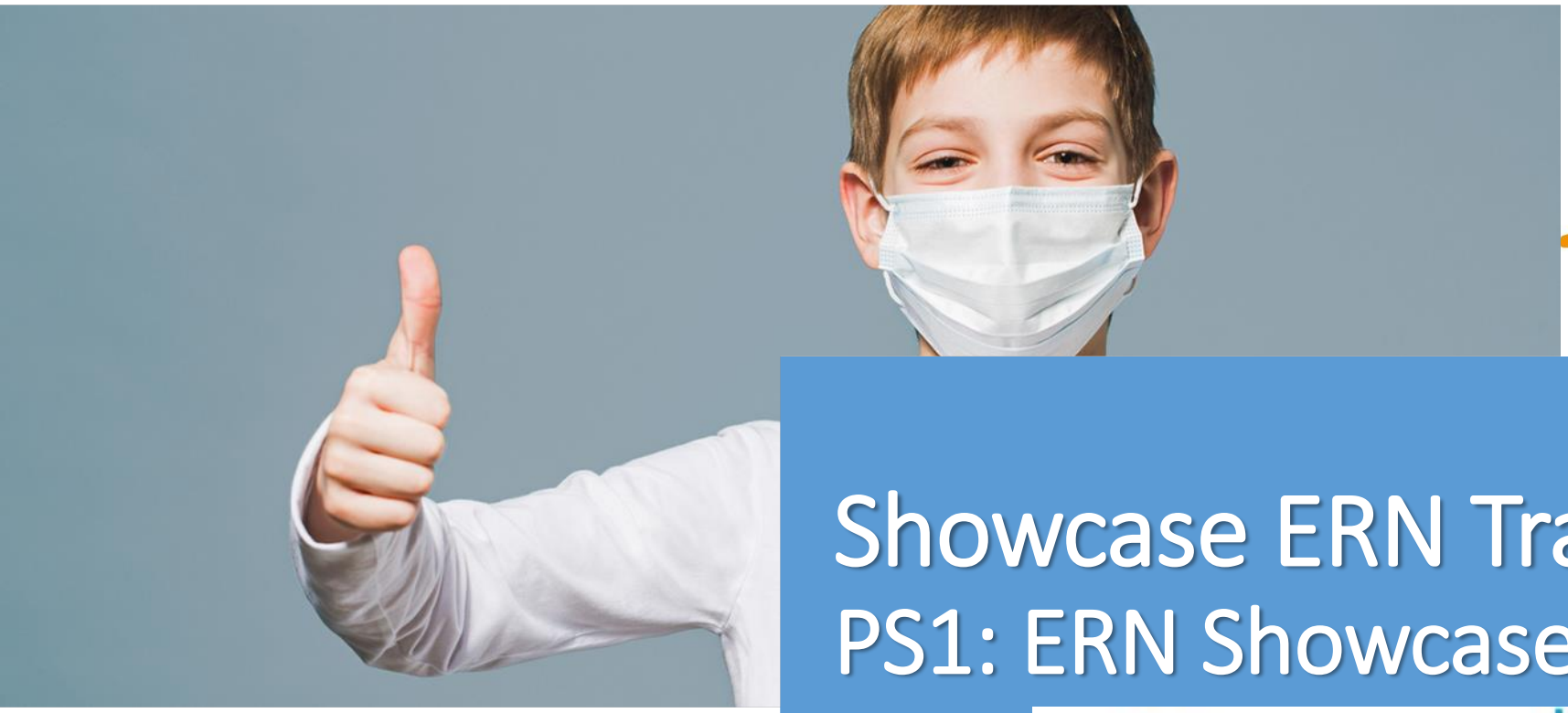


Showcase ERN TransplantChild
PS1: ERN Showcases

European Reference Network

Transplantation in Children (ERN TRANSPLANT-CHILD)

