Management of allergy transfer upon solid organ transplantation

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Allergy transfer upon solid organ transplantation has been reported in the literature, although only few data are available as to the frequency, significance, and management of these cases. Based on a review of 577 consecutive deceased donors from the Swisstransplant Donor-Registry, 3 cases (0.5%) of fatal anaphylaxis were identified, 2 because of peanut and 1 of wasp allergy. The sera of all 3 donors and their 10 paired recipients, prospectively collected before and after transplantation for the Swiss Transplant Cohort Study, were retrospectively processed using a commercial protein microarray fluorescent test. As early as 5 days posttransplantation, newly acquired peanut-specific IgE were transiently detected from 1 donor to 3 recipients, of whom 1 liver and lung recipients developed grade III anaphylaxis. Yet, to define how allergy

Abbreviations: IgE-Bcs, IgE-producing B cells; SOT, solid organ transplantation; SPT, skin prick test; STCS, Swiss Transplant Cohort Study.

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†The Swiss Transplant Cohort Study members are listed in the Appendix.

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Anaphylaxis is a frequent cause of hospitalization with an estimated annual fatality rate of ≈0.5 per 1 000 000. Food allergy being the most common cause for anaphylaxis in children and young adults, death due to food allergy was found in ≈25% of the reported patients.1 Peanuts or tree-nuts were the causative allergens in >70% of the cases in which the responsible allergen was identified. Other allergens frequently involved in fatal anaphylaxis are fish, milk, and egg but also bee and wasp venom, and drugs.1

The first cases of transplant-associated allergy transfer were reported after hematopoietic stem cell transplantation, likely caused by IgE-specific B cells or T helper type 2 cells that were cotransferred with hematopoietic stem and progenitor cells.2 Subsequently, cases of allergy transfer were also described after solid organ transplantation (SOT), predominantly after liver, lung, or combined pancreas-kidney transplantation (Table 1).3-11 Only very few data are available as to the frequency, significance and mechanisms of IgE transfer in the setting of SOT. In addition, the impact of immunosuppression on IgE sensitization is poorly understood. The objectives of this study were (1) to identify the frequency and significance of allergy transfer based on retrospective analysis from the Swiss Transplant Donor Registry and the Swiss Transplant Cohort Study (STCS); (2) to evaluate whether allergy testing is feasible early after SOT; and (3) to make recommendations for the diagnosis and management of allergy transplant after SOT.

We retrospectively reviewed the data of 577 consecutive deceased donors from the Swisstransplant Donor-Registry (from January 2012 to May 2017) and identified 3 donors who died of anaphylaxis. In this registry, the individual history of severe allergy was not recorded. We then collected the prospectively stored sera of each donor-paired recipient from the STCS (Table 2),12 a prospective multicenter cohort including SOT performed in Switzerland as of May 2008. Sera of the recipients are prospectively collected at baseline (day of transplantation), 6 and 12 months after transplantation. In addition, sera were individually collected throughout the different centers at specific time points after transplantation. To assess the IgE profile of the donor and recipient’s sera, a commercial protein microarray fluorescent test bearing recombinant allergen molecules (ISAC™, ThermoFisher Scientific, Waltham, MA) was used. ISAC standardized units (ISU-E) were assessed using a cut-off value defined at 0.35 ISU. All recipients gave written informed consent for participation. Local ethics IRB committee (ID 2017-1058, CCER-GE) and Swisstransplant approved the study.

Skin prick tests (SPT), specific IgE values, and clinical symptoms were monitored in 5 adult living-donor kidney transplant recipients with symptomatic allergic rhinoconjunctivitis between November 2016 and August 2018. The rhinoconjunctivitis score was based on the subject’s nasal (runny nose, blocked nose, sneezing, itchy nose) and eye symptoms (gritty feeling/red/itchy eye and watery eye) using a 3-point scale (none = 0, slight symptoms = 1, moderate symptoms = 2, and severe symptoms = 3) for the 6 symptom classes. All recipients gave written informed consent (ID 2018-00965, CER-VD).

