Starship Clinical Guidelines
developed by clinicians at Starship Child Health

Severe Combined Immunodeficiency (SCID)

*This document is only valid for the day on which it is accessed. Please read our **disclaimer**.*

When the diagnosis is suspected

Infants diagnosed with Severe Combined Immunodeficiency (SCID) have severe defects in lymphocyte development and function. Infants with SCID may be recognised because there is a family history of previous affected children, or they can present early in life with severe, recurrent or opportunistic infections. Other manifestations include severe erythroderma with Omenns Syndrome or immune dysregulation in hypomorphic variants, which may present in older infants.

SCID is a paediatric emergency as it is invariably fatal without definitive treatment. Diagnosis and initiation of management is a priority.

Since 7/12/17 infants born in New Zealand have had screening for SCID on their Newborn Screening Test. Newborn Screening **will not detect all cases of SCID**.

Patients may still present with clinical manifestations including:

- **Infections**
  - Opportunistic infections eg PJP or CMV pneumonitis
  - Recurrent, severe or prolonged infections with common pathogens eg RSV, parainfluenza, influenza, adenovirus
  - Persistent / extensive oral or nappy candidiasis
  - Diarrhoea (including persisting GI infections eg rotavirus)
- **Failure to thrive**
- **Persistent lymphopaenia**
  - A normal or high lymphocyte count does not exclude a diagnosis of SCID. Examples of this include Omenn's syndrome, MHC class II deficiency and maternal engraftment.
- **Other**
  - Skin rash: maternal engraftment or Omenn's Syndrome
  - BCGosis: SCID patients who have been given BCG at birth are at risk of disseminated BCG infection
  - Family history

Investigations

Immunology

Initial investigations must include: (see **sample requirements below**)

Full blood count
Immunoglobulin - IgG, IgA, IgM
Lymphocyte phenotype, including naïve and memory T cells
Lymphocyte proliferation to PHA. If T cells are absent we do not expect any proliferation, but this needs to be documented prior to referral for transplantation
CMV PCR on whole blood*
Tissue typing for Class 1 and Class 2

Further investigations (depending on lymphocyte phenotype and other results)

HLA DR
Blood Group
Microarray or FISH if clinically indicated (e.g. 22q11del)
Studies for maternal engraftment
V beta repertoire
Serum IgE
ADA/PNP (Pathology Queensland Central Laboratory, Royal Brisbane Womens Hospital), uric acid
Other proliferation assays
Investigation for possible radiosensitivity
Tetanus, diphtheria and HiB antibodies (if already vaccinated and has measurable IgG)

Genetic testing

- Blood to lab for extraction and saving of DNA
- Investigation for underlying cause of SCID should be initiated, informed by the lymphocyte phenotype (see Figure 1 below).
  If there is a clear candidate gene for which analysis is available locally then initiate testing. If not then use Invitae® SCID panel, and consider add on testing of additional genes as clinically indicated (eg for ATM) as needed.

Figure 1 - *from Gaspar 2013*

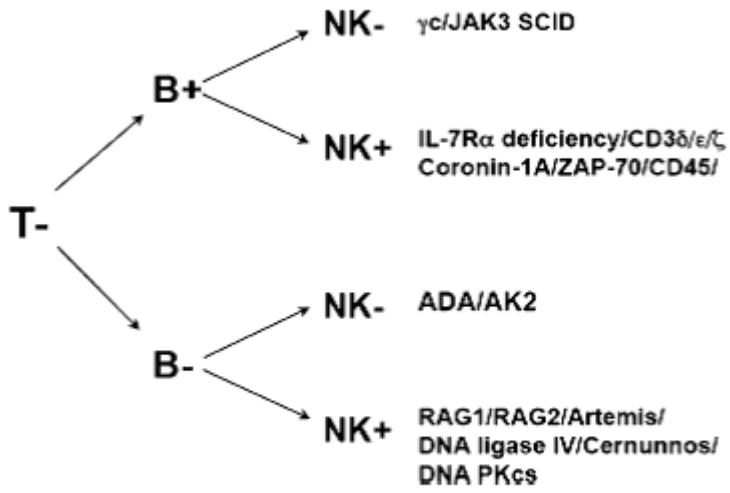


Figure 1. Immunophenotypes in SCID.

