.1)	2636 (55.8)
Liver	8 (19.5)	1025 (21.7)
Heart	4 (9.8)	357 (7.6)
Lung	6 (14.6)	429 (9.1)
Combined	0	228 (4.8)
Other[a]	0	46 (1.0)
Prior transplantation, n (%)	9 (22.0)	518 (11.0)
Living donor, n (%)	7 (17.1)	1145 (24.3)
Induction immunosuppression[b], n (%)		
Thymoglobulin	11 (26.8)	680 (14.4)
Basiliximab	25 (61.0)	3333 (70.6)
Maintenance immunosuppression[b,c], n (%)		
Tacrolimus	25 (61.0)	3506 (74.3)
Cyclosporine	13 (31.7)	963 (20.4)
Mycophenolate	35 (85.4)	4180 (88.5)
Azathioprine	1 (2.4)	67 (1.4)
Steroids	39 (95.1)	4238 (89.8)
mTOR inhibitor	1 (2.4)	136 (2.9)
Other	0	19 (0.4)
Antimicrobial prophylaxis[d], n (%)		
Ganciclovir/Valganciclovir	24 (58.5)	2073 (43.9)
Acyclovir/Valacyclovir	4 (9.8)	278 (5.9)
TMP-SMX	36 (87.8)	3999 (84.7)
Pentamidine/atovaquone	4 (9.8)	106 (2.2)
Inhaled Amphotericin B	4 (9.8)	450 (9.5)
Azoles	7 (17.1)	335 (7.1)
Caspofungin	2 (4.9)	67 (1.4)
Follow-up in years, median (IQR)	4.82 [1.69, 7.28]	3.85 [1.50, 6.82]

IQR, interquartile range; mTOR, mammalian target of rapamycin; SOT, solid organ transplant; TMP-SMX, trimethoprim-sulfamethoxazole.
[a] including Islets, pancreas, small bowel.
[b] Patients may have received more than one agent for induction and maintenance immunosuppression.
[c] at hospital discharge after transplantation.
[d] last prophylaxis regimen started within 30 days from transplantation.

1.51- 6.83). There were 2659 (55.8%) kidney, 1033 (21.7%) liver, 435 (9.1%) lung and 361 (7.6%) heart transplant recipients; 228 (4.8%) patients received a combined transplantation and 46 (1.0%) another type of organ (pancreas, islets or small bowel). Most patients received induction therapy with basiliximab (70.5%) and a maintenance immunosuppressive regimen including tacrolimus (74.1%), mycophenolate (88.5%) and steroids (89.8%). Initial prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX), antiviral prophylaxis with either (val-)ganciclovir or (val-)acyclovir and antifungal prophylaxis were administrated to 84.7%, 49.9% and 18.1% of the patients, respectively. Table 1 shows the demographic and clinical characteristics of the study population.

Epidemiology of CNS infections

Overall, we identified 42 cases of CNS infections in 41 (0.8%) patients, corresponding to an incidence rate of 2.06 per 1000 patient/years (95% confidence interval [CI], 1.49–2.79). CNS infections occurred in 23/2659 (0.9%) of kidney, 8/1033 (0.8%) liver, 6/435 (1.4%) lung and 4/361 (1.1%) heart transplant recipients. The frequency and type of CNS infections are described in Table 2. Viral infections were the most frequent cause of CNS infection (22/42, 52.4%), followed by fungal (11/42, 26.2%) and bacterial infections (5/42, 11.9%). There were three cases of probable viral meningitis/encephalitis (7.1%) and one case of probable bacterial meningitis (2.4%). All diagnosis of probable infections were based on clinical, radiological, laboratory CSF findings consistent with an infectious etiology (see Table S1), and they had a favorable outcome. The rate and pattern of CNS infections was similar throughout the study period and among the different transplant centers.

Time of CNS infection onset after transplantation differed according to the type of pathogen and transplanted organ, ranging from 0.6 to 97 months (Fig. 1). While 73% of fungal infections and 44% of HSV/VZV meningitis/encephalitis occurred within 6 months after transplant, a late onset was common among infections such as progressive multifocal leukoencephalopathy (PML) (3 cases, range 15–28 months), nocardiosis (3 cases, range 19–97 months) and cerebral EBV-related PTLD (6 cases, range 17–79 months). At the time of CNS infection, nearly 40% of patients were on TMP/SMX prophylaxis, 14.6% were on antiviral and 12.2% on antifungal prophylaxis.