One young organ donor died of peanut-allergy-induced anaphylaxis leading to cardiac arrest with subsequent brain death. Upon admission, tryptase was >100 ng/mL (normal results: <10 ng/mL). With the consent of the relatives, the heart, lungs, liver, and kidneys were procured for transplantation. The liver was further split and transplanted into 2 recipients (Figure 1A). On posttransplant follow-up, the kidney of 1 recipient had to be explanted within the first week...
TABLE 1  Systematic review of the literature for allergy transfer

|                  | Series 1 | Series 2 | Series 3 | Series 4 | Series 5 | Series 6 | Series 7 | Series 8 |
|------------------|----------|----------|----------|----------|----------|----------|----------|----------|
| **Organ(s) with allergy transfer** | Liver    | Liver    | Liver    | Liver, lung | Liver-kidney | Pancreas-kidney, liver (no information provided) | Lung | Lung |
| **Organ(s) without allergy transfer** | Kidney, kidney-pancreas | — | Kidneys, heart | Kidney, pancreas | Pancreas-kidney | Kidney | — | Kidney, kidney-pancreas |
| **Cause of donor death** | Anaphylaxis | Anaphylaxis | Anaphylaxis | Car accident | Anaphylaxis | Anaphylaxis | Obstructed ventriculo-peritoneal shunt | Anaphylaxis |
| **Supposed responsible allergen for death** | Peanut, cashew, nut, sesame seed | Unknown | Peanut | — | Peanut | Peanut | — | Peanut |
| **Donor history of allergy** | Atopic dermatitis, asthma | Allergy to nuts, kiwi, seafood, and wheat | Asthma | Peanut allergy | — | Peanut allergy | Peanut allergy | Peanut allergy |
| **Anaphylaxis events (Muller classification) in the recipient** | POD 25 (grade 2), POW 32 (unclear) | POD 8 (grade 3) | POD 10 and 28 (grade 1) | Liver: POM 2 (grade 4), lung: POM 3 (grade 3) | POM 3 (grade 3) | — | POW < 4 (4 episodes, up to grade 4) | POD 4 (asthmatic crisis), POW 5-16 (asthmatic crisis), POM 7 (grade 3) |
| **Time to allergy test** | POW 9-10 | POW 4 | POD > 28 | Liver: POD 1, lung: POM 4 | POW > 12 | POW 4 | POW 8 | POW > 28 |
| **Duration of allergy (supposed)** | >48 wk | >3 wk | >4 wk | Liver: <8 mo, lung: >18 mo | >12 wk | <24 wk | <1.5 y | >7 y |
| **Skin Test** | Positive for peanut, cashew, sesame (POW 6) | Negative | Positive for peanut (POD28) | — | Positive for peanut (POM 1), negative (POM 6) | Positive for peanut (POM 2), negative (1 y after Tx) | Positive for peanut (POM > 7), negative (5 y after Tx) |
| **IgE serology** | Negative | Negative | Negative | Liver: positive for rAra h3 (POD 1), negative (POM 5), lung: positive for rAra h1-2-3 (POM 4-8-18) | Positive for peanut (POM 1), negative (POM 3) | Positive for rAra h1-2 (POM 1), negative (POM 6) | Negative | Negative (5 y after Tx) |
| **Oral challenge** | — | Positive for walnuts (grade 3, POW 4-5) | — | Liver: negative (POM 8) | — | Negative (POM 6) | Negative (1.5 y after Tx) | Positive (asthmatic crisis) 7 y after Tx |
| **Immunosuppression** | Tacrolimus, Azathioprine, Glucocorticoids | Tacrolimus, MMF, Glucocorticoids | Cyclosporine, Glucocorticoids | Liver: Cyclosporine, MMF, Glucocorticoids, lung: Tacrolimus, MMF Glucocorticoids | Cyclosporine, Azathioprine, Glucocorticoids | Azathioprine, Cyclosporine | Cyclosporine, Azathioprine, Glucocorticoids | (Continues) |
Muller et al.

Posttransplant because of multiple surgical complications and the patient was subsequently excluded from the analysis. Recombinant peanut-specific IgE known to be major elicitors of clinically relevant allergy could be detected in the donor (Ara h1: 42 ISU-E, Ara h2: 85 ISU-E, Ara h3: 36 ISU-E, and Ara h6: 61 ISU-E), and in both liver (LiverR1, LiverSplitR2) and lung recipients (LungR3), but neither in the kidney nor in the heart recipients of the same donor (Figure 1B,C).

