Stem Cell Transplantation for Primary Immunodeficiency Diseases (PID)

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SCT for PID

Background

SCID
γ def, ADA def
Choice?

Non-SCID
WAS, CGD
HLH: XIAP
Primary Immune Deficiency Diseases (PID)
(Autosomal recessive unless otherwise stated)

**Severe combined immunodeficiency (SCID)**
- Functional
  - T- B- NK-
    - ADA deficiency
    - Reticular dysgenesis
  - T- B- NK+
    - RAG deficiency
    - SCID with Artemis
  - T- B+ NK-
    - γ deficiency *(X linked)*
    - Jak 3 kinase deficiency
  - T- B+ NK+
    - IL7 Rα deficiency
    - ZAP70
- Other
- Unspecified

**WASP deficiency *(X linked)*
**CD40 ligand deficiency *(X linked)*
**XLP *(X linked)*

**Haemophagocytic syndromes**
- Immunodeficiency with partial albinism
- Familial HLH
- Griscelli disease
- Chediak-Higashi syndrome
- XIAP

**Phagocytic Cell disorders**
- Schwachman’s syndrome
- Granule deficiency
- LAD
- CGD *(X linked/AR)*
- Kostmann’s syndrome
- IFN-γ receptor deficiency
- Other

**T cell immunodeficiency / SCID variants**
- CD4 lymphopenia
- Zap 70 kinase deficiency
- MHC Class II deficiency
- PNP deficiency
- Omenn’s syndrome
- Severe DiGeorge complex (22q 11del)
- CID with skeletal dysplasia
- Cartilage hair hypoplasia
- Other

**Autoimmune/Immune dysregulatory**
- ALPS, IPEX
- Other
Worldwide Organisation of PID

- UK – NCG \( (n=60) \)
- Europe – EBMT/ESID  IEWP
- USA – PIDTC
- Worldwide – CIBMTR WPIE & ID
SCID
Clinical presentation of SCID

- 1:75 000 live births usually present by 3mo of age
- Early diagnosis crucial
- Severe and frequent common infections or opportunistic infections
- Diarrhoea, dermatitis, failure to thrive
- 50% may be engrafted with maternal T cells
- At risk of transfusion associated GVHD
- Avoid BCG, (rotavirus vaccine)
Biochemical defect in ADA deficiency

DNA

\[ \text{d-adenosine} \]

\[ \text{d-adenosine} \]

\[ \text{d-ATP} \]

\[ dCydK \]

\[ \text{d-inosine} \]

\[ \text{ADA} \]

Increase in d-ATP due to dCydK is toxic to lymphocyte function.

- 15-20% delayed onset/partial ADA deficiency, present 2-3 years of life.
- Non-Immunological abnormalities: skeletal dysplasia, costochondral abnormalities, neurological abnormalities, hepatic dysfunction, sensorineuronal deafness, behavioural/psychological abnormalities.
How I treat SCID - Choice?
MSD SCT for SCID X1

• First success 1968 (Gatti et al)
• No conditioning or GVHD prophylaxis required
• Since 1985 cure rate >80%, probably now >90%
• Usually only T cells become donor; myeloid and erythroid remain recipient
• < 50% have donor B cells, but only minority require supplementation with IVIG
Survival without a second procedure

Hassan et al EBMT 2013

p=0.0005
HLA-mismatched family donor for SCID

- First success 1983 (Reisner et al)
- T cell depletion required
  - $<1\times10^4$/kg CD3+ cells
- Survival 66% (Gennery 2010)
- B- SCID do worse than B+ SCID
- ADA deficiency and Reticular Dysgenesis poor outcome 29%
- Role of conditioning
  - Simple infusion 95% success < 3 months of age (Buckley 1999)
  - No conditioning - delayed T cell and lack of B cell engraftment
- Slow immune reconstitution
  - Allodepletion / Suicide gene insertion / αβ depletion
- T cell exhaustion
Unrelated Cord Blood SCT for SCID

• Rapid availability (8 days)
• Less GVHD
• Greater proliferative life span
• Slower engraftment
• Lack of virus specific T-cells / no boost
  – But rapid CD4 recovery without ATG \textit{(Chiesa 2011)}
• 16/20 (80\%) matched for 3-6/6 HLA antigens survived with B cell reconstitution
 \textit{(Slatter & Gennery 2006)}
Kinetics of Ig therapy discontinuation and overall survival in the 2 study groups.

