Bone marrow transplant and Sickle Cell Disease

A Good Match?

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BMT - The Concept

- Patient receives high dose chemotherapy/radiation therapy (conditioning) to ablate bone marrow/immune system
- Hematopoietic stem cells collected from donor and infused - ***"Day 0"***
- Neutrophil count recovers (engraftment)
- Red cell and platelet counts recover
- Patient regains normal immune function/ normal life

Typical Hospital Course

- Admitted for 6-10 days for conditioning regimen
- Patients with non-malignant diseases receive busulfan-based conditioning
- Stem cells infused on Day 0
- Neutrophil engraftment between D 21-25
- Discharge once all medications oral, infectious issues resolved, no uncontrolled GVHD
- Often 10-20 discrete medications given 3-6 times a day

Transplant Acute Toxicities

- Nausea, vomiting
- Diarrhea
- Anorexia and need for PN
- Muscositis and need for IV narcotics
- Fever
- Hair loss

- Infection
- Veno-occlusive disease
- Bleeding
- IPS

Acute GVHD

- Patients receive prophylaxis for ~ 6-9 months
- Incidence of acute GVHD 10-20%
- Target Organs:
  - Skin
    - Rash
    - Desquamation
  - GI tract
    - Diarrhea
    - Anorexia
  - Liver
    - Increased bilirubin

Post-Discharge Care

- Norm is to stay near transplant center for 2-4 months post transplant
- Clinic visits 2-5 times a week for transfusions, electrolyte infusions, antibiotics or antivirals
- CVL retained during this time
- Readmission common:
  - Zoster
  - Fever
  - Cough
  - GI symptoms
  - Management of HTN

Sequelae

- Immune Dysfunction - restrictions
- Gonadal failure
- Growth impairment
- Hypothyroidism
- Cataracts
- Osteopenia/osteoporosis
- Second malignancies
- Chronic GVHD

BMT and HbSS Disease

Hemoglobin SS Disease

- Affects 1/400 African-Americans
- Inherited disorder of hemoglobin production leading to polymerization and decreased deformability of the red cell in the deoxygenated state

Disease of total body endothelial damage –

clinically most prominent in capillaries of lung, cerebral-vascular system, spleen, skeleton, kidneys, eyes, penis

Approaches in 2012

- Supportive care
- Transfusion therapy
- Hydroxyurea
- Stem Cell Transplant
  - Family donor/unrelated donor

SCT and SS Disease

Advantages

–CURE

Obstacles | Impediments

- Donor Availability
- Acute Mortality
- Social Restrictions
- Graft Rejection
- Sequelae of Therapy

Cure

- First BMT in Hb SS disease with curative intent reported in 1988 (Vermylen,Lancet)
- Most patients have received standard myeloablative conditioning regimen with busulfan, cytoxan and ATG

In intervening 20 years we have learned that approximately 80% of patients undergoing BMT from a sibling donor will be cured and have a very good to excellent quality of life

Cure = Normal hemoglobin production

- Resolution of VOC
- Stable pulmonary disease
- Possible correction of reticuloendothelial dysfunction (Ferster, Blood 1993)
- Possible correction of osteonecrosis (Bernaudin, BMT 1997)
- Possible improvement in growth
- Stable neurologic function/MRI
- Very good performance status

Advantages

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Donor Availability

- Currently BMT restricted to patients with available matched family donor or those on research protocol
- Statistically each sibling has a 1-in-4 chance of being a match
- Epidemiologically 14-30 % of Hb SS patients in US have an acceptable matched sibling donor
- Some potential donors ineligible/unwilling/unavailable
  - Infection
  - Hb SS trait
  - Privacy issues
- Role of PGD

Preimplantation Genetic Diagnosis

- Current technology can be used to create an HLA matched sibling
- Sibling can be “disease –free” if genetic mutation identified
- >95% Accuracy

Drawbacks

- Takes ~ 1 year to have baby
- Umbilical cord blood collected may have inadequate cell dose
- Expensive/insurance does not cover
- Ethical issues

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Acute Transplant Related Mortality