In the case of LiverR1, an inadvertent oral ingestion of 2 peanuts on postoperative day (POD) 11 resulted in stomach pain, vomiting, and transient dyspnea. LungR3 underwent an oral challenge on POD 30 with a starting dose of 6 mg peanut (=1.5 mg peanut protein ED05). After the fifth dose, the patient developed urticaria, acute asthma, and stomach pain. The oral challenge was negative in LiverR2. However, the test was performed 9 months after transplantation when peanut-specific IgE were not detectable anymore in the patient's sera.

LiverR1 and LungR3 responded to treatment with antihistamines, glucocorticoids, and inhaled salbutamol. Two years after transplantation, an oral challenge with peanuts was well tolerated by recipient LiverR1 after SPT had become negative, whereas LungR3 refused a repeat oral challenge. Of note, recipients with de novo transferred-IgE were atopic as defined here by the presence of specific IgE against pollen, animal dander, or house dusts mites (Figure 1D). These data indicated that de novo occurrence of specific IgE to recombinant peanut allergen IgE (Ara h1, 2, 3, and 6) may predict allergy transfer in SOT.

3.2 Donor cases 2

The second donor had a history of wasp allergy and developed cardiac arrest after a wasp sting despite the self-application of epinephrine. Analysis of the sera upon admission showed a tryptase level of 3.95 ng/mL without significant elevation of specific IgEs to crude and recombinant wasp venom allergens (rVes v5 1.1 ISU-E, wasp IgE negative). An ISAC performed in both the donor and 2 recipients (kidney and lung) did not show any IgE transfer. In this case, failure to document an elevation of the tryptase or specific IgEs does not exclude the diagnosis of IgE-mediated anaphylaxis in light of the personal history, although a non-IgE-mediated anaphylaxis (mast cell release, IgG- or complement-mediated) might be possible. Overall, these data suggest that if the exact nature of an allergy is not appropriately documented in the donor, the pretest probability of identifying allergy transfer is likely reduced.

3.3 Donor cases 3

The third donor had an anaphylactic reaction with cardiac arrest supposedly mediated by peanut ingestion. On admission, tryptase was elevated (38.1 ng/mL) whereas serum IgE (measured by UniCAP™, ThermoFisher) to peanut (3.04 kUI/L), hazelnut (6.74 kUI/L), almond (1.14 kUI/L), cashew nut (1.27 kUI/L), and pistachio (3.24 UI/L) were only moderately elevated. Interestingly, in the sera of the donor a high level of nAct d1 (actindin) was...
**TABLE 2** Baseline clinical data of the recipients. Atopic status was assessed by the presence of specific IgE against, pollen, animal dander, or house dusts mites using commercial protein microarray bearing recombinant allergenic molecules (ISAC)

| Recipients organ | Donor | Baseline disease | Atopic status | Age at Tx (y) | Induction immunosuppression | Maintenance immunosuppression (6 mo) | Maintenance immunosuppression (12 mo) |
|------------------|-------|------------------|---------------|--------------|-----------------------------|--------------------------------------|--------------------------------------|
| Heart            | 1 (peanut) | Dilated cardiomyopathy (anthracycline-induced sarcoma) | Negative    | 11           | ATG, Glucocorticoids, TAC, MMF | TAC, MMF, Glucocorticoids | TAC, MMF, Glucocorticoids |
| Lung             | 1 (peanut) | Cystic fibrosis | Positive      | 25           | Basiliximab, CsA, MMF, Glucocorticoids | TAC, MPA, Glucocorticoids | TAC, MPA, Glucocorticoids |
| Liver left       | 1 (peanut) | Biliary atresia  | Positive      | 1            | Basiliximab, Glucocorticoids, TAC | Glucocorticoids, TAC | TAC |
| Liver right      | 1 (peanut) | Primary biliary cholangitis | Positive | 17           | Basiliximab, TAC, MMF | TAC, MMF | TAC, MMF |
| Kidney left      | 1 (peanut) | Hypertension/renovascular glomerulosclerosis | Negative | 76           | Thymoglobulin, TAC, MMF, Glucocorticoids | TAC, MMF, Glucocorticoids | TAC, MMF, Glucocorticoids |
| Lung             | 2 (wasp)   | Cystic fibrosis  | Positive     | 20           | Basiliximab, TAC, MMF, Glucocorticoids | TAC, MMF, Glucocorticoids | TAC, MMF, Glucocorticoids |
| Kidney left      | 2 (wasp)   | Glomerulonephritis/vasculitis | Negative   | 58           | Basiliximab, TAC, MMF, Glucocorticoids | Basiliximab, TAC, MMF, Glucocorticoids | Basiliximab, TAC, MMF, Glucocorticoids |
| Heart and kidney | 3 (peanut) | Ischemic heart disease, Hypertension/renovascular glomerulosclerosis | Negative | 49           | ATG, Glucocorticoids, CsA, MMF | Glucocorticoids, CsA, MMF | Glucocorticoids, CsA, MMF |
| Liver (left)     | 3 (peanut) | Sclerosing cholangitis | Negative | 5            | Basiliximab, TAC, MMF, Glucocorticoids | TAC, MMF | TAC, MMF |
| Kidney pancreas  | 3 (peanut) | Diabetic nephropathy (type 1 DM) | Negative | 49           | Thymoglobulin, TAC, MPA, Glucocorticoids | TAC, MPA | TAC, MPA |