Co-funded by the Health Programme of the European Union

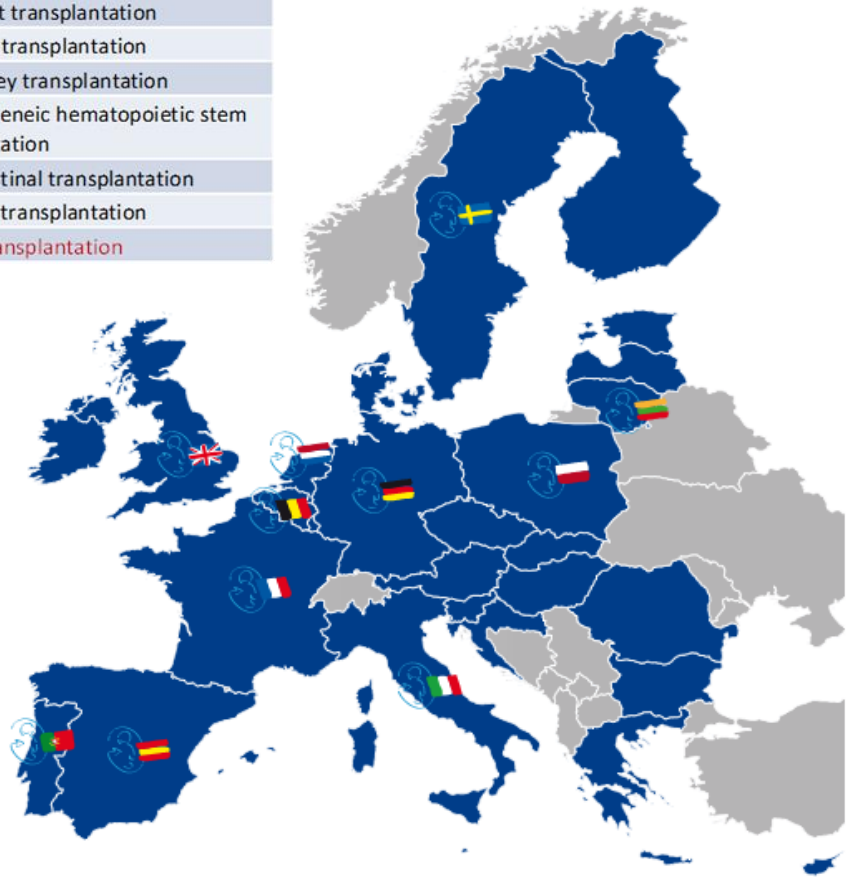
Antonio Pérez Martínez

Brussels, 21nd November 2018

Conflict of interest

- *"I have no actual or potential conflict of interest in relation to this program/presentation".*

Specific condition
Pediatric heart transplantation
Pediatric liver transplantation
Pediatric kidney transplantation
Pediatric allogeneic hematopoietic stem cell transplantation
Pediatric intestinal transplantation
Pediatric lung transplantation
Multiorgan transplantation



