Evidence Review Workgroup

Advisory Committee on Heritable Disorders in Newborns and Children

Report February 2009

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Current Progress and Activities

- SCID
  - Final report submitted—January 2009
  - Discussion Today
- Krabbe Disease – Review in process

SCID Report

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Severe Combined Immunodeficiency (SCID)

- Group of disorders characterized by absence of both humoral and cellular immunity due to defects in T cell production and function.
- May also have defects in B-lymphocytes and/or NK-cells.
- Mutations in at least 15 genes lead to SCID.
- Infants with SCID develop severe infections, as protection from maternal antibodies wanes.

Rationale for Review

- Without disease-specific treatment SCID leads to death in early childhood.
- Earlier treatment may decrease mortality and morbidity associated with SCID and its treatment.
- Methods to screen infants for SCID, most commonly using quantitative PCR for T-cell receptor excision circles (TREC), have been developed.

Materials Included in Final Report

- Detailed methods
- Summarization of the evidence
- Tables highlighting key data from abstracted articles
- Materials provided to interviewees
- Conflict of interest form
- Bibliography of all identified articles

Methods of Review

- Systematic literature review, in order to summarize the evidence available from published studies
- Assessment of critical unpublished data from key investigators

Specific Topics Reviewed

- Incidence/prevalence
- Natural history
- Testing
  - Screening
  - Diagnostic
- Treatment
- Critical information still needed

Systematic Review

- January 1988- October 2008: Medline, OVID In-Process and Other Non-Indexed Citations database
  - English language only
  - Human studies only
  - Excluded: non-human data, reviews, editorials or other opinion pieces, case-series of <4 patients, studies containing only adult subjects, studies not addressing at least one of the key questions
- Also reviewed references from nomination form and bibliography of review papers
- ***725 abstracts selected for preliminary review***
- ***60 articles selected for review and abstraction***

Papers Meeting Review Criteria

Study Design	Number of papers
Experimental intervention	0
Cohort study	11
Case-control study	8
Case series total	38
Sample size ≤ 10	11
Sample size 11 to 50	18
Sample size ≥ 51	9
Economic Evaluation	1
Other design	2
Total	60

Quality Assessment Methods Used

- By Study Design
  - Compare within, rather than between, study design categories
- By Study Goal
  - Natural history, Treatment, Screening test, Economic evaluations
    - Example: Sensitivity and specificity of screening
      - Data obtained from screening program in U.S. population or similar
      - Data from systematic studies other than whole population screening
      - Estimated from known biochemistry of the condition

Unpublished Data

- Contacted experts identified through literature review, discussion within workgroup and recommendation by other experts
- Included experts from varying SCID domains
  - Example: screening, treatment, advocacy, etc.

Experts Contacted

- Mei Baker*
- Barbara Ballard*
- Francisco Bonilla*
- Marcia Boyle*
- Rebecca Buckley*
- Anne Comeau*
- Lisa Filipovich
- Alain Fischer
- Alan Knutsen
- Ronald Laessig*
- Edward McCabe*
- Sean McGhee*
- Vicki Modell*
- Luigi Notarangelo*
- Hans Ochs
- Sung-Yun Pai*
- Ken Pass*
- Jennifer Puck*
- Robert Vogt*

*Indicates the individual responded to our inquiry

Quality Assessment: Natural History

Genotype/Phenotype Correlation	**12**
I. Data from retrospective screening studies in U.S. or similar population.	0
II. Data from systematic studies other than whole population screening.	5
III. Estimated from the known clinical features of the condition as described for individual cases or short series.	7

Incidence (cases per 100,000), average within the U.S.	**4**
I. Data obtained from whole-population screening or comprehensive national surveys of clinically detected cases.	1
II. As in I, but more limited in geographical coverage or methodology.	2
III. Extrapolated from class I data for non-U.S. populations.	0
IV. Estimated from number of cases clinically diagnosed in U.S.	1

Adapted from Pandor et al. 2004, Pollitt et al. 1997

Incidence

- Chan and Puck, 2005
  - 1:105,000 live births
    - Extrapolated from XSCID samples sent to single lab
- Stephan et al., 1993
  - 1:100,000 live births
    - 5 years of referrals to specialized units in France
- Jones et al., 1991
  - 52/100,000 births in Navajo families
    - Death records