CsA, cyclosporine; DM, diabetes mellitus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; TAC, tacrolimus; TX, transplantation.
found, a serological marker that can be associated with severe allergic reactions to kiwi. However, the serological analysis of the 3 recipients of this donor (i.e., pancreas-kidney, heart-kidney, and liver) showed no peanut and kiwi IgE at 6 months’ posttransplantation. Interestingly, the donor was also highly sensitized to animals (rCanf1: 87 ISU-E, rCanf5 46 ISU-E, rEqu c1: 19 ISU-E), ash/olive pollen (rOle e1 29 ISU-E), and mites (rDerp1 36 ISU-E), in contrast to the recipients in whom none of these specific IgE were detected. Notably, none of the recipients was atopic either (based on serology). In this case, a kiwi-induced anaphylaxis could not be excluded, emphasizing the importance of assessing the allergy profile of the donor at the time of transplantation.

3.4 | Diagnosis of IgE sensitization early after transplantation

So far, it remains unclear whether IgE and allergy transfer are affected by the immunosuppressive therapy. Also, the important question about whether detection of IgE sensitization is possible early after transplantation is unanswered. The overall number of IgE sensitizations of all 5 atopic recipients remained unchanged within the first 6 months after transplantation (Figure 1E). We therefore decided to study the impact of immunosuppressive therapy on IgE and allergy maintenance. To this purpose, we performed a prospective follow-up analysis on 5 symptomatic patients with pre-existing allergic rhinoconjunctivitis undergoing living donor kidney transplantation. None of the patients had been treated with antihistamines at the time of transplantation. All 5 patients received a standard induction and maintenance immunosuppressive therapy with basiliximab and methylprednisolone followed by oral tacrolimus, prednisone, and mycophenolate mofetil (Figure 2A).

SPT and serological analysis were performed before, 7 days, and 3 months after transplantation, respectively. Surprisingly, the immunosuppressive therapy only moderately affected the skin tests (SPT) results 7 days after transplantation (Figure 2B,C) and had no impact on the specific and total IgE levels (Figure 2D,E). Twenty-two of 23 and 21/23 of SPT remained positive 7 days and 3 months after transplantation, respectively. Finally, the rhinoconjunctivitis score (daily nasal and eye symptoms using a 4-point scale: none, mild, moderate, and severe) before and 3 months after transplantation did not show a significant improvement (Figure 2F). Overall, these results indicate that IgE sensitization is weakly affected early...
after transplantation and can be detected based on SPT and IgE serologies despite immunosuppressive therapy.