Infectious screening

- For infants diagnosed on Newborn Screening, maternal CMV serology and infant CMV PCR on whole blood may be the only initial infectious screening that is needed
- For infants diagnosed because of illness (rather than Newborn Screening) testing will depend on organ involvement and may include:
  - Stool MC&S and faecal viral panel
  - Blood cultures
  - Nasopharyngeal swab for respiratory panel and atypical panel
  - Consider BAL
  - MC&S, viral PCRs, fungal culture, AFB and PJP stains and / or PCR
- Serology is not useful and should not be ordered.
- Weekly monitoring of CMV for first 4 weeks after birth then monthly monitoring for CMV, EBV and adenovirus by blood PCR

Other investigation

CXR
Renal and liver function, calcium
Hearing - may be abnormal in ADA SCID and useful as baseline for all patients
Ophthalmology review for infants with CMV or VZV disease
Other - as clinically indicated eg neurological in ADA or PNP deficiency, cardiac/endocrine/ENT in DGS

Management

Protective isolation

See consideration of where to manage the patient for futher information.

- If in hospital, management should include a positive pressure room (at Starship this will generally be 26B or BMTU depending on availability)
- Doors closed
- Strict handwashing
- Visitors must be limited to healthy adults
- Staff with infections (including minor respiratory tract infections or cold sores) should not care for the child
- If child needs investigations that cannot be undertaken in the room (eg radiology), the department must be aware that the child must not be placed in a waiting area with other children. If a wait is unavoidable, a separate room must be provided.

Mitigating CMV transmission risk

- All newly diagnosed infants should have CMV whole blood PCR tested urgently as per initial investigations.
- If a mother is breast feeding at time of diagnosis the mother should have CMV IgG and IgM tested. Even if CMV serology has been negative on previous maternal testing, tests should be repeated in case there has been more recent exposure and seroconversion.
- Breast feeding should be stopped until mother and infant results available. The mother may continue to express milk.
  There is no data about the safety of pasteurisation of breast milk in the setting of profound immune deficiency.
- If the mother is seronegative, restarting breast feeding can be discussed. Newly acquired maternal CMV would pose significant risk to the infant.
- If the mother seropositive and infant CMV PCR negative there should be no further breast feeding.
  - Midwifery advice may be needed to manage mother's milk production.
  - Family will need appropriate advice about ensuring sterility of infant formula.
- If mother seropositive and infant CMV PCR positive, breast feeding may be restarted.
- Families should be advised that CMV can also be transmitted by saliva and other secretions so care should be taken to avoid accidental transmission (eg if a pacifier is used the parents shouldn't put the pacifier in their own mouth).

Transfusion precautions

Blood products must be CMV negative, leucodepleted and irradiated. Ensure blood bank has been informed of this alert

Immunoglobulin replacement

- For infants diagnosed on Newborn Screening, start IVIG at 4 weeks of age. Give 400mg/kg each 2-4 weeks to keep trough IgG >8g/l.
- Infants who are older at diagnosis will generally have hypogammaglobulinaemia. Consider loading dose of 1g/kg over 1-2 days then 400mg/kg/2-4 weeks to keep trough IgG >8g/l.
- Subcutaneous immunoglobulin replacement can also be considered.

Prophylactic medications

Co-trimoxazole PJP prophylaxis (start at 4 weeks of age) • Dose 2.5mg/kg trimethoprim component twice daily three days per week. • If the patient is neutropenic (ANC<0.5) discuss options (eg use of pentamidine).
Fluconazole 6mg/kg once daily (start at 4 weeks of age).
Aciclovir not routine but consider if parent or other carer has a history of frequent cold sores.