Natural History

- Most children are diagnosed after recurrent infections
- Timing of first opportunistic infection may vary by SCID subtype
- Without specific treatment for immunodeficiency, children with SCID die from infection in early childhood.
- Known phenotype/genotype differences do not affect main findings related to infection and death

Quality Assessment: Screening Test Characteristics

Overall sensitivity and specificity of screening & false-positive rate	**3**
I. Data obtained from screening programs in U.S. population or similar.	0
II. Data from systematic studies other than from whole population screening.	3
III. Estimated from the known biochemistry of the condition.	0
Repeat specimen rate	**0**
I. Data obtained from screening programs in U.S. population or similar.	0
II. Data from systematic studies other than whole population screening.	0
III. Estimated from the known biochemistry of the condition.	0
Second-tier testing	**1**
I. Data obtained from screening programs in US population or similar.	0
II. Data from systematic studies other than whole population screening.	1
III. Estimated from the known biochemistry of the condition.	0

Adapted from Pandor et al. 2004, Pollitt et al. 1997

Proposed Screening Methods

- Whole blood
  - Lymphocyte counts
- Dried blood spot
  - Quantitative polymerase chain reaction
  - Enzyme-linked immunosorbent assay (ELISA)

Screening Test Literature

Study	Population	Screening Methods	Accuracy of Screen; Sens/Spec.
Hennewig et al. 2007	36 children with rotavirus gastroenteritis: 18 with SCID, 18 without SCID.	•SCID children were more likely to have: •Low white blood cell count, eosinophilia and lymphopenia	^Sensitivity: 55.6% to 94.4% ^Specificity: 44.4% to 100%.
Chan, Puck 2005	23 children with SCID 2 with non-SCID immunodef. 242 anonymized newborn screening cards.	•DNA amplification of TREC from dried blood spot. •No detectable levels of TREC among SCID cases •Children with non-SCID immunodef. had TREC. •Several presumed false-positives in which beta-actin could be amplified but TREC could not.	*False positive rate: 1.5% from routine nurseries; 5% from special-care nurseries. ^Sensitivity: 84%-100% ^Specificity: 97-97.1%
McGhee et al. 2005	13 children with SCID 183 anonymized dried blood spots	•Discuss 2-tiered screening with IL-7 measured first and TREC measured in those with elevated IL-7	*Combined specificity of 100% (confidence interval, 97-100%) *Combined sensitivity of at least 85%
Hague et al. 1994	45 children with SCID 90 children without SCID.	•Used first available lymphocyte count. •Children with SCID had significantly lower levels of lymphocytes which persisted	*False-positive rate: 8% ^Sensitivity: 86.3%, and ^Specificity: 94.4%

**Calculation stated in article*
^Our calculation using data provided in article

Wisconsin Screening Experience

•**Number Screened:**	**70,397 (01/01/2008-12/31/2008)**
Premature (<37 weeks)	6487
Full term	63910
•**Abnormal Results:**	**32 (0.045%)**
Premature (<37 weeks)	20 (0.308%)
Full term	12 (0.019%)
•**Inconclusive Results**	**118 (0.168%)**
Premature (<37 weeks)	97 (1.50%)
Full term	21 (0.033%)

Courtesy of Dr. Mei Baker, presented at the Newborn Screening Symposium, November 2008, updated January 2009

Wisconsin Screening Experience

Abnormal Results:	Inconclusive Results:
-Full Term 1 DiGeorge Syndrome 1 Downs Syndrome with sepsis at birth 1 Idiopathic T-cell lymphopenia 1 Neutrophil migration defect with RAC2 mutation 2 normal Flow Cytometry results 4 normal results on repeated newborn screening 1 pending case 1 expired case **-Premature** 1 DiGeorge Syndrome (36 weeks) 1 chylous effusions (chylothorax and chylous ascites) 3 normal Flow Cytometry results 9 normal results on repeated newborn screening 4 pending cases 2 expired cases	**-Full Term** 1 Abnormal results on repeated NBS and abnormal Flow Cytometry (Idiopathic T-cell lymphopenia) 17 normal results on repeated newborn screening 1 pending cases 2 expired cases **-Premature** 1 DiGeorge Syndrome (36 weeks) 1 Abnormal results on repeated NBS and abnormal Flow Cytometry (gastrochisis) 72 normal results on repeated newborn screening 2 pending cases 21 expired cases