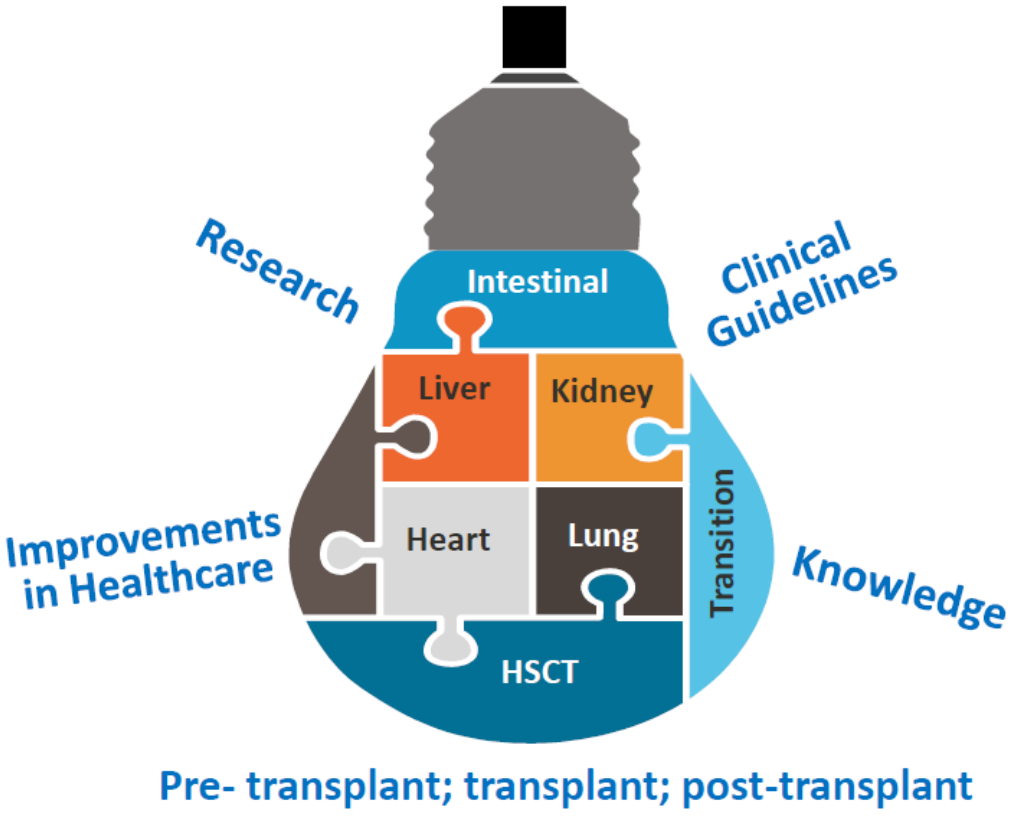
TransplantChild

TRANSPLANTATION IN CHILDREN

(Solid Organ Transplantation & Hematopoietic Stem Cells Transplantation)

- **TRANSplantCHILD** is focused on a **low prevalent** and **complex clinical condition: the transplant process in children**, and the **chronic rare medical status of transplanted children**.
- It **does not include primary diseases** or conditions that lead to or indicates the need of transplantation.
- **It includes** both HSCT/SOT, multiorgan/combined transplants, and all post-transplant common complications and therapeutic procedures.
- *Allocation of/and access to organs for the purpose of organ transplants **is not included** in the network scope as established in the Directive 2011/24/EU.*

TRANSPLANTCHILD: Background



- **18 healthcare providers** from 11 European countries
- **460** Pediatric Solid Organ Transplants (SOT) / year
- **171** Pediatric Hematopoietic Stem Cell Transplants (HSCT) / year
- Estimated n TRANSplantCHILD lifespan: up to **2500 SOT** and **1000 HSCT**

The Clinical Case

- A **10 years old boy** with a **previous deceased donor liver transplantation** for a fulminant hepatic failure

- After liver transplantation, he developed **EBV reactivation** with **HLH symptoms** (fever, hepatosplenomegaly, hypertrigliceridemia, hiperferritinemia, and cytopenias) that were resistant to withdrawn the immunosuppresion and rituximab.

- **HLH-2004:** Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis was started (dexamethasone, cyclosporine, and etoposide)

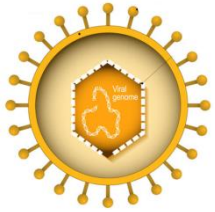
- Following a **confirmed episode of HLH**, it was to rule out a **genetic defect of FHL** or **primary immunodeficiency syndrome**