Cell Source: T-CELL Recovery Following Cord Blood Transplant
CD3+/CD4+/CD8+ T cells @ 2 months after HSCT

LYMPHOCYTE COUNT (X 10⁹/L)

- CBT no seroth (n=28)
- CBT with seroth (n=7)
- Sibling no seroth (n=23)
**CD4+ RECOVERY VIA PERIPHERAL EXPANSION**

Median CD4+ T-cell / TRECs count after UCBT (n=17)

**CD4+ T-CELL COUNT (X 10^9/L)**

- **CD4+**
- **TRECS**

**TRECS/10^6 CD3+ T-cells**

- 1 month
- 2 months
- 3 months
- 6 months
- 12 months

**PERIPHERAL EXPANSION**

**THYMIC RECOVERY**
Spectratype @ 1 and 2 months post CBT (pt LS)
Gamma-capture: T-cell response to Adenovirus @ 2 months

JB 7/10 mm cord rTALL/Bu Cy Mel/CyA,MMF - T cell responses to viral antigens at 2 months (feb09). SD/WQ
acute GvHD g II-IV

Log rank
none-early $p=0.002$
early- late $p= 0.003$
none-late $p< 0.001$

61% +/- 9%
43% +/- 9%
17% +/- 5%
Gennery et al.

SCID
How I treat SCID-X1

(Gaspar et al Blood 2013 in press)

90% DFS

> 80% survival
B cell function 20%

70% DFS

22 patients:
most clinical benefit
5 developed T-ALL
How I treat ADA-SCID

- Clinical benefit: 25/36 (69%)
- 67% DFS
- 86% DFS

Flowchart:

1. MSD/MFD available
   - +/− PEG-ADA
   - HSCT – no conditioning
     - In case of lack of access to PEG-ADA treatment
     - Enroll into gene therapy trial
     - OR
     - HSCT with conditioning from MUD/mMUD/haplo

2. MSD/MFD unavailable
   - MSD/MFD search
   - Enroll into gene therapy trial
   - Reinitiate PEG-ADA
   - Engraftment failure

3. Stabilise with PEG-ADA
   - Continue PEG-ADA
   - MUD

4. Lack of access to ERT or thymic function
   - *
Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening.

Probands
n=45

- Death before HSCT
  n=14
  31% mortality

- Progress to HSCT
  n=31

- Deaths after HSCT
  n=13
  41%

Overall mortality/survival: 27/45 (60%) (40%)

Siblings
n=55

- Death before HSCT
  n=1
  1.8% mortality

- Progress to HSCT/GT
  n=54

- Deaths after HSCT/GT
  n=3
  5.5%

Overall mortality/survival: 4/55 (7.2%) (92.8%)

Comparison of age at diagnosis and age at HSCT

<table>
<thead>
<tr>
<th></th>
<th>Proband</th>
<th>Sibling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age at Diagnosis</strong></td>
<td>124 Days</td>
<td>5 Days (43)</td>
</tr>
<tr>
<td><strong>Mean Age at HSCT</strong></td>
<td>216 Days</td>
<td>34 Days</td>
</tr>
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</table>
# Infections

<table>
<thead>
<tr>
<th>Type of infections</th>
<th>Proband</th>
<th>Sibling</th>
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<tbody>
<tr>
<td>RSV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTRO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOLI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHV6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norovirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARAFLU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>17</td>
</tr>
</tbody>
</table>

The bar chart shows the number of instances of various infections, categorized as Proband and Sibling. The highest number of instances is for Other.
Non-SCID
Non-SCID Immunodeficiency