Courtesy of Dr. Mei Baker, presented at the Newborn Screening Symposium, November 2008, updated January 2009

Treatment Methods

- Allogeneic hematopoietic stem cell transplant (HSCT)
  - Sources include bone marrow, umbilical cord blood, peripheral blood
- Enzyme replacement therapy (ERT)
  - ADA-deficient SCID
- Gene therapy
  - X-linked or ADA-deficient SCID

Quality Assessment: Treatment

Effectiveness of treatment	**47**
I. Well-designed RCTs.	0
II-1. Well-designed controlled trials with pseudorandomization or no randomization.	0
II-2. Well-designed cohort studies:	8
A. prospective with concurrent controls	0
B. prospective with historical control	1
C. retrospective with concurrent controls.	7
II-3. Well-designed case-control (retrospective) studies.	0
III. Large differences from comparisons between times and/or places with and without intervention	4
IV. Opinions of respected authorities based on clinical experience, descriptive studies and reports of expert committees.	35

Adapted from Pandor et al. 2004, Pollitt et al. 1997

Treatment Evidence: HSCT Efficacy

Large case-series

Study	Population	Significant Findings
Buckley et al. 1999	89 children total; 22 less than 3.5	• 72 (81%) alive 3 months-16.5 years post-transplant, with a median follow up of 5.6 years. • 65 survived greater than 1 year, 38 greater than 5 years and 21 greater than 10 years. • Poor B cell function with 45 kids requiring IVIG. • NK-cell activity low in γc-chain deficiency and JAK3 deficiency, normal in other SCID subtypes.
van Leeuwen et al. 1994 *	31 patients total; 1-94 months old at BMT.	• HLA-identical related 6/10 (60% survived) • HLA haplo-identical related: 9/19 (47% survived). • HLA-matched unrelated: 0/2 (0% survived). • Major causes of death were graft and respiratory failure. • All who died of respiratory failure had a lung infection prior to transplant.
Stephan et al. 1993*	117 patients with SCID (from 1970 to 1992); 85 children were treated with BMT.	• HLA-identical transplant from a related donor 21/25 (84%) survived. • Pheno-identical transplant (HLA genotypically haplo-identical) from related donor 2/5 (40%) survived. • HLA haplo-identical transplant without T-cell depletion 0/5 (0%) survived. • T-cell depleted haplo-identical transplant 28/50 (56%) survived.

**May contain some of the same patients.*

Treatment Evidence: Long term survival following HSCT

Study	Population	Significant Findings	Quality of Evidence
Friedrich, Honig & Muller 2007 Cohort study	32 children total; all at least 10 years out from transplant.	•Most patients had normal and stable T-cell numbers and functions. •3 patients' had decreasing T-cell numbers. •4 patients' had decreasing PHA responses •HLA-haploidentical with no conditioning had lower levels of naïve CD4+ cells and impaired B cell functioning.	IV
Antoine et al. 2003 * Cohort study	475 patients (total of 566 transplants); patients from 37 European centers between 1968 and 1999.	•Three-year survival with sustained engraftment was 77% for HLA-identical and 54% for HLA-non-identical transplants. •Survival has improved over time for both HLA-identical and HLA-non-identical transplant recipients. •SCID phenotype was not associated with difference in survival	II-2 C
Haddad et al. 1998 Case series	193 patients total; from 18 European centers between 1982 and 1993.	•116 alive with evidence of engraftment 5 months after BMT; 24 later died (20%). •T-cell function improved during the 2 years after BMT and continued to be better than B-cell function. •Poor outcomes associated with: absence of T-cell reconstitution, presence of chronic GVHD 6 months after transplant, B- SCID (multivariate analysis). •At last follow up (median, 6 years after transplant), 93% of survivors had normal T-cell function and 68% had normal B-cell function.	IV
Fischer et al. 1990 * Case series	183 patients total; from 15 European centers between 1968 and 1989.	•Survival significantly better for HLA-identical (76% survival) than HLA-non-identical transplants (50% survival). •Lung infection before HSCT and absence of a protective environment significantly affected outcome (multivariate analysis). •A total of 27% had acute GVHD of grade II or higher and 25% developed chronic GVHD. •97% survival in those treated since 1983.	IV