The Clinical Case

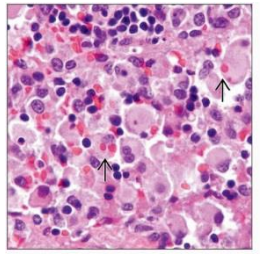
- **No genetic alterations** were found in conventional FHL genetic test neither in Next Generation Sequencing Panels.
- Although negative genetic work up with undetected mutations or underlying acquired conditions, the **Hemophagocytic Lymphohistiocytosis recurrence**.
- At this time the patient was **sent to our hospital to consider HSCT** from a MUD 9/10 donor
- HCT-CI score and morbidities at this time were related to:
  - **Long-term administration of dexamethasone** (hypertension, obesity, glucose intolerance, and insulin dependent diabetes mellitus, decrease bone formation and increase bone resorption, susceptibility to infections, myopathy, insomnia, mood swings, personality changes.
  - **Liver moderate dysfunction** (ASTx 3, ALT x 8, GGT x 10 times with normal bilirrubin level).

The Clinical Case

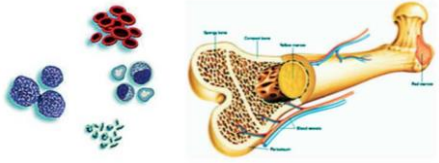
Liver transplantation



EBV reactivation and HLH



HLH syndrome



Evaluation pre-HSCT

September 2016

December 2016

+4m post liver transplantation :

- Tacrolimus withdrawn and rituximab
- HLH-04 protocol (dexamethasone, etoposide, cyclosporine)
- Genetic test

February 2017

+6m post liver transplantation:

- Fever, malaise, hepatosplenomegaly, jaundice, hypertriglicericemia, hyperferritinemia, and cytopenias
- CMV reactivation

Reference to our Hospital

November 2017

HCT-CI score >3:

- Long-term administration of dexamethasone
- Liver moderate dysfunction secondary to liver transplantation complications and HLH activity

Clinical Questions

1.- Should we transplant this patient with negative genetic HLH and high HCT-CI score?

2.- If yes, ¿which donor, source and conditioning should be to perform?

Why do we need an expert`s consultation?

- **The multidisciplinary team** IS CRITICAL for this discussion at our hospital involving:
  the paediatric haematologist, the immunologist, the paediatric hepatologist and the paediatric surgeon's teams
- **No previous experience** at the local level from similar cases.
- **Scarce data** al scientist literature

The Clinical Case

Evaluation pre-HSCT

HCT-CI score >3:

November 2017 | January 2018 | February 2018 | March 2018

Virtual Consultation

Transplantchild

Open | Panel Selection | Data Completion | Assessment | Outcome | Sign-off | Closed

TRANSPLANTCHILD Advisory structure

Pre- transplant

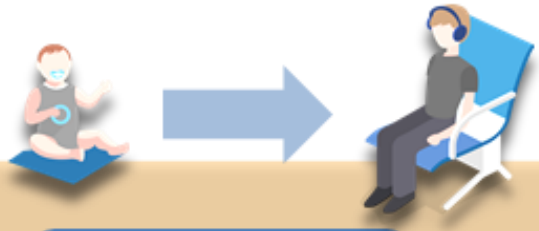
- The clinical assessment of the candidate: biopsies, endoscopies, exploratory procedures.
- Donors and patients Immunological assessment.
- Selection and handling of inoculum (SOT or HSCT).
- Surgical candidate selection.

Transplantation

- Advice on how to transplant with a multidisciplinary approach (infectious, pharmacology, anesthesia, pain unit, etc.)
- Selection of conditioning or immunosuppressive regimens .
- Optimisation of adult organs for PT.

Post- transplant

- Prevention of complications: approach to chronicity and treatment of secondary diseases.
- Diagnostic services
- Therapeutic services and follow-up services:
  - ✓ Medical/surgical consultations
  - ✓ Immunosuppression treatments and monitoring, antimicrobial therapy and monitoring, adjuvant immunotherapy, etc.