Vaccination

- Vaccines must be withheld.
    - The infant will get passive protection from immunoglobulin replacement and would not be expected to mount an immune response to vaccination.
    - Live vaccines risk vaccine infection (including rotavirus, BCG, MMR, VZV).
- Influenza vaccination should be recommended for family members.
- The need for pertussis booster for all family members should be reviewed.
- Administration of live vaccines (e.g. MMR, VZV) to other family members living with the patient (e.g. older siblings) should be discussed with the immunologist or paediatrician

Other care

- Document height, weight and head circumference at diagnosis and monitor on a regular basis.
- Dietetic review and consider nutritional support if faltering growth.
- Establish central venous just before eventual HSCT - discuss with transplant team and surgeons.
- In some instances central access will be required prior to HSCT. Double or triple lumen Hickman if possible.

Definitive treatment

- Most infants with SCID will be managed with stem cell transplant (HSCT).
- Gene therapy is available for some forms of SCID and may need to be considered for ADA SCID patients if there is not a sibling match for HSCT.
- Thymic transplant is available through centres in the USA and UK for patients with complete DiGeorge Syndrome.
- Refer to the paediatric bone marrow transplant service, who will assist with tissue typing of the patient, parents, and siblings, and commence search for unrelated donor if needed.

Consideration of where to manage the patient

- There will be a lag between diagnosis of SCID by Newborn Screening and being ready to undertake HSCT.
- The optimal location for the patient during this time will depend on various factors and will need to be made on a case by case basis. Factors to consider include:
    - The number of children (in particular pre-schoolers) in the home environment
    - The ability to isolate in the home environment.
    - Access to hospital care in the event of illness.
- If managed at home families need clear understanding of when they should present for urgent care, including onset of any new symptoms, any fever >38°C.
- During hospital visits SCID patients should not be placed in communal waiting areas or shared hospital rooms.

Approach to early management of a new infant with a lymphocyte subset profile consistent with SCID or leaky SCID

Table 1 *(from Dorsey 2017)*

TABLE I. Approach to early management of a new infant with a lymphocyte subset profile consistent with SCID or leaky SCID

- Isolate in a single room in SCID treatment center; prohibit ill contacts
- Diagnose and treat any clinical abnormalities, such as respiratory distress or signs of infectious or autoimmune conditions
- Introduce social worker to help with support and services for family
- Omit live vaccines for patient or household contacts, including rotavirus vaccine
- Avoid infection:
  - Advise mother to suspend nursing while evaluating her prior exposure by using CMV IgG serology
  - If mother is CMV seronegative, encourage her to resume nursing
  - If mother is CMV seropositive and the baby is CMV negative based on blood and urine PCR, advise the mother to avoid nursing, given the risk of breast milk transmission of CMV
  - Obtain infant blood CMV PCR weekly for 4 weeks and periodically thereafter (more often if CMV is clinically suspected, such as with an increase in liver transaminase levels)
- Intravenous access needed for gammaglobulin replacement with coordination of blood draws to decrease frequency of venipuncture; establish more permanent intravenous access just before eventual HCT
- Provide nutritional support, including monitoring for iron deficiency
- Transfuse if symptomatic or hemoglobin <8 mg/dL using only CMV-negative, leukoreduced, irradiated packed red cells
- Administer immunoglobulin to maintain IgG level >800 mg/dL
- Administer palivizumab during the respiratory syncytial virus season
- Begin prophylactic fluconazole, acyclovir, and trimethoprim-sulfamethoxazole (the latter after 30 days of age)*
- Perform HLA typing on parents and full siblings to evaluate as potential HCT donors; in the absence of a matched sibling, initiate search for an unrelated adult or cord blood donor

*See Appendix Table I for prophylactic medication dosing.