**A subset of patients in Fischer et al. 1990 are also included in Antoine et al. 2003*

Treatment Evidence: HSCT in neonates/infants

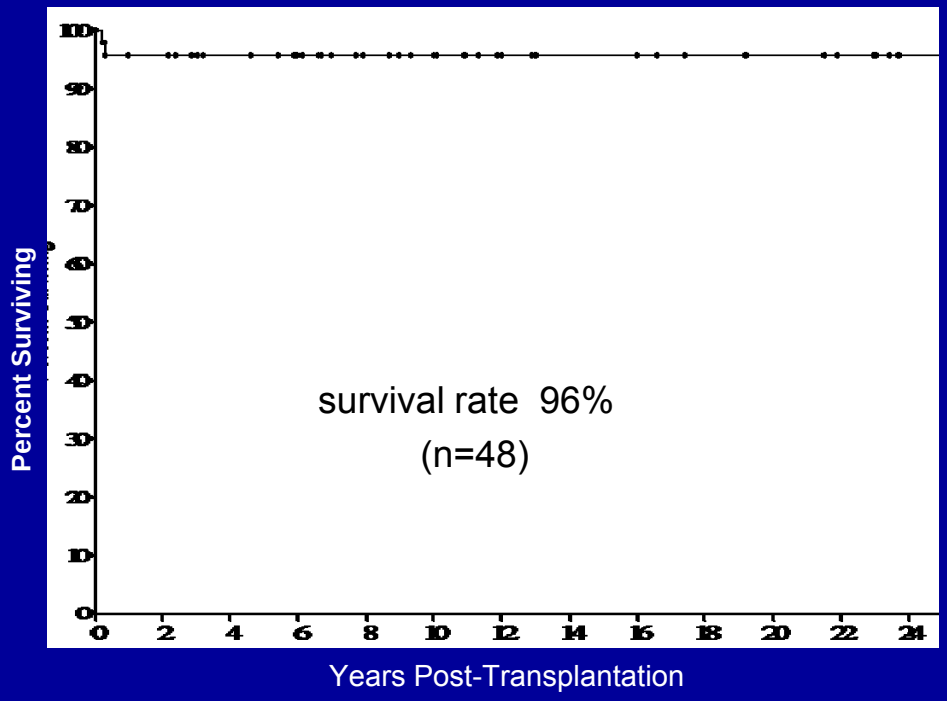
Study	Population	Significant Findings	Quality of Evidence
Myers et al. 2002* Cohort study	21 children transplanted prior to 28 days of life; 96 children transplanted at a median age of 190 days	•20/21 (95%) early treatment children survived. •71/96 (74%) late treatment children survived. •Early transplantation did not have an affect on B-cell function.	II-2 C
Kane et al. 2001 case-series	13 children total; transplanted between 7 and 68 days old.	•All patients alive and well 0.5-11.5 years after transplant (median 3 years). •2 children developed chronic GVHD. •3 children required more than one transplant. •All children achieved neutrophil engraftment and normal levels of IgA;7 have normal IgG; 12 have normal IgM. •10/12 have normal neuro-development; 1/12 has trouble with communication and interactive skills, and 1/12 has motor delay.	IV
Buckley et al. 1999* Case series	89 children total; 22 less than 3.5 months old at transplant.	•21/22 (95%) infants alive at follow-up 51/67 (76%) who received transplants at 3.5 months or older survived to follow-up •Median follow-up 5.6 years (range 3 months -16.5 years)	IV