Transition to adulthood

- Training for patient and families /self-control.
- Rehabilitation: motor, intestinal, cardiac and/or respiratory.
- Physical growth
- Neurocognitive function
- Adherence
- Psychosocial progress and social integration
- Psychological and socio-economic issues

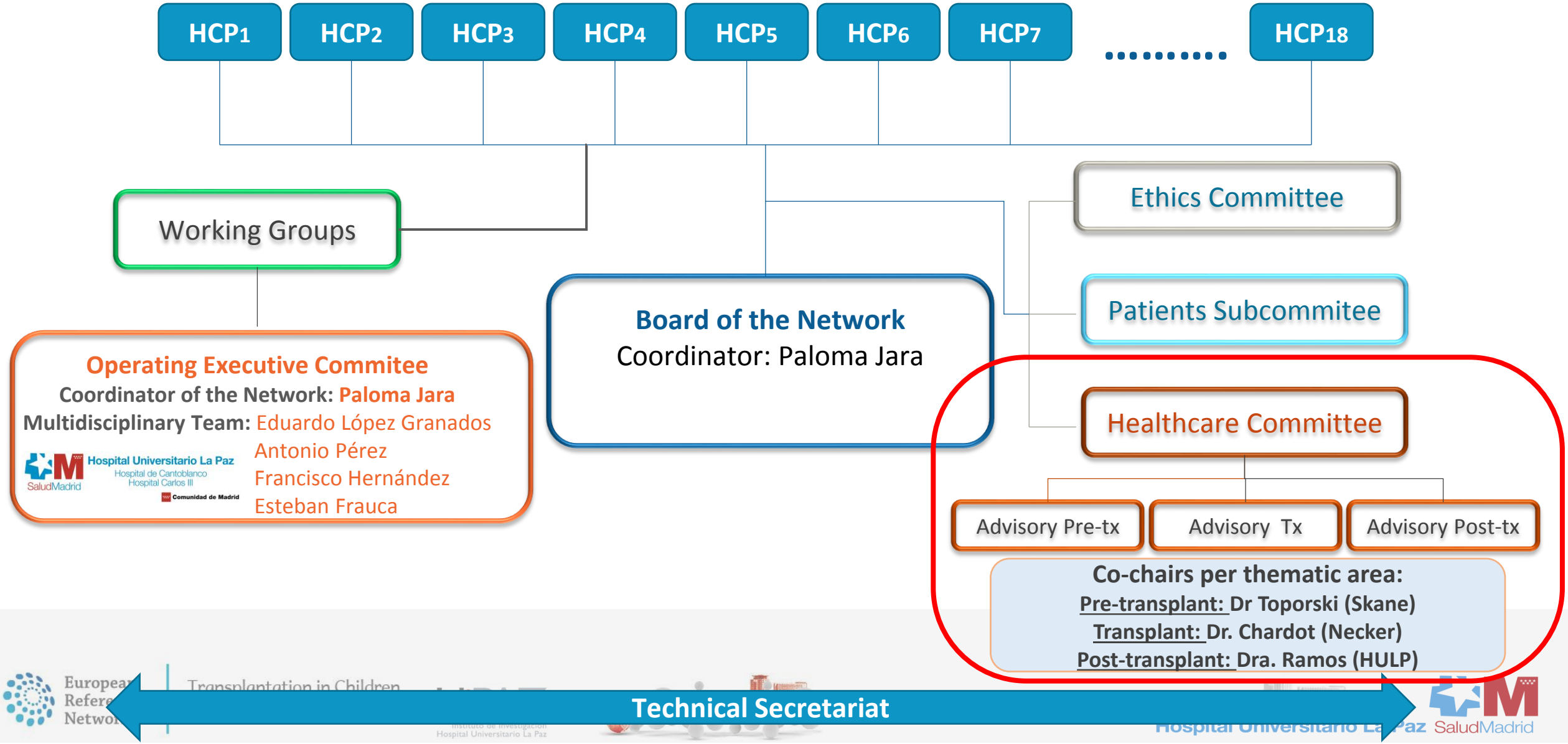
KNOWLEDGE

CLINICAL GUIDELINES

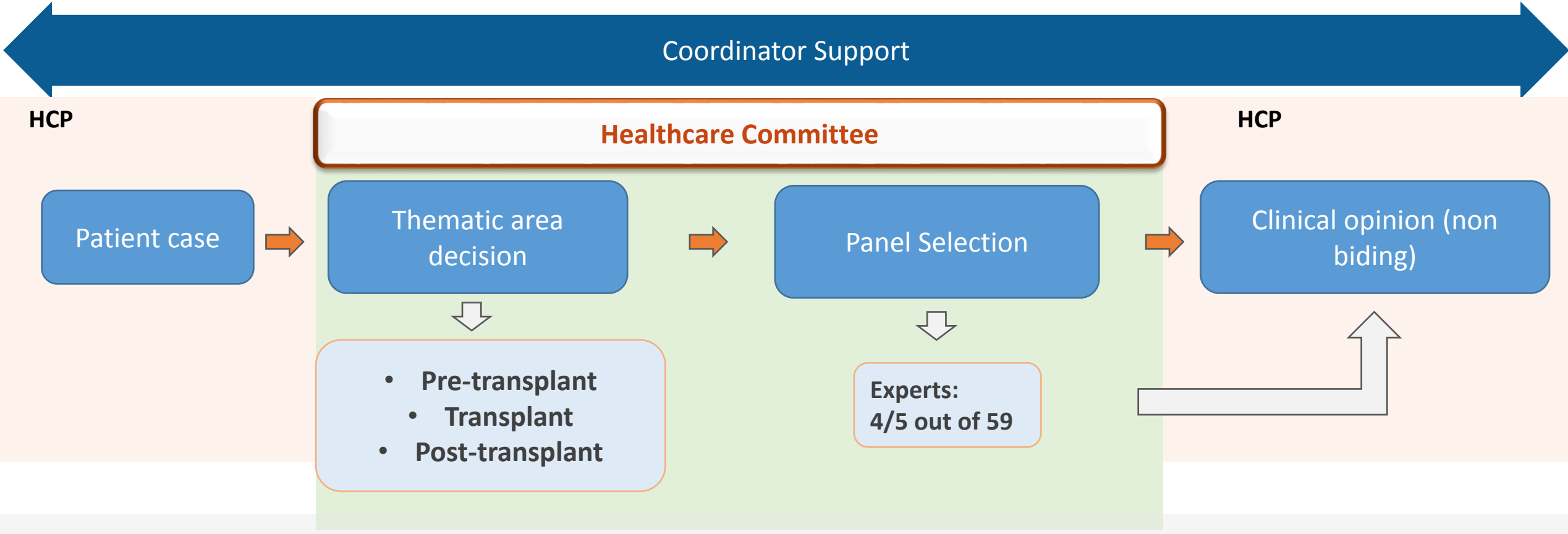
RESEARCH

CARE

TRANSPLANTCHILD structure



CPMS Virtual Advisory pathway in TRANSplantCHILD



The Clinical Case

Evaluation preHSCT

HCT-CI score >3:

HEALTHCARE COMMITTEE PRETRANSPLANTATION ADVISORY RESPONSE

November 2017 | January 2018 | February 2018 | March 2018

Virtual Consultation

Open → Panel Selection → Data Completion → Assessment → Outcome → Sign-off → Closed