- Requirement for conditioning
- Previously myeloablative conditioning
- Co-morbidities consider reduced intensity SCT
Non-SCID
Improvement in Outcome of Haematopoietic Cell Transplantation for T cell Immune Deficiency

Wiskott-Aldrich Syndrome (WAS)

- X-linked, 4 per million live births
- Triad of thrombocytopenia, eczema, progressive immunodeficiency
- Without SCT most succumb to Infection, bleeding, autoimmune disease or lymphoproliferative disease
- Thrombocytopenia may respond to splenectomy
- SCT survival MSD/UD/CBT/Haplo: 88%/71%/80%/52% (Filipovich 2001)
- Results better with myeloablative SCT < 5 yrs
- Aim for 100% donor chimerism lymphoid/myeloid lineages
Influence of the degree of donor cell engraftment on the reconstitution of lymphocyte counts and autoimmunity after HCT.

Chronic Granulomatous Disease (CGD)

- Defective NADPH oxidase phagocyte killing
- Despite septrin/itraconazole/IFN 2-5% annual mortality, with 25% deaths due to aspergillus
- MSD for CGD with one significant complication 85% survival (*Seger 2002*).
- SCT during active infection may be complicated by severe inflammation
- Recent success with MSD/MUD SCT – ATG/Alemtuzumab + submyeloablative Bu/Flu conditioning
Reduced Toxicity Conditioning in CGD
MFD vs MUD (Guengoer 2013)

MUD

- Fludarabine 180 mg/sqm
- Alemtuzumab 0.5* mg/kg
- Low dose/targeted Busulfan
- CsA
- MMF

MFD

- Fludarabine 180 mg/sqm
- Low dose/targeted Busulfan
- ATG* 7.5 m/kg
- CsA
- MMF
Treosulfan-based conditioning regimens for hematopoietic stem cell transplantation in children with primary immunodeficiency: United Kingdom experience.
# Reduced Intensity Conditioning

<table>
<thead>
<tr>
<th>PROTOCOL</th>
<th>CHEMOTHERAPY</th>
<th>SEROTHERAPY</th>
<th>GVHD PROPHYLAXIS</th>
</tr>
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<tbody>
<tr>
<td>B</td>
<td>Busulfan (iv) (AUC dosing)$^2$</td>
<td>Campath 1H (TD 0.6-1mg/kg) OR ATG (TD 7.5-10mg/kg)</td>
<td>CyA or CyA + MMF or MTX (as 2$^{nd}$ agent)</td>
</tr>
<tr>
<td></td>
<td>Fludarabine 180 mg/m2</td>
<td>Campath 1H (TD 0.6-1mg/kg)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Fludarabine 150 mg/m2</td>
<td>Campath 1H (TD 0.6-1mg/kg)</td>
<td>CyA or CyA/MMF</td>
</tr>
<tr>
<td></td>
<td>Melphalan 140 mg/m2</td>
<td>Campath 1H (TD 0.6-1mg/kg)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Treosulphan 42 g/m2</td>
<td>None or Campath 1H (0.6-1mg/kg)</td>
<td>CyA or CyA/MMF</td>
</tr>
<tr>
<td></td>
<td>Fludarabine 150 mg/m2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- $^2$AUC dosing for iv Bu = 60+/- 5 mg*h/L. (see appendix for specific protocols for different donor sources and dosing)
- Avoid Melphalan 140mg/m$^2$ < 1 year of age unless HLH
- Treosulphan 36g/m$^2$ < 1 year of age (see appendix for specific protocols)
- If using ATG with protocols C or D – be aware of increased incidence of EBV-PTLD
- For these protocols if using matched UD or MFD – PBSCs are stem cell source of choice
- If using BM consider decrease in Campath 1H dose to 0.6mg/kg esp if condition requires full donor chimaerism as in WAS or MHC class II deficiency
Haemophagocytic Syndromes