4 | DISCUSSION

4.1 | Mechanisms of allergy transfer after SOT

As reviewed in the literature (Table 1), allergy transfer was demonstrated after liver, lung, and pancreas transplantation, but so far not in heart and kidney recipients alone. One could therefore speculate that allergy transfer is a donor organ–specific phenomenon. Interestingly, in the case series reported by Berry et al, allergy transfer occurred in the pancreas-kidney recipient but not in the recipient of an isolated kidney, possibly because of the cotransplantation of a small bowel portion together with the pancreas. These data suggest that kidney and heart tissues are less likely to contain sufficient IgG1-memory B cells (IgG1-MBcs) and/or IgE-producing B cells (IgE-Bcs) (Figure 3). Thus, the majority of allergen-specific IgE in the blood does not originate from blood-derived B/plasma cells, suggesting that local IgE production in tissues is indeed the major source of allergen-specific IgE. Furthermore, it is known that persistence of some tissue-resident T cell clones can be organ-specific (ie, influenza-specific CD8+ T cells are predominantly found in the lungs whereas hepatitis-specific CD8 are predominantly found in the liver). The fact that plasmatic IgE can be detected as early as 24 hours after transplantation and that it persists up to several months/years suggests that the primary mechanism lies in the transfer of IgE-producing cells rather than in passive transfer of IgE only, because the half-life of free circulating IgE is known to be only 2 to 4 days. Interestingly, several groups reported positive SPT without elevation of blood IgE, suggesting that IgE alone can be also passively transferred and secondarily binds to mastocytes, which increases IgE half-life (Table 1 and Figure 3). Thus, SPT and IgE serological analysis can be complementary in the diagnosis of allergy transfer.
4.2 Persistence of sensitization and allergy

The persistence of sensitization after allergy transfer in SOT recipients over time is poorly understood. In our series, LiverR1 had detectable IgE for >393 days (Figure 1C), which turned negative 2 years after transplantation, whereas in LiverSplitR2 peanut-specific IgE were positive for <53 days. LiverR1 received an extended liver graft and eventually increased number of passenger leukocytes, but on the other hand LiverSplitR2 has never been exposed to peanut before peanut-specific IgE levels turned negative. Thus, early exposure to allergen after SOT may lead to expansion of IgE-Bcs, or alternatively switch from IgG1-MBcs into IgE-producing cells (Figure 3).

Interestingly, in lung transplant recipients, allergy transfer seems to persist longer than in liver recipients (Table 1), probably due to the high amount of immune cells in human lung tissue including 100 000 mast cells per gram of tissue. Khalid et al reported a lung recipient who developed an acute asthma attack without other symptoms of anaphylaxis 7 years after transplantation upon exposure to peanuts with negative SPT and negative peanut-specific IgE (Table 1, Series 8). This corroborates older data showing that previously nonasthmatic recipients can become asthmatic after lung transplantation from mildly asthmatic donors.

Finally, results from hematopoietic stem cell transplantation suggest that matured Th2-like cells or hematopoietic progenitor stem cells are also sufficient to induce and maintain long-term allergy transfer for (more than) 16 years. Thus, duration and persistence of the transferred allergy status over time may depend on the organ transplanted and mechanisms of allergy transfer.

4.3 Immunosuppression and allergy

Importantly, our data and that of others (Table 1) indicate that the conventional immunosuppression does not affect IgE-sensitization. This finding is not surprising since donor-specific IgG-producing B cells can mediate acute and/or chronic allograft rejection, which are 2 conditions that are associated with limited response to therapy despite several lines of treatments. Interestingly, it is also known that IgG-producing "passenger lymphocytes" can mediate acute hemolysis or idiopathic thrombocytopenic purpura within the first 2 weeks after liver transplantation.

It has been previously shown that sensitization and allergy symptoms in children after SOT might not be controlled by immunosuppression. On the contrary, the rate of sensitization in patients...
treated with tacrolimus was even increased. Our data from the 5 living-donor kidney recipients with allergic rhinoconjunctivitis support the observation that diagnosis of donor-derived IgE sensitization based on IgE and SPT is possible early after transplantation despite an immunosuppressive regimen based on basiliximab induction, methylprednisolone/prednisone, tacrolimus, and mycophenolate mofetil as maintenance treatment. Further studies assessing the impact on SPT and IgE of other commonly used immunosuppressive drugs (ie, thymoglobulin, azathioprine, or rapamycin) are warranted.