Pre Transplant Advisory Group
Chair: Dr. Toporski

PANEL OF 5 EXPERTS:
2 HAEMATOLOGIST
1 HEPATOLOGIST
1 IMMUNOLOGIST
1 GASTROENTEROLOGIST

CPMS discussion

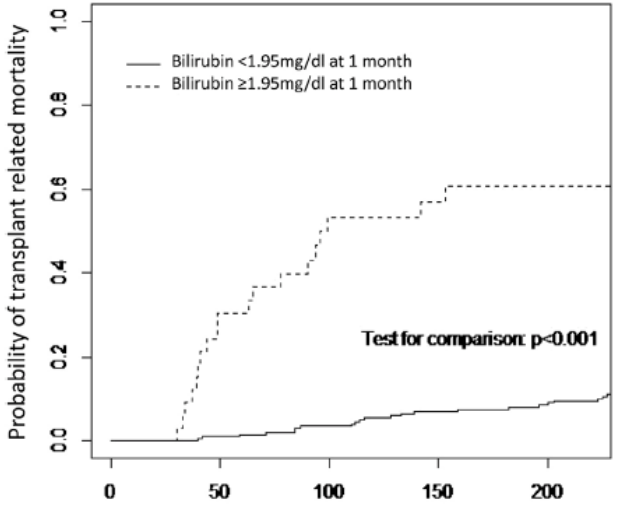
Risk for the liver

Biol Blood Marrow Transplant 19 (2013) 912–917

Risk Factors Associated with Liver Injury and Impact of Liver Injury on Transplantation-Related Mortality in Pediatric Recipients of Allogeneic Hematopoietic Stem Cell Transplantation

Kavita Radhakrishnan [1], Jacquelyn Bishop [1], Zhezhen Jin [2], Komal Kothari [1], Monica Bhatia [1], Diane George [1], James H. Garvin Jr. [1], Mercedes Martinez [1], Nadia Ovchinsky [1], Steven Lobritto [1], Yasmin Elsayed [1], Prakash Satwani [1,*]

[1] *Department of Pediatrics, New York-Presbyterian Morgan Stanley Children's Hospital, Columbia University, New York, New York*
[2] *Department of Biostatistics, New York-Presbyterian Morgan Stanley Children's Hospital, Columbia University, New York, New York*



CPMS discussion

HSCT following SOT

Bone Marrow Transplantation (2011) 46, 1321–1325
© 2011 Macmillan Publishers Limited All rights reserved 0268-3369/11
www.nature.com/bmt

ORIGINAL ARTICLE

Hematopoietic stem-cell transplantation following solid-organ transplantation in children

T Schechter[1], A Gassas[1], S Weitzman[1], D Grant[2], S Pollock-BarZiv[2], A Dipchand[2], S Alexander[1], M Ali[1], Y Avitzur[2] and J Doyle[1]

[1]*Department of Paediatrics, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada and* [2]*SickKids Transplant Centre, The Hospital for Sick Children, Toronto, Ontario, Canada*

SOT following HSCT

Pediatr Transplantation 2010: 14: 1030–1035
© 2010 John Wiley & Sons A/S.
Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2010.01401.x

Solid organ transplants following hematopoietic stem cell transplant in children

CPMS discussion

ORIGINAL ARTICLE

AMIR ET AL.

Liver Transplantation for Children With Acute Liver Failure Associated With Secondary Hemophagocytic Lymphohistiocytosis

Achiya Z. Amir,[1,2] Simon C. Ling,[2] Ahmed Naqvi,[3] Sheila Weitzman,[3] Annie Fecteau,[4] David Grant,[6] Anand Ghanekar,[6] Mark Cattral,[6] Nadya Nalli,[6] Ernest Cutz,[5] Binita Kamath,[2] Nicola Jones,[2] Maria De Angelis,[6] Vicky Ng,[2] and Yaron Avitzur[2]

[1]Division of Gastroenterology, Hepatology and Nutrition; Divisions of [2]Paediatric Gastroenterology, Hepatology and Nutrition, [3]Haematology and Oncology, [4]General Surgery, [5]Pathology, and [6]Transplant and Regenerative Medicine Centre, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

were less favorable, with only 2 of 5 children responding.