In the subgroup of patients with available lymphocyte counts (n = 37) and immunoglobulin levels (n = 14) within 3 months before the diagnosis of CNS infection, median lymphocyte counts were 0.85 cells/mm^3 (range 0.1–5.9) and 21.4% of patients had immunoglobulin G levels <7 g/L. Overall, 11/41 (27%) of transplant recipients had experienced acute rejection in the 6 months preceding the CNS infection (6 fungal, 4 confirmed or probable viral and 1 bacterial infections) that required treatment with high-dose steroids or the use of thymoglobulin in 6/11 patients.

Characteristics of CNS infections

Twenty-five cases of meningitis/encephalitis and 17 cases of brain-space occupying lesions were identified. Table 2 shows the clinical characteristics of CNS infections. There were 23 cases

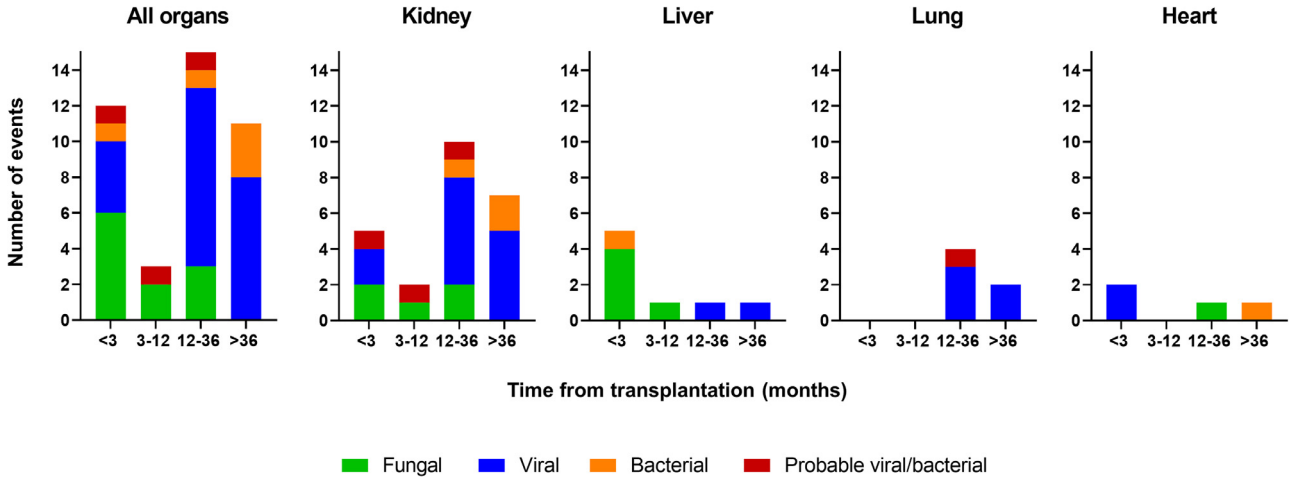

Fig. 1. Timeline of CNS infections according to type of pathogen and transplantation. The majority of fungal CNS infections occurred in liver and kidney transplant recipients within 3 months after transplantation, whilst viral and bacterial CNS infections occurred more frequently after 12 months post-transplantation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of opportunistic infections (23/38, 60.5%) and 15 cases of non-opportunistic infections (15/38, 39.5%).

The majority of microbiologically-documented meningitis/encephalitis had a viral etiology (16/21, 76.2%) and were considered non-opportunistic (15/21, 71.4%). Patients with meningitis/encephalitis presented at admission with headache (11/25, 44.0%), fever (10/25, 40.0%), altered mental status (9/25, 36.0%), and focal neurological signs (9/25, 36.0%) and were diagnosed through molecular assays performed on the CSF (15/21, 71.0%). A concurrent extra-neurological disease localization was present in 20% (5/25) of cases.

All cases of brain-space occupying lesions were opportunistic infections. *Aspergillus* spp. was the most frequent (8/17, 47%), followed by cerebral EBV-related PTLD (6/17, 35.3%) and nocardiosis (3/17, 17.7%). Patients with brain-space occupying lesions presented more frequently at admission with altered mental status (7/17, 41.2%), fever (6/17, 35.3%) and focal neurological signs (5/17, 29.4%) and had disseminated infection at the time of the diagnosis of CNS infection (12/17, 70.6%). Most of brain-space occupying lesions had a histopathologic or culture diagnosis obtained from a brain biopsy or at autopsy (13/17, 77%).

Laboratory and radiological characteristics of CNS infection according to type of pathogen are detailed in Table S1. Up to 9.8% of patients (4/41) developed CNS infection despite receiving effective antimicrobial prophylaxis regimens at the time of disease onset: one case of VZV meningitis/encephalitis occurred in a patient on prophylactic valganciclovir, and three liver transplant recipients who developed cerebral aspergillosis were receiving caspofungin or itraconazole.