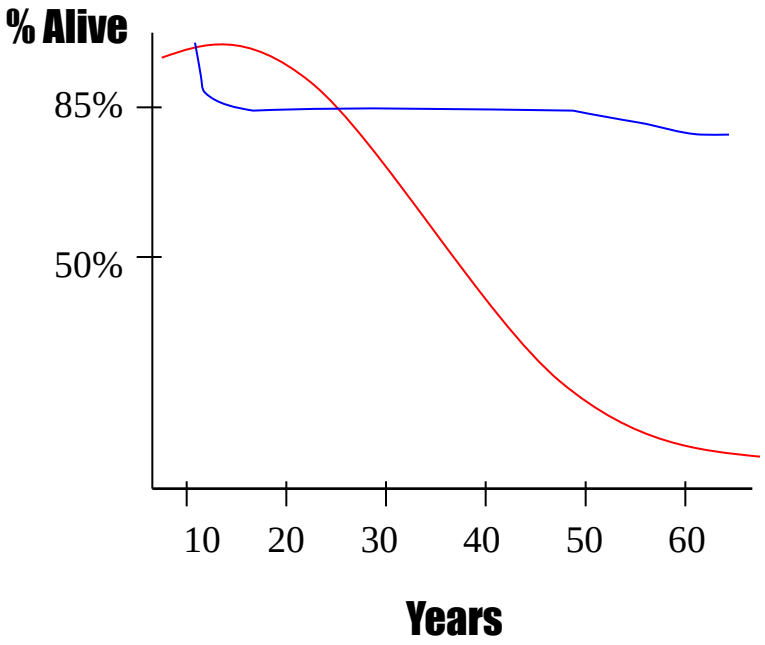
- 10-20% 100 day TRM with matched sibling donor
- Usually due to infection or lung, liver and/or kidney toxicity
- TRM increases if poor performance status, prior end organ toxicity, prior infections
- TRM increases with age of both patient and donor

TRM in Hb SS Patients

- Increased TRM reported in early studies primarily due to intracranial hemorrhage, complications of GVHD
  - 1/3 of pts with prior CVA experienced intracranial hemorrhage post-BMT
- Experience has lead to improved results
  - Pre-BMT partial exchange transfusions
  - Blood pressure management
  - Seizure prophylaxis
  - Platelet transfusion parameters
  - Pre-BMT MRI/MRA
  - Magnesium replacement

Walters, NEJM 1996

Causes of death



- **Infection**
- **Acute Chest Syndrome**
- **Organ Failure**
- **CVA**
- **Pulmonary Hypertension (Gladwin,NEJM 2006)**

Advantages

– CURE

Obstacles | Impediments

- Donor Availability
- Acute Mortality
- Social Restrictions
- Graft Rejection
- Sequelae of Theory

Restrictions

- Social Isolation until off immunosuppression for 3 months for a total duration of 9-12 months following BMT
  - Only nuclear family, tutor allowed in house
  - No school, church, mall, movies, bars etc.
  - Outside activities allowed

  Requires adequate family and economic infrastructure

Advantages

– CURE

Obstacles | Impediments

- Donor Availability
- Acute Mortality
- Social Restrictions
- Graft Rejection
- Sequelae of Theory

Graft Rejection

- Patient may fail to engraft or have subsequent autologous recovery

- Risk Factors:
  - Cell dose
  - Multiple transfusions
  - Reduced conditioning
  - Mismatched donor

Advantages

– CURE

Obstacles | Impediments

- Donor Availability
- Acute Mortality
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- Sequelae of Theory

Expected Sequelae

- Gonadal failure/infertility
  - Majority of children have infertility and/or gonadal failure after allogeneic myeloablative BMT for malignant conditions
  - In Hb SS population most females found to have primary amenorrhea, elevated LH, FSH post-BMT; most males have normal testosterone levels
  - No data on fertility/outcomes of fertility preservation interventions in SS population

Possible Sequelae

- Risk of thyroid dysfunction, cataracts, growth retardation
- Question of increased neurologic problems post-transplant in Hb SS population – perhaps secondary to increased viscosity and thrombosis (Abboud,BMT 1996)
- Risk of second malignancy
- Chronic GVHD

Chronic graft versus host disease

- Chronic state of immune dysregulation
- Manifestations:
- Discoloration and/or sclerosis of skin
- Failure to thrive
- Xerostomia/xerophthalmia
- Chronic liver dysfunction
- Pulmonary insufficiency

Chronic graft versus host disease

- Predictors:

Degree of donor match

Age of patient

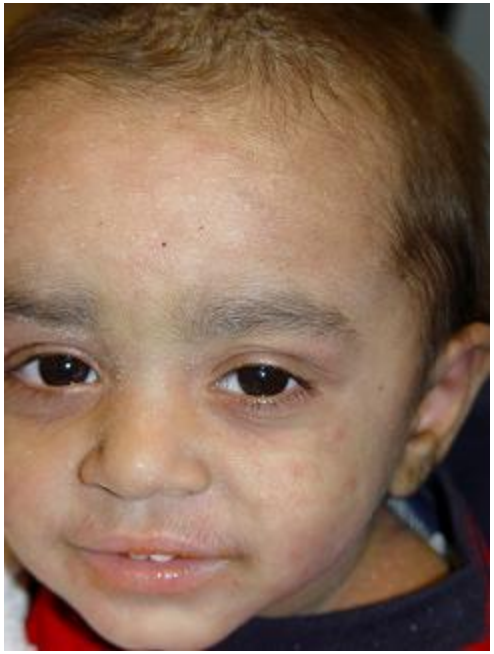
Age and gender of donor

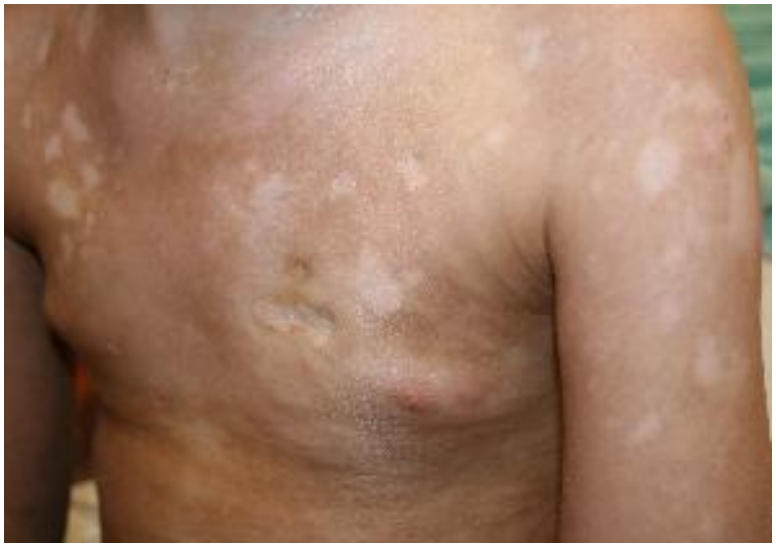
Infectious history of patient

Medication compliance

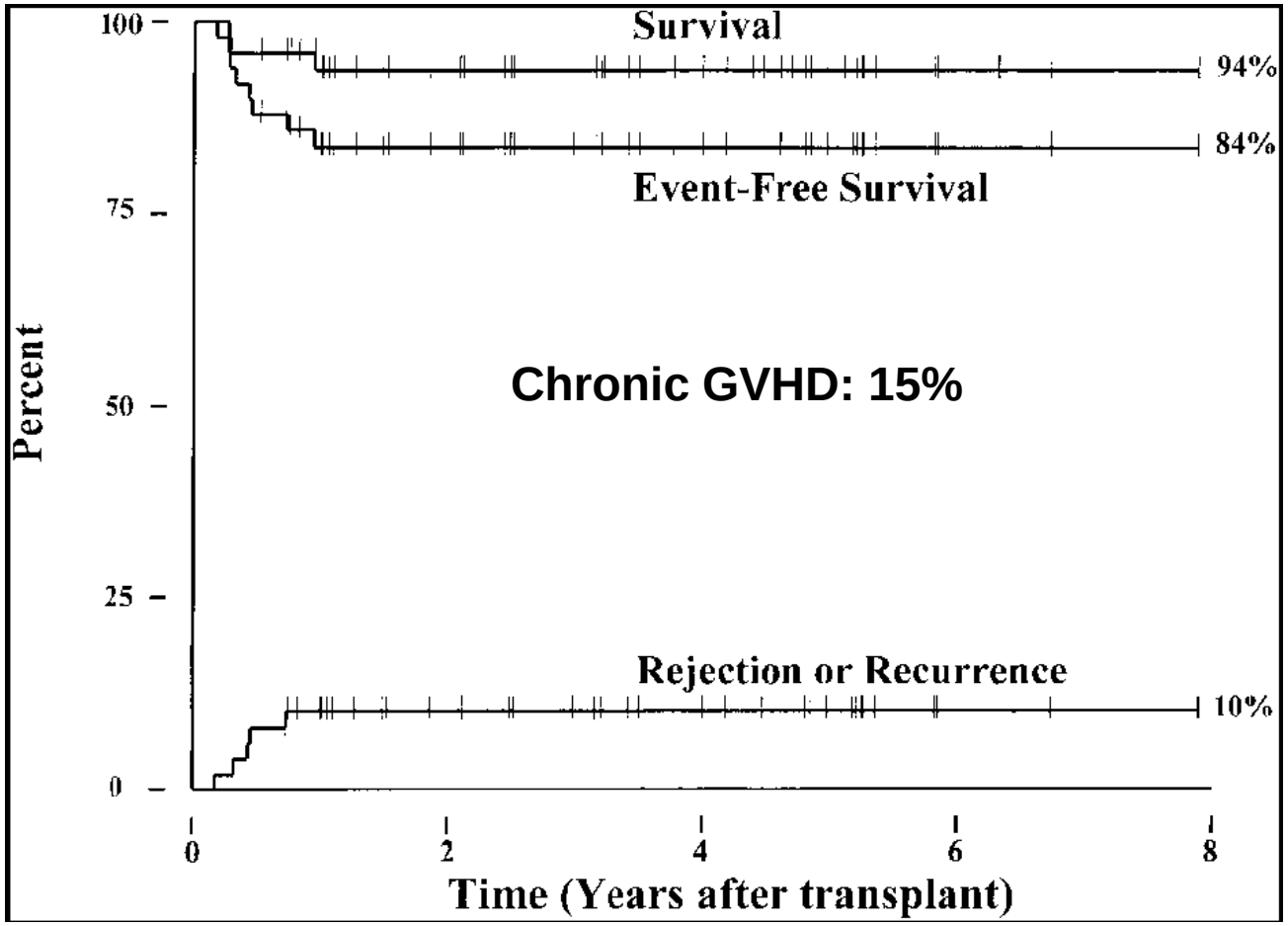
Stem cell source

Chronic graft versus host disease





Outcome



Walters, NEJM 2000

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Newer approaches under investigation

- Non-myeloablative “mini” BMT
  - Less intense conditioning
  - May preserve fertility but graft failure/chronic GVHD remain obstacles
- Unrelated donor BMT
  - Ongoing multi-center trial
- In utero transplantation
  - No preparative regimen
  - Graft rejection has been insurmountable problem outside of immunodeficiency disorders

Who should be transplanted?

Indications for BMT with family donor

- Vary by country
- In US BMT offered if patient less than 17 years old and: (Walters, NEJM 1996)
  - Recurrent ACS
  - Sickle nephropathy
  - Chronic priapism
  - Osteonecrosis of multiple joints
  - Alloimmunization on chronic transfusion therapy
  - Sickle lung disease
  - 2 or more VOC per year for several years
  -

Using these criteria it is estimated that 5-30% of Hb SS patients will be "eligible" for BMT

Who decides?

- Parent preference (Kodish, NEJM 1991)