• Familial Haemophagocytic Lymphohistiocytosis (FHL)
  – 1:50 000, present with fever, hepatosplenomegaly, pancytopenia, hypertriglyceridaemia, hypofibrinogenaemia, haemophagocytosis in bone marrow
  – Mutation in perforin/MUNC/syntaxin genes leads to uncontrolled activation T lymphocytes
  – Fatal without immunosuppresive therapy and SCT
  – Outcome MFD/MUD/Haplo/mMUD = 71%/70%/54%/54%
    • Improved with inactive disease
Haemophagocytic Syndromes

other genetic causes:

- Chediak-Higashi Syndrome (CHS) Accelerated
- Griscelli’s Syndrome (GS) RAB27a
- XLP1 (SAP deficiency)
- X-linked inhibitor of apoptosis protein (XIAP) [XLP2]
  - Inflammatory bowel disease, LPD, HLH
Good News!
### History of SCT for HLH since 2000: Alem/Flu/Mel RIC Improves Patient Survival

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Prep</th>
<th>Survival</th>
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</thead>
<tbody>
<tr>
<td>Henter et al, 2002</td>
<td>65</td>
<td>Ablative</td>
<td>55% 3 yr DFS</td>
</tr>
<tr>
<td>Horne et al, 2005</td>
<td>86</td>
<td>Ablative</td>
<td>64% 3 yr DFS</td>
</tr>
<tr>
<td>Ouachee-Chardin et al, 2006</td>
<td>48</td>
<td>Ablative</td>
<td>58.5%</td>
</tr>
<tr>
<td>Baker et al, 2008</td>
<td>91</td>
<td>Ablative</td>
<td>49% 5 yr DFS</td>
</tr>
<tr>
<td>Marsh et al, 2010</td>
<td>14</td>
<td>Ablative</td>
<td>43% 3 yr DFS</td>
</tr>
<tr>
<td>Cooper et al, 2006</td>
<td>12</td>
<td>Reduced-Intensity</td>
<td>75%</td>
</tr>
<tr>
<td>Cooper et al, 2008</td>
<td>25(-12)</td>
<td>Reduced-Intensity</td>
<td>84%</td>
</tr>
<tr>
<td>Marsh et al, 2010</td>
<td>26</td>
<td>Reduced-Intensity</td>
<td>92% 3 yr DFS</td>
</tr>
</tbody>
</table>
Kaplan-Meier 3-year survival curves for the MAC and RIC groups

2003-2009

n=26

n=14

n=5

n=6

p<0.01

MAC --- RIC

Survival Distribution Function

Time (Days Following HCT)

Donor and recipient chimerism within the RIC group.

Bad News!

"Would you please elaborate on 'then something bad happened'?"
HCT IN HLH: OUTCOME

32 PATIENTS

21 ALIVE (66%)

11 DEATHS (34%)

AML (BM)
SEPSIS (BM)
PARAFLU (BM)
PARAFLU (CORD)
CMV PNEUMONIA (CORD)
SEPSIS (BM)
MELPHALAN TOX (BM)
RSV/GvHD/PAH (CORD)
IPS (CORD)
IPS (PBSC)
PAH (CORD)

MORTALITY

PBSC 1/11 (9%)
BM 5/14 (36%)
CORD 5/7 (71%)
Allogeneic Hematopoietic Cell Transplantation for **XIAP Deficiency**: An International Survey Reveals Poor Outcomes. (7/19 surviving)

*Blood. 2013 Feb 7;121(6):877-83.*
Conditioning and HLH Activity

Survival Distribution Function

Follow Up (Days)