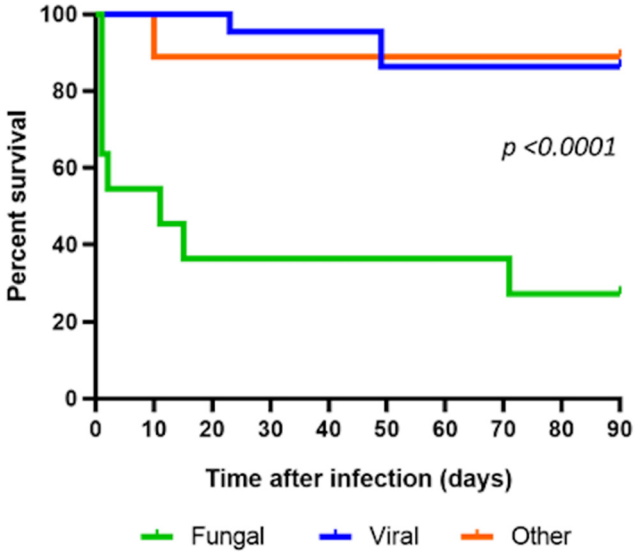

Fig. 2. Survival rate after CNS infections according to pathogen. Ninety-day mortality was 72.7% (8/11) for fungal infection (green line), 13.6% (3/22) for viral infection (blue line), and 11.1% (1/9) for other infections, including bacterial and probable viral and bacterial (orange line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Management and outcomes of CNS infections

Hospital admission was required in nearly all episodes of CNS infection (41/42, 97.6%) and 40.0% (16/40) were admitted to the intensive care unit (ICU). Median hospital and ICU length of stay were 26.5 (IQR, 16.7–49.2) and 14.5 (IQR, 5.0–20.7) days, respectively.

Seven out of the 42 episodes of infection were due to pathogens for which no specific therapy is available [3 cases of PML, 2 cases of tick-borne encephalitis (TBE), 2 of enterovirus meningitis]. Overall, 32/35 (91.4%) of patients with a treatable infection received an appropriate treatment, either empirically (14/35, 40%) or after microbiological confirmation (18/35, 51.4%). Three patients who did not receive antifungal treatment were diagnosed *postmortem* with disseminated aspergillosis.

In 50% of CNS infections, at least one immunosuppressive drug was withdrawn. No experimental therapies were given to patients diagnosed with PML and tapering of immunosuppressive regimen was done in all patients. In one case, the reduction of immunosuppression was followed by acute rejection, graft loss and eventually death 2 months later. All cerebral EBV-related PTLD were treated with reduction of immunosuppression, the anti-CD20 monoclonal antibody rituximab with or without methotrexate and/or radiotherapy. Of note, all patients diagnosed with PTLD were EBV seropositive before transplantation.

Overall 90-day mortality was 28.6% (12/42) and was significantly higher after fungal CNS infection (72.7% for fungal, 13.6% for viral and 11.1% for bacterial and probable viral/bacterial infections, $p<0.0001$) (Fig. 2). Among viral infections, no deaths were

Table 2
Microbiological and clinical characteristics of CNS infections.

	All CNS infections (n = 42)
Type of infection, n (%)	
Viral infection	22 (52.4)
VZV meningoencephalitis	7
EBV-related CNS PTLD	6
PML	3
HSV meningoencephalitis	2
Tick-borne encephalitis	2
Enterovirus meningitis	2
Fungal infection	11 (26.2)
Aspergillosis (*A. fumigatus, Aspergillus* spp.)	8
Cryptococcosis (*C. neoformans*)	3
Bacterial infection	5 (11.9)
Nocardiosis (*N. farcinica*)	3
Neuroborreliosis	1
Enterococcus spp/*E. coli* meningitis	1
Probable viral meningitis/encephalitis	3 (7.1)
Probable bacterial meningitis	1 (2.4)
Signs and symptoms at presentation[a], n (%)	
Fever	16 (38.1)
Headache	14 (33.3)
Nausea/vomiting	5 (11.9)
Neck stiffness	5 (11.9)
Focal neurological deficits	14 (33.3)
Seizure	7 (16.7)
Cognitive impairment	6 (14.3)
Altered mental status	16 (38.1)
Other	8 (19.0)
Glasgow Coma Scale at presentation, n (%)	
≥14	32 (76.2)
8–13	4 (9.5)
<8	6 (14.3)
Disseminated infection[a], n (%)	17/38 (44.7)
Respiratory tract, n (%)	9/38 (23.7)
Nocardiosis	2/9
Aspergillosis	6/9
Cryptococcosis	1/9
Mucocutaneous, n (%)	7/38 (18.4)
VZV meningoencephalitis	4/7
Nocardiosis	2/7
Cryptococcosis	1/7
Peri/myocardial, n (%)	3/38 (7.9)
Aspergillosis	3/3
Abdominal, n (%)	3/38 (7.9)
Aspergillosis	1/3
EBV-related PTLD	1/3
Nocardiosis	1/3
Bone, n (%)	2/38 (5.3)
Nocardiosis	2/2
Other[b]	2/38
Non-infectious neurologic complication[a,c], n (%)	10 (23.8)
CNI toxicity	3 (7.1)
Cerebrovascular event	1 (2.4)
Metabolic disorder	5 (11.9)
Other	1 (2.4)