  - Standard reference gamble used to assess point of “too much risk” – 50% not willing to accept any risk, 13% willing to take 15% risk of early mortality, 15% risk of CGVHD for cure; risk acceptance related to parental education, presence in family of another child with Hb SS disease ; not related to clinical course of child to date
- Cultural norm
  - European standard is to offer BMT preferentially particularly to children in resource poor countries as chronic medical care suboptimal
  - Role of HU vs BMT in Low Income Countries (Howard, PedBloodCancer 2006)

Recommendations

- Global education
  - All parents/older patients are informed that BMT is a possibly curative option
    - Issues of parental advocacy
  - HLA typing of siblings available if family desires
    - ❖Insurance issues
  - Meeting with BMT physician and pediatrician/hematologist if parents/patient request to discuss advantages and obstacles to BMT
  - Ongoing DFCI/BMC study of how to best educate parents

The Role of Stem Cell Transplantation in Pediatric Sickle Cell Disease

Is there a cure for Sickle Cell Disease? YES

Stem cell transplantation (SCT) is currently the only treatment option that offers the possibility of cure in sickle cell disease (SCD)

More than 250 SCD patients have now received transplants worldwide

SCT has its own risks and benefits, which are best discussed with your hematologist and / or a specialist in transplantation

There is hope that, in the future, gene therapy will also provide a curative therapy for sickle cell disease. However, this is currently not yet available.

