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TRANSPLANT INFECTIOUS DISEASE

REVIEW ARTICLE

Donor-derived infections: The Swiss perspective

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Abstract

While Switzerland has not yet established a systematic approach, the small size of the country and the intensive collaboration between the transplant infectious disease teams facilitate a rapid communication once a donor-derived infection is suspected. Critical information regarding donor infections is shared rapidly, and appropriate measures are discussed. The long-term observational Swiss Transplant Cohort Study, which includes >92% of all solid organ recipients collects all relevant infectious disease episodes and facilitates detection of patterns of potential donor-derived infection.

KEYWORDS
donor-derived infection, Swiss perspective, Swiss Transplant Cohort Study

1 | INTRODUCTION

Solid organ transplantation in Switzerland is centrally coordinated at the national level. Five organ donation networks oversee all pre-donation processes, including the detection and assessment of potential organ donors. A national organ allocation system matches the organ offers with potential recipients. Organ-specific national working groups determine criteria for inclusion and prioritization on the national waiting list. *Swisstransplant*, a national non-profit foundation, is entrusted by the Federal Conference of Cantons (states) to oversee the coordination of organ transplantation, which includes facilitating occasional foreign organ exchange and conducting quality control measures. In 2023, a total of 584 organs were transplanted across six designated transplant centers. The partition is similar to other regions: approximately 50% of transplants involve kidneys, 25% livers, 12% lungs, 10% hearts, and 3% pancreases. Since 2008, all potential recipients are offered the participation in the nationwide Swiss Transplant Cohort Study (STCS, www.stcs.ch). All consenting solid organ transplant (SOT) recipients are enrolled, initiating prospective data and sample collection from the moment of transplantation. Data collected encompass patient and organ-specific variables; additionally, infectious disease (ID) events are gathered by a transplant ID specialist in each center. During the first year, viable cells, plasma, and DNA are stored in a biobank. Consent rate exceeds 92% of all SOT recipients for the extensive dataset and sampling. Nonetheless, in accordance with national transplant legislation, all patients are systematically followed with a minimal dataset. Outcomes, such as organ loss, death, and malignant tumors, have to be reported to the health care authorities once a year.[1]

Currently, Switzerland lacks specific reporting requirements for adverse events across all categories, as recommended by the World Health Organization.[2] This stands in contrast to other regions, particularly Europe, where an European Framework of the Evaluation of Organ Transplants has formulated recommendations on the vigilance of human organs intended for transplantation.[3] Each member country is responsible for implementation of such a rapid alert system. The German experience was recently published.[4] In the latest update of the Swiss Bylaw on transplantation, this gap has been addressed and

Switzerland is currently in process of implementing such a system. *Swisstransplant* has been mandated to oversee and host this vigilance system.

Some donor-derived infections clearly fulfill the criteria for reporting in a vigilance system. The majority of organs from multi-organ donors will be allocated for transplantation in Switzerland. Fostered by the close collaboration in the STCS, the respective transplant ID specialists have built a well-connected working group, which so far served as an informal rapid exchange of information related to potential ID problems of organ donors (and recipients). This group is open to all interested in transplant IDs. In addition, a formal Swisstransplant ID working group was created, which is an official part of Swisstransplant and has an advisory function, for example, uniform SARS-CoV-2 screening guidelines were developed and constantly adapted. Any Swiss-wide donor-related guidelines would have to be proposed by this group and approved by the respective bodies of Swisstransplant.

Critical questions about eligibility of donors with infections are discussed on a case-by-case basis. If unexpected and early infections occur, other centers are notified, and information is gathered and shared. This process is facilitated via *Swisstransplant*, with additional information exchange taking place among local transplant ID specialists. The advantage is rapid dissemination of crucial information within a small network, enabling discussions and streamlining a uniform response. This collaboration led to the identification of a potential gap in preventive measures in liver transplantation with discordant donor–recipient Herpes simplex virus (HSV)-1 and HSV-2 serology, which was subsequently analyzed, leading to adaptation of national recommendations on HSV prophylaxis.[5] This may be a first step to a possible harmonization of antimicrobial prophylaxis in Switzerland—all centers still have their individual approach.