CNI: calcineurin inhibitors; CSF: central nervous system; EBV: Epstein-Barr virus; HSV: Herpes-simplex virus; PML: Progressive multifocal leucoencephalopathy; PTLD: Post-transplant lymphoproliferative disease; VZV: Varicella-zoster virus.
[a] more than one findings could be present.
[b] including eye and urinary tract.
[c] they were concomitant with the CNS infection.

observed in transplant recipients with HSV and VZV meningoencephalitis as opposed to patients with PML (2/3, 67.0%), TBE (1/2, 50.0%) and cerebral EBV-related PTLD (2/6, 33.0%). Among patients who were alive 90 days following the CNS infection, long-term neurological sequelae in terms of severe or moderate disability were reported in 6/27 (22.2%), including 3 cases of HSV encephalitis, 1 case of PML, 1 case of aspergillosis and 1 case of bacterial meningitis.

Discussion

In this nationwide cohort, CNS infections represented a rare complication of SOT recipients with the majority of cases being viral meningoencephalitis followed by fungal brain-occupying lesions. Our data suggest that SOT recipients are affected not only by opportunistic pathogens, but also by infections occurring in the general population, so that these should always be considered in the differential diagnosis of CNS infections in immunocompromised patients. Moreover, fungal infections involving the CNS were associated with a poor outcome compared to the other etiologies. This multicenter observational study represents, to our knowledge, the largest comprehensive overview over 10 years of CNS infections during the current era of immunosuppression, universal antimicrobial preventive strategies, and advanced diagnostic techniques.

Incidence rates of CNS infections in SOT recipients reported in the literature range from 1% to 24% and vary widely according to the study period and the transplanted organ[2,6-16]. In our study, 0.8% of transplanted patients developed a CNS infection, as reported in most recent studies[2,7,11]. Compared to other cohorts of SOT recipients[1,11,16], we observed a different spectrum of pathogens, probably due to geographical variations in epidemiology and different use of preventive strategies. We did not observe cases of *Listeria* meningitis, while two cases of TBE were diagnosed, reflecting the epidemiology of these pathogens in the general population in Switzerland (incidence of 0.6 and 4.4 per 100,000 person/year in 2018 for listeriosis and TBE, respectively)[23,24]. Moreover, no episodes of cerebral toxoplasmosis were reported; this is consistent with the results from a European survey of SOT recipients[25] and may be explained by the universal prophylaxis with TMP/SMX.

Time of occurrence of CNS infections after transplantation varies widely according to the etiology. Invasive aspergillosis was more often an early post-transplant complication, occurring during the first three months after transplantation, especially in liver transplant recipients[26-28]. Conversely, nocardiosis and PML were characterized by a late onset after transplantation[29,30]. In agreement with a large European registry of SOT recipients, cerebral PTLD occurred in our study mainly between the second and the seventh year post-transplant[31].

The clinical presentation of CNS infections in our cohort greatly differed according to the pathogen, but some clinical clues may help guide the differential diagnosis. For instance, all brain abscesses due to nocardiosis and *Aspergillus* occurred in patients with disseminated disease. *Nocardia farcinica* is the species we identified in all our cases of nocardiosis, which is known for its preferential tropism for the CNS, skin and soft tissues[29,32]. Concurrent pulmonary involvement has been documented in more than 70% of patients with CNS aspergillosis, suggesting a hematogenous dissemination of infection. Most of VZV meningitis/encephalitis are associated with dissemination (57% in our cohort) or a prior episode of herpes zoster[33,34], although absence of a rash is documented in about half of the cases of VZV encephalitis[35].