4.4 | Management and patient care

In summary, increased attention has to be given to the risk of allergy transfer after SOT. Unfortunately, the exact frequency and clinical consequences of IgE transfer remain poorly understood because the allergy/atopy status of the donors and recipients are rarely consequently assessed. This is a limitation of the present study, because we focused on donors with fatal anaphylaxis only. In cases of possible or probable fatal anaphylaxis, specific IgE testing in the donor should be performed as 1 of the first-line investigations to evaluate the possibility of allergy transfer (Figure 4). As donors with a history of severe allergy may die of other reasons than anaphylaxis (Table 1), we would also suggest to carefully explore history of severe allergic reaction to food, hymenoptera venom, and drugs with the family of the donor, albeit concise recommendations in this setting are difficult to implement in light of our current knowledge.

Regarding the recipients of organ donors with fatal anaphylaxis, those receiving a liver, lung, and pancreas should be closely monitored after transplantation. Furthermore, we encourage initially checking the atopic status of the recipient by using a qualitative serological screening test (eg, Phadiatop) and measurement of total IgE, because atopic patients may be at a higher risk of allergy transfer. Strict avoidance of eliciting food allergens is strongly advised and emergency medication (including self-injectable epinephrine device) should be prescribed. A detailed allergy work-up as well as follow-up of the sensitization profile is important. In case of donor-derived IgE sensitization transfer, SPT and IgE should be monitored over time. Food challenge should only be considered when SPT and IgE have turned negative (Figure 4) or in cases of low persisting food-specific IgEs when IgEs to recombinant allergens known to induce severe anaphylaxis are below the threshold level.

In conclusion, we demonstrate that SPT and IgE analysis can be performed as early as 7 days after transplantation. Therefore, postponing the allergological investigation is unnecessary. Prescription of antihistamines should be omitted in any case 7 days prior to SPT as per standard recommendation. Finally, good medical practice would include a food challenge to prove tolerance (Figure 4).

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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APPENDIX
The members of the Swiss Transplant Cohort Study are: Patrizia Amico, John-David Aubert, Vanessa Banz, Guido Beldi, Christian Benden, Christoph Berger, Isabelle Binet, Pierre-Yves Bochud, Sandra Branca, Heiner Bucher, Thierry Carell, Emmanuelle Catana, Yves Chalandon, Sabina de Geest, Olivier de Rougemont, Michael Dickenmann, Michel Duchosal, Laure Elkhrief, Thomas Fehr, Sylvie Ferrari-Lacraz, Christian Garzoni, Paola Gasche Soccal, Christoph Gaudet, Emiliano Giostra, Déla Golshayan, Karine Hadaya, Jörg Halter, Dimitri Hauri, Dominik Heim, Christoph Hess, Sven Hillinger, Hans H. Hirschl, Günther Hofbauer, Uyen Huynd-Do, Franz Immer, Richard Klaghofer, Michael Koller (Head of the data center), Bettina Laesser, Guido Laube, Roger Lehmann, Christian Lovis, Pietro Majno; Oriol Manuel, Hans-Peter Marti, Pierre Yves Martin, Michele Martinelli, Pascal Meylan, (Head, Biological samples management group), Philippe Morel, Nicolas J. Mueller (Chairman Scientific Committee), Antonia Müller, Thomas Müller, Beat Müllhaupt, Manuel Pascual (Executive office), Jakob Passweg, Clara Posfay-Barbe, Julianne Rick, Eddy Roosnek, Anne Rosselet, Silvia Rothlin, Frank Ruschitzka, Urs Schanz, Stefan Schaub, Aurelia Schnyder, Christian Seiler, Jan Sprachta; Susanne Stampf, Jürg Steiger (Head, Executive Committee), Antonia Müller, Thomas Müller, Beat Müllhaupt, Manuel Pascual (Executive office), Jakob Passweg, Clara Posfay-Barbe, Julianne Rick, Eddy Roosnek, Anne Rosselet, Silvia Rothlin, Frank Ruschitzka, Urs Schanz, Stefan Schaub, Aurelia Schnyder, Christian Seiler, Jan Sprachta; Susanne Stampf, Jürg Steiger (Head, Executive Office), Guido Stirnimann, Christian Toso, Christian Van Delden (Executive Office), Jean-Pierre Venetz, Jean Villard, Madeleine Wick (STCS coordinator), Markus Wilhelm, Patrick Yerly.