This brochure attempts to introduce you to the role of stem cell transplantation for kids with sickle cell disease

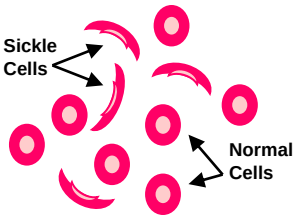
Disclosure:

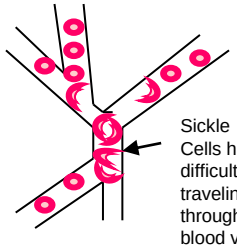
This brochure is meant for educational purposes only. Decisions about transplant for a specific child should be made only after discussion with a hematologist and transplant physician.

THE BASICS

Sickle Cell Disease (SCD):

You probably know a lot about sickle cell disease through your experience with your children. Sickle cell disease is a condition in which hemoglobin, the molecule that carries oxygen in the blood, has an increased tendency to precipitate (clump) under stressful conditions and thereby alters the shape of the red blood cell. As the affected cells travel through small vessels they get stuck and block the blood flow. This prevents blood from flowing through vital organs and causes pain as well as damage to the organ. Pain crises, acute chest syndrome, stroke, and osteonecrosis are some examples of complications from SCD.





Sickle Cells have difficulty traveling through small blood vessels

Recent progress:

Sickle cell disease patients are often treated with:
- Vaccines, routine as well as special, to prevent infection
- Antibiotics (like penicillin) to prevent infection
- Hydroxyurea
- Blood transfusions

These therapies have allowed children to live longer than in the past. However, each of these therapies has their own risks and benefits. For example:

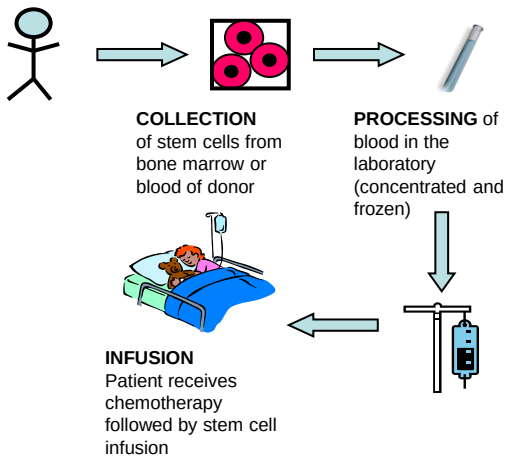
- **Hydroxyurea:** This is the first choice of treatment for patients with frequent pain crises or acute chest syndrome episodes. However, it is not known to be effective in reducing risk of stroke or priapism.

- **Blood transfusions:** Simple transfusion (one time transfusion) is often used when acute chest occurs. Chronic transfusion (ongoing transfusions) is often used to prevent a second stroke. However, 1 in 10 children will have a second stroke despite therapy.

STEM CELL TRANSPLANT

What is a stem cell or bone marrow transplant?

The bone marrow is located in the liquid /central portion of bones. It serves as a home for the stem cells. Stem cells have the capacity to create all the blood cells (red cells, white cells, and platelets). During a stem cell transplant or a bone marrow transplant, stem cells are taken out of the donor's bone marrow or blood and infused (injected) into the recipient (patient). From there on, the patient will have a new group of cells creating all the blood cells. This means that normal hemoglobin will be produced and circulate in the blood stream. The only draw back is that in order for the patient to accept these stem cells, the patient's immune system has to be turned off for a few months. Eventually, as the stem cells grow, they will form a new immune system and protect the patient from infection.



COLLECTION of stem cells from bone marrow or blood of donor

PROCESSING of blood in the laboratory (concentrated and frozen)

INFUSION Patient receives chemotherapy followed by stem cell infusion

What is a cord blood transplant?