Although differentiating primary from secondary HLH may be challenging, it is likely that post-LT HLH-recurrence in familial HLH will be universal. Furthermore, mortality is high in children who undergo BMT following LT.[29] Because of the absence of chil-

Brief report

Successful stem cell transplantation following orthotopic liver transplantation from the same haploidentical family donor in a girl with hemophagocytic lymphohistiocytosis

Susanne Matthes-Martin, Christina Peters, Alfred Königsrainer, Gerhard Fritsch, Thomas Lion, Andreas Heitger, Klaus Kapelari, Martina Kronberger, Felix Offner, Fritz Wrba, Raimund Margreiter, and Helmut Gadner

In the case reported, diagnosis of FHL was established only after living-related liver transplantation, which had been performed for the treatment of acute liver failure. Haploidentical SCT has turned out to be a feasible alternative for children with FHL lacking an HLA-identical donor.[5,6,20] In this particular patient, an unrelated donor search was not initiated, and haploidentical SCT from the organ donor was considered the first choice for 2 reasons: (1) Microchimerism after liver transplantation might facilitate donor stem cell engraftment. (2) Complete bone marrow donor chimerism in the organ recipient might not only cure the underlying disease, but the chimerism might also prevent organ rejection without the necessity of prolonged immunosuppression, thus reducing the risk of EBV-associated lymphoproliferative disease. In the case of

CPMS discussion

Pediatr Transplantation 2016: 20: 888–897

© 2016 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Pediatric Transplantation
DOI: 10.1111/petr.12725

Outcomes of pediatric identical living-donor liver and hematopoietic stem cell transplantation

The Clinical Case

Evaluation preHSCT

HCT-CI score >3:

Virtual Consultation

HEALTHCARE COMMITTEE PRETRANSPLANTATION ADVISORY RESPONSE

November 2017 | January 2018 | February 2018 | March 2018

Open → Panel Selection → Data Completion → Assessment Outcome → Sign-off → Closed

LOCAL MULTIDISCIPLINARY DISCUSSION

FEASIBILITY OF ADVISORY RESPONSE AND FINAL DECISION FROM THE LOCAL TRANSPLANTATION TEAM

CPMS Assessment

1.- Should we transplant this patient with negative genetic HLH and high HCT-CI score?

Expert's Contributions

HSCT seems to be a therapeutic option for this patient.

2.- If yes, ¿which donor, source and conditioning should be to perform?

Expert's Contributions

1. However, MUD SCT has the following **risks for the liver**:
    a) risk of liver toxicity increasing with the intensity of conditioning, SOS
    b) risk of liver GvHD
    c) risk of liver rejection by the new immune system.

2. Haplo SCT **could be an option**:
    a) Standard conditioning we use is FLU, TT, MEL, and this combination has quite low liver toxicity.
        i. If this combination is recognized as too weak one could intensify by adding VP16 in a low dose (e.g 10-15 mg/kg it will have additional anti HLH effect) and/or TLI 7 Gy in one dose (alt TBI 2 Gy)Haplo SCT with T-cell depletion has a very low risk for GvHD.
    b) If the liver will be rejected the liver retransplantation with the same haplo donor without any additional immunosuppression could be done.

Challenges in virtual consultation

HCP Members

CPMS

1. Core Activity for ERNs

ERN

2. Specific adaptations of the plataform

Request advice

Give advice

3. Ensure a response time adapted to the each case

ERN: Experts

Contribute to the panel

4. Increase the number of Experts involved into the Advisory group

Diagnosis/ Treatment

Patients

6. To achieve a sustained activity over time

HCP Affiliated/ Non-Members

5. To get a access to other HCP centers

TRASPLANTCHILD: ADDED VALUE

01 Paediatric focus for complex cases as presented .

02 Highly complex procedure.

03 Multidisciplinary approach involving different paediatric transplantation programs.

04 HSCT and SOT.

05 Rare condition with scarce published data.

06 A consensus in order to identify the approach (conditioning, surgical timing, and feasibility).

07 Combined transplantation as a future strategy to improve transplantation results (nephrologist, haematologist and hepatologist, etc), regarding solid organ tolerance or original diseases which need an HSCT to be cured and debuts with a solid organ failure.

THANKS FOR YOUR ATTENTION

Contact us via:

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Twitter: @Transplantchild

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