** Potential patient overlap of Myers et al. 2002, Buckley et al. 1999*

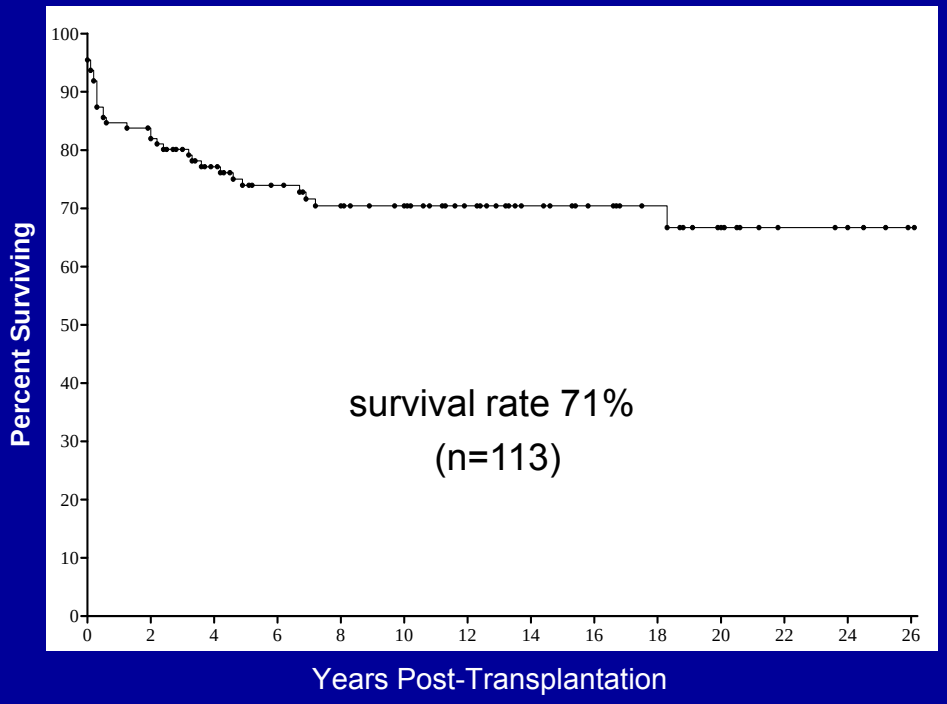
Early Treatment for SCID

- 161 SCID infants transplanted over the past 26 years, overall survival rate of 125/161 (78%)

Graph 1A. Transplanted in First 3.5 Months of Life



Graph 1B. Transplanted *after* First 3.5 Months of Life



The Kaplan-Meier graphs from Dr. Buckley (with permission)

Treatment for SCID: Availability

- From SCID expert interviews:
  - An informal survey an NIAID/Rare Diseases workshop identified 34 centers in the United States and Canada that currently perform HSCT for SCID
  - Others report 15 major and 34 minor centers in the U.S. and Canada currently performing stem cell transplantation for SCID.

Evidence of Harms from Screening, Diagnosis and Treatment

- Screening
  - No studies identified
- Diagnosis
  - No studies identified
- Treatment (2 studies)
  - 8/41 children undergoing HSCT developed auto-immune hemolytic anemia; 3 died from complications
  - 4 children (of the 9/10 who had successful gene therapy) developed leukemia between 30 and 68 months after gene therapy; 3/4 were successfully treated with chemotherapy

Evidence of Cost-Effectivenss

- McGhee et al, studied a deterministic decision-tree model
  - Compared universal and targeted screening approaches
  - Health care system perspective
  - Found an 86% likelihood of screening being cost-effective at a threshold of $100,000 per QALY gained
- Discussion with experts suggests treatment costs may have been underestimated

Key Findings

- ***Key findings:***
  - SCID incidence at least 1/100,000 newborns in the US
  - Population-based screening trials are underway
  - No population-based screening trial has been completed
  - Without curative treatment, newborns develop severe infections leading to early death
  - Treatment, most commonly with hematopoietic stem cell transplant, decreases morbidity and mortality associated with SCID
  - Some evidence supports the benefit of pre- or early symptomatic treatment compared to later treatment

Critical Evidence Needed: Screening

- No systematic method of case-finding exists.
- Pilot screening programs should serve to systematically identify cases in their screened populations.
- The new consortium of treatment centers (USIDNET) may facilitate systematic case-finding.

Critical Evidence Needed: Screening

- **Accuracy of Screening**
  - Current data are limited.
  - Early data from Wisconsin suggests a low false-positive rate.
  - No data exist regarding the accuracy of other screening methods in population-based protocols.
- **Feasibility of Screening**
  - Wisconsin's experience suggests screening is feasible.
  - Massachusetts has just initiated a screening pilot for SCID.
  - No data exist regarding the ability of other newborn screening programs to offer SCID screening
- **Acceptability of Screening**
  - No data describe consumer or physician acceptance of newborn screening for SCID

Critical Evidence Needed: Treatment

- **Value of early treatment**
  - Current evidence is limited
- **Cost-effectiveness (of screening and treatment)**
  - Cost-effectiveness analyses utilizing measured costs and utilities, as well as applicable sensitivity analyses, are needed
- **Adequacy of available treatment centers**
  - No current data address variation in treatment success among centers.
  - The number of centers in the United States and their capacity to provide treatment for SCID is unclear.
  - Future data from USIDNET and CIBMTR may provide evidence for treatment availability and variation

Thank you