Stem cells are also present in the blood of a baby's umbilical cord. This is blood that would normally be discarded after the baby is delivered. This blood can be collected upon delivery and stored for future use. After special processing, it can be used for stem cell transplant. For details on how to have cord cells saved: **http://www.marrow.org** or call 1 (800) 627-7692

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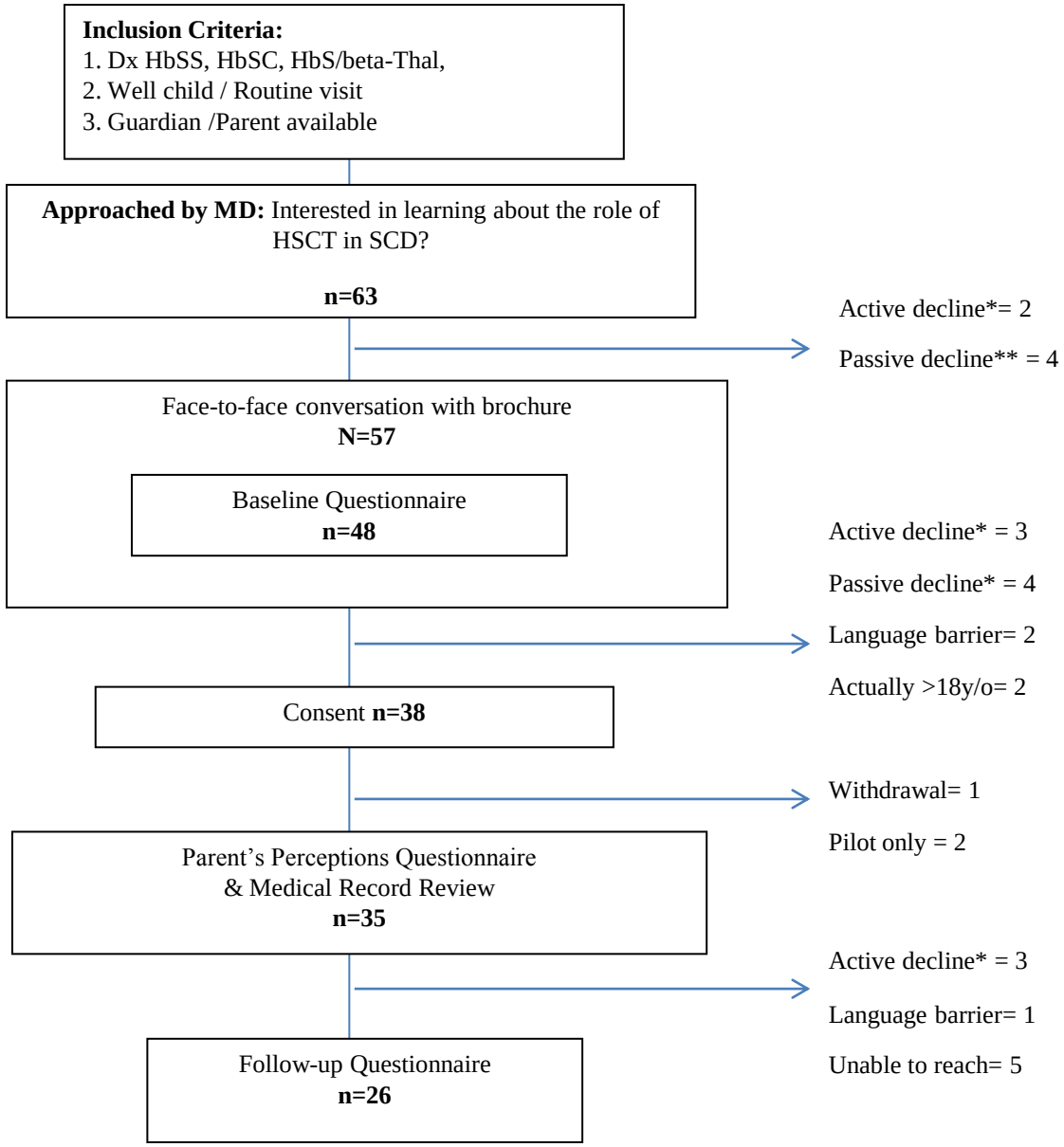

Figure 1. Subject enrollment. *Active decline = parent expressed preference against participation. **Passive decline = parent would neither decline nor accept to participate (see "Methods" for details)