RIC, Remission
MAC, Remission
RIC, No Remission
MAC, No Remission

STRATA:
- Conditioning=MAC HLH_In_Remission=No
- Conditioning=MAC HLH_In_Remission=Remission
- Conditioning=RIC HLH_In_Remission=No
- Conditioning=RIC HLH_In_Remission=Remission
- Censored Conditioning=RIC HLH_In_Remission=Remission

p=0.03 (log-rank test)
## Toxicities in MAC Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>VOD&lt;sup&gt;^&lt;/sup&gt;</th>
<th>Pulmonary Hemorrhage</th>
<th>Pneumonitis or ARDS&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>NR&lt;sup&gt;+&lt;/sup&gt;</td>
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<tr>
<td>2</td>
<td>+</td>
<td>-</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>Not clinically, autopsy +</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>+ (related to fungal septic thrombosis of the pulmonary veins and pulmonary artery)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>6</td>
<td>+</td>
<td>+</td>
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<td>7</td>
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<td>+</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>+</td>
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# Toxicities in RIC Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>VOD(^\wedge)</th>
<th>Pulmonary Hemorrhage</th>
<th>Pneumonitis or ARDS(^*)</th>
</tr>
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<tbody>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>10</td>
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<td>-</td>
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<tr>
<td>11</td>
<td>-</td>
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<td>+</td>
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<tr>
<td>12</td>
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<td>13</td>
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<td>17</td>
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<td>18</td>
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<tr>
<td>19</td>
<td>-</td>
<td>-</td>
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Monoclonal Antibody-based Minimal Intensity Conditioning (MIC)

*Straathof KC et al Lancet. 2009 Sep 12;374(9693):912-20.*

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
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</thead>
<tbody>
<tr>
<td>Day - 8</td>
<td>fludarabine</td>
<td>anti-CD52</td>
<td></td>
</tr>
<tr>
<td>Day - 7</td>
<td>fludarabine 30mg/m²</td>
<td>cyclophosphamide 300mg/m²</td>
<td>anti-CD52</td>
</tr>
<tr>
<td>Day - 6</td>
<td>fludarabine</td>
<td>cyclophosphamide</td>
<td>anti-CD52</td>
</tr>
<tr>
<td>Day - 5</td>
<td>fludarabine</td>
<td>cyclophosphamide</td>
<td>anti-CD45</td>
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<tr>
<td>Day - 4</td>
<td>fludarabine</td>
<td>cyclophosphamide</td>
<td>anti-CD45</td>
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<td>Day - 3</td>
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<td>anti-CD45</td>
</tr>
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<td>Day - 2</td>
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<td>anti-CD45</td>
</tr>
<tr>
<td>Day - 1</td>
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</tr>
<tr>
<td>Day 0</td>
<td>Stem Cell Transplantation</td>
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</table>
Haemopoietic stem-cell transplantation with antibody-based minimal intensity conditioning: a phase 1/2 study.


SCID

Percent survival

MIC
RIC
Bu/Cy
days post SCT
Percent survival

Number at risk
MIC  8  8  8  8  8  8  8
RIC  21 15 15 15 15 15 15
Bu/Cy 31 25 24 24 24 24
Refractory HLH

- 29% of patients in HLH 94 died before SCT, 97% with active disease
- Patients with non-active HLH at time of SCT do better 72% vs 58%
  - Trottestam H et al Blood 2011, 118:4577-4584
- Multiple attempts to induce / re-induce remission lead to co-morbidities
- Can you identify bad players early:
  - Diagnosis: Bilirubin >50, ferritin > 2000, CSF pleocytosis > 100
  - 2 weeks into therapy: platelets <40, ferritin > 2000, fever, anaemia
- Approach: ATG / Alemtuzumab / anti-Interferon –γ followed by MIC SCT
## Cognitive and Social Outcomes