Our findings emphasize the unique challenge in the diagnosis of CNS infection in SOT recipients because of the atypical or blunted clinical presentation and the frequent presence of concomitant non-infectious complications. Only 38% of patients with CNS infection in our cohort presented at admission with fever and almost 25% had a metabolic disorder or drug toxicity with associated neurologic symptoms mimicking CNS infection. Invasive CNS aspergillosis was diagnosed *postmortem* in more than 60% of the cases in our cohort, potentially due to the absence of specific signs and symptoms, a fulminant evolution, atypical lesion at

neuroimaging and/or suboptimal yield of microbiological diagnostic tests. Clinicians should have a low threshold for including infection in the differential diagnosis in SOT recipients with subtle and unspecific neurological complaints.

We observed a significantly higher mortality rate of invasive fungal infections as compared to other etiologies. CNS localization of *Aspergillus* is known to be associated with increased risk of death[4,27,36] that remains above 80%, as we observed in our cohort. Based on our present experience showing that *Aspergillus* was the most frequent cause of brain-space occupying lesions (47% of the cases), a more aggressive management might be pursued in patients presenting with space-occupying brain lesions with immediate administration of empiric antifungal therapy and diagnostic work-up[37,38].

This study has several limitations. First, despite the prospective design of the STCS, some data was retrospectively collected by chart review. Additionally, it was not possible to analyze the risk factors for the development of CNS infections in SOT recipients because of the rarity and heterogeneity of the events. To this aim, multinational cohorts would be needed. Moreover, the epidemiology of infections found in our study is only representative of Switzerland; larger multinational cohorts would also allow describing the burden of disease in other geographical contexts. Nevertheless, inclusion of almost all SOT recipients and the systematic follow-up within the STCS makes the data presented here representative of the epidemiology and burden of CNS infections in the modern transplant era in a Central Europe country.

In conclusion, the incidence of CNS infections is low in the current era of immunosuppression and antimicrobial prophylaxis in comparison to previous studies. CNS infections remain an important cause of death in SOT recipients, particularly fungal infections. Despite improved diagnostic tests and better treatment options, CNS infections in SOT recipients remain uniquely challenging, underscoring the need for an increased awareness and aggressive diagnostic and therapeutic approaches in this population.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.05.019.

Appendix

List of active members of the Swiss Transplant Cohort Study (STCS)

The members of the Swiss Transplant Cohort Study are: Patrizia Amico, Andres Axel, John-David Aubert, Vanessa Banz, Beckmann Sonja, Guido Beldi, Christoph Berger, Ekaterine Berishvili, Isabelle Binet, Pierre-Yves Bochud, Sanda Branca, Heiner Bucher, Thierry Carrel, Emmanuelle Catana, Yves Chalandon, Sabina De Geest, Olivier De Rougemont, Michael Dickenmann, Joëlle Lynn Dreifuss, Michel Duchosal, Thomas Fehr, Sylvie Ferrari-Lacraz, Christian Garzoni, Paola Gasche Soccal, Christophe Gaudet, Déla Golshayan, Nicolas Goossens, Karine Hadaya, Jörg Halter, Dimitri Hauri, Dominik Heim, Christoph Hess, Sven Hillinger, Hans Hirsch, Patricia Hirt, Günther Hofbauer, Uyen Huynh-Do, Franz Immer, Michael Koller (Head of the Data Center), Bettina Laesser, Brian Lang, Roger Lehmann, Alexander Leichtle (Head of the Biobank), Christian Lovis, Oriol Manuel, Hans-Peter Marti, Pierre Yves Martin, Michele Martinelli, Valérie McLin, Katell Mellac, Aurélia Merçay, Karin Mettler, Nicolas Mueller (Chairman Scientific Committee), Antonia Müller, Thomas Müller, Ulrike Müller-Arndt, Beat Müllhaupt, Mirjam Nägeli, Graziano Oldani, Manuel Pascual (Executive office), Klara Posfay-Barbe, Juliane Rick, Anne Rosselet, Simona Rossi, Silvia Rothlin, Frank Ruschitzka, Urs Schanz, Stefan Schaub, Aurelia Schnyder, Macé Schuurmans, Thierry Sengstag, Federico Simonetta, Katharina Staufer, Susanne Stampf, Jürg Steiger (Head, Excecutive office), Guido Stirniman, Ueli Stürzinger, Christian Van Delden (Executive office), Jean-Pierre Venetz, Jean Villard, Julien Vionnet, Madeleine Wick (Coordinator), Markus Wilhlem, Patrick Yerly

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