The measures taken if an infection is reported in a donor are decided on a case-by-case basis. The goal is always to enable transplantation if the risk is reasonable. In a donor with a positive blood culture, the transplant ID working group usually recommends a 7-day course of a targeted antibiotic treatment in the recipient, taking into account the treatment of the donor. If possible, follow-up blood cultures are done in the donor before organ retrieval. If colonization is present (rectal swab, urine, other locations), preemptive treatment of the recipient is only initiated under special circumstances. Switzerland has a still low prevalence of multidrug-resistance pathogens, and routine surveillance has not been implemented so far. Currently, except for SARS-CoV-2, there are no uniform donor screening guidelines in place in Switzerland, and the decision lies with the respective center. No mandated follow-up of patients is requested for specific potential donor-derived infections. Again, the centers decide on a case-by-case basis.

One example of such a potential donor-derived infection, where a pro-active management might have mitigated the risk for the recipients, is the case of a potential donor with an adrenal mass, which was histologically assessed before transplantation and malignancy ruled out, but central necrosis and peripheral calcifications were noted. The donor was cleared for transplantation, when the subsequent work-up yielded a positive polymerase chain reaction for *Echinococcus multilocularis*. A (retrospective) extensive work-up did not show any other foci in the donor, with no radiological or serological signs of active disease. Nevertheless, after extensive consultation among the group and taking into consideration the type of transplant (kidneys, lungs, and liver were transplanted), it was decided to give some preemptive treatment to the liver and kidney, but not the lung recipient. All were followed with serology, which has been negative since.

2 | THE POTENTIAL OF THE SWISS TRANSPLANT COHORT STUDY

No systematic reporting was required so far, and adverse events were analyzed on a case-by-case basis. While early, unexpected infections in SOT recipients usually raise concerns about the possibility of a donor-derived infection, later infections do less, but still may be related to the donor. The STCS is uniquely suited as most recipients are enrolled with the full dataset, allowing detection of some patterns also at later time points after transplantation. The data collection is not restricted to ID events, malignant tumors, among many other variables, are collected as well.

Since 2012, for each transplant ID event, transplant ID physicians have to classify in the STCS database if the episode constitutes a potential donor-related infection. An embedded project is planned to retrospectively categorize all episodes flagged as potential donor-derived infection using the proposed classification by Ison et al.[6] In a preliminary feasibility analysis, 1220 ID episodes in 846 patients were marked as a potential donor-derived infection. The distribution of events closely mirrors the transplant activity: kidney transplant recipients with 557 potential episodes (46%), followed by liver recipients with 286 episodes (23%) and lung and heart recipients with 185 (15%) and 131 (11%) episodes, respectively.

Some of these events are likely to be categorized as "expected," that is, cytomegalovirus primary infection in case of a high-risk serology constellation. The structure of the cohort will allow identifying all recipients of any given donor, even if not transplanted in the same center. Once an informed consent is obtained and ethical approval is granted for the nested project, this information can be analyzed collectively throughout the entire follow-up period. After categorization, a risk profile with variables potentially impacting the donor-derived infection rate can be established. Short- and mid-term effects on graft function, graft failure, and death can be analyzed; however, a careful adjustment for confounding factors will be necessary. Besides this retrospective analysis, the role of the STCS has to be defined in any mandatory reporting system. A real-time assessment for donor-derived infections will not be possible, as some information is added with a delay. However, it can serve to validate any events reported in the context of a vigilance system to analyze potential gaps in reporting, and will also be able to look at the mid- and long-term follow-up of any such patients.

The importance of another nationwide cohort study, the Swiss HIV cohort study (www.shcs.ch), became evident when Switzerland

performed the first liver transplantation from a human immunodeficiency virus (HIV)-positive donor to a recipient living with HIV. The comprehensive treatment and resistance history allowed for a rapid assessment of both donor and recipient.[7]

3 | SUMMARY

Despite a Swiss national law and bylaw specifically dedicated to transplantation (even including xenotransplantation already in 2007), the requirement for a reporting system has only been recently introduced into legislation. The details are currently being worked out between the stakeholders. The informal processes in place between the centers, fostered by a close collaboration in the STCS, have ensured a rapid dissemination of information on potential donor-derived infection, with immediate actions taken if necessary in each center.

A planned nested project embedded in the STCS will analyze potential donor-derived ID episodes and allow a more granular view on prevalence, risk factors, and impact of donor-derived infections.

AUTHOR CONTRIBUTIONS

Conceptualization: Nicolas J. Mueller. *Writing—original draft, review, and editing*: Nicolas J. Mueller, Cédric Hirzel, and Oriol Manuel.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

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