*Jessica Jackson et al manuscript in preparation*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Norms</th>
<th>HLH</th>
<th>Comparison with norms</th>
<th>Sibling</th>
<th>Comparison with norms</th>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>t (df)</td>
<td>p-value</td>
<td>Mean (SD)</td>
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<tr>
<td><strong>IQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>100 (15)</td>
<td>86.0 (18.6)</td>
<td>-3.4 (19)</td>
<td>0.003**</td>
<td>99.8 (17.2)</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>100 (15)</td>
<td>81.5 (19.1)</td>
<td>-4.3 (19)</td>
<td>0.001***</td>
<td>100.4 (12.9)</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>100 (15)</td>
<td>81.1 (19.8)</td>
<td>-4.3 (19)</td>
<td>0.001***</td>
<td>99.2 (15.4)</td>
</tr>
<tr>
<td><strong>SDQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8.4 (5.8)</td>
<td>14.3 (7.5)</td>
<td>3.4 (17)</td>
<td>0.004**</td>
<td>9.3 (6.8)</td>
</tr>
<tr>
<td>Emotional</td>
<td>1.9 (2.0)</td>
<td>3.7 (2.6)</td>
<td>3.0 (17)</td>
<td>0.008**</td>
<td>2.1 (1.7)</td>
</tr>
<tr>
<td>Conduct</td>
<td>1.6 (1.7)</td>
<td>2.5 (1.9)</td>
<td>2.0 (17)</td>
<td>0.063</td>
<td>2.2 (2.1)</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>3.5 (2.6)</td>
<td>5.3 (3.6)</td>
<td>2.1 (17)</td>
<td>0.047*</td>
<td>3.2 (2.9)</td>
</tr>
<tr>
<td>Peer r/ships</td>
<td>1.5 (1.7)</td>
<td>2.8 (2.4)</td>
<td>2.2 (17)</td>
<td>0.040*</td>
<td>1.7 (1.6)</td>
</tr>
<tr>
<td>Impact</td>
<td>0.4 (1.1)</td>
<td>2.6 (3.3)</td>
<td>2.9 (17)</td>
<td>0.010**</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td><strong>PEDS-QL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>89.1 (12.3)</td>
<td>68.3 (18.1)</td>
<td>-4.3 (13)</td>
<td>0.001***</td>
<td>88.4 (18.6)</td>
</tr>
<tr>
<td>Emotional</td>
<td>82.2 (12.7)</td>
<td>60.0 (23.4)</td>
<td>-2.9 (13)</td>
<td>0.012*</td>
<td>71.4 (22.6)</td>
</tr>
<tr>
<td>Social</td>
<td>78.3 (15.5)</td>
<td>57.9 (20.1)</td>
<td>-5.4 (13)</td>
<td>0.001***</td>
<td>84.5 (17.5)</td>
</tr>
<tr>
<td>School</td>
<td>86.8 (15.4)</td>
<td>58.2 (18.3)</td>
<td>-4.8 (13)</td>
<td>0.001***</td>
<td>85.5 (17.1)</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>81.5 (16.1)</td>
<td>58.7 (15.7)</td>
<td>-5.6 (13)</td>
<td>0.001***</td>
<td>80.3 (16.4)</td>
</tr>
<tr>
<td>Total</td>
<td>84.6 (11.2)</td>
<td>62.1 (13.7)</td>
<td>-6.2 (13)</td>
<td>0.001***</td>
<td>83.3 (16.0)</td>
</tr>
<tr>
<td><strong>Vineland</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>100 (15)</td>
<td>80.3 (14.1)</td>
<td>-6.4 (20)</td>
<td>0.001***</td>
<td>-</td>
</tr>
<tr>
<td>Daily living</td>
<td>100 (15)</td>
<td>83.5 (16.5)</td>
<td>-4.6 (20)</td>
<td>0.001***</td>
<td>-</td>
</tr>
<tr>
<td>Socialisation</td>
<td>100 (15)</td>
<td>81.1 (14.8)</td>
<td>-5.8 (20)</td>
<td>0.001***</td>
<td>-</td>
</tr>
</tbody>
</table>

Outcome not affected by age or CNS involvement

? conditioning or donor chimerism
Future

• Newborn screening for SCID
• Next generation sequencing: most PID children in the future will have a genetic diagnosis (200 PID genes)
• Move away from MAC to RIC/MIC
  – anti-c-kit SCID study October 2014
  – ? achieve 0% TRM
• Late effects and long-term chimerism will decide best RIC protocol
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