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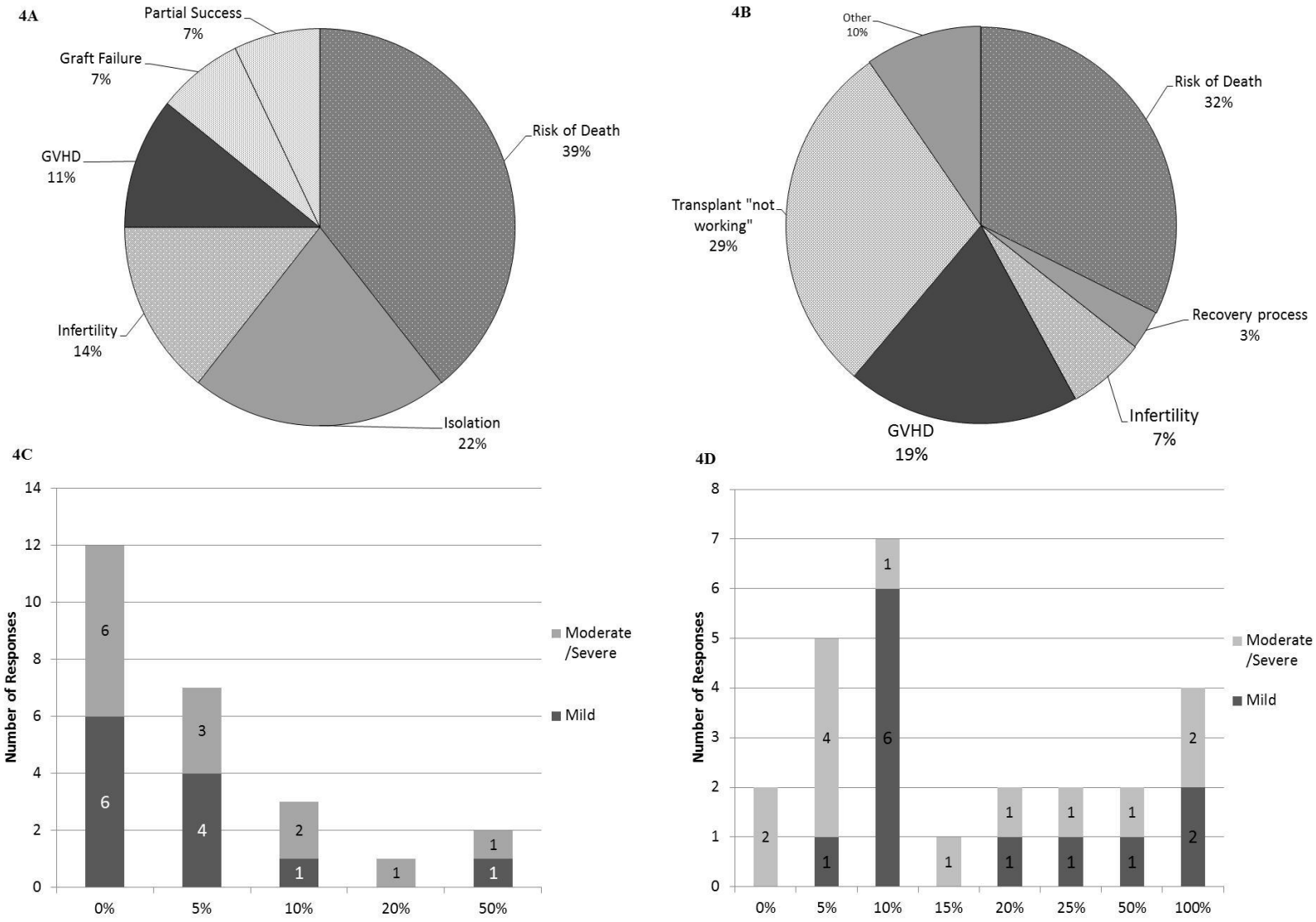

Figure 4. Parent's response to "Among the risks of transplant explained to me today, I am most concerned about:" immediately after educational session (n=23, Panel A) and during Follow-up Questionnaire (n=26, Panel B). Parent's response about mortality (Panel C) and infertility (Panel D) risk willing to take based on a hypothetical scenario in which HSCT was guaranteed to be 100% successful.

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Future goals

- Continued efforts to risk stratify in terms of both patient and disease factors
- Formation of parent network to promote education/research initiatives/support/barriers to care
- Collaboration with adult hematologists to better understand medical and social sequelae of disease and assessment of “pediatric bias”
- Investigation of role of BMT vs supportive care vs HU in less-developed countries
- Gene therapy

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Acknowledgements

- SMT medical and nursing staff
- Pediatricians and hematologists
  - Increased risk of graft rejection
  - Impact on fertility unknown
  - ? More chronic GVHD
- Families and patients

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