Early clinical and laboratory assessment for a new infant with suspected SCID

Table 2 *(from Dorsey 2017)*

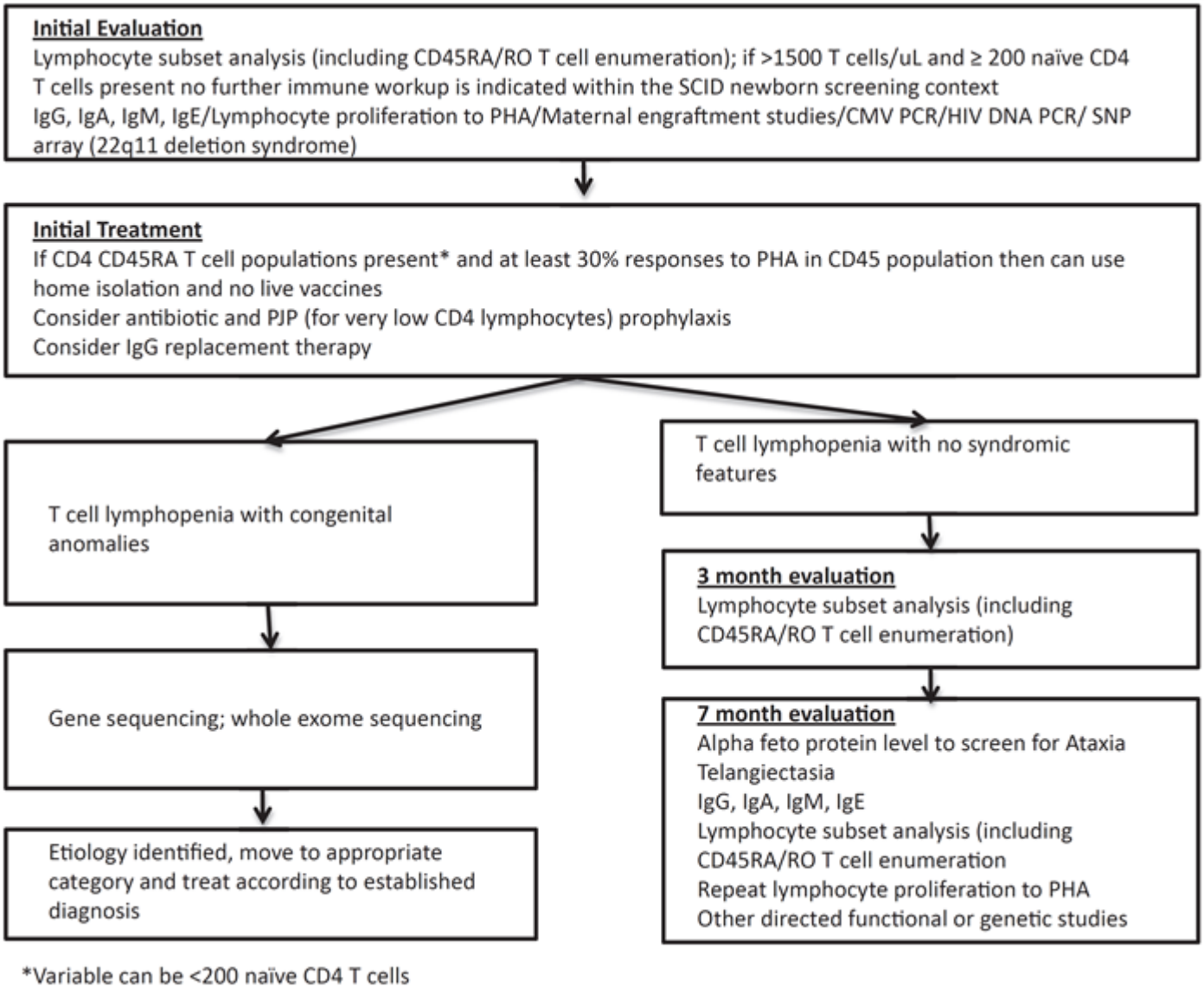
TABLE II. Early clinical and laboratory assessment for a new infant with suspected SCID

- Directed history, including infections, family history, pedigree analysis, consanguinity
- Physical examination, including documentation of any signs of infection, skeletal features, and congenital anomalies associated with certain SCID variants, rash of GVHD or erythroderma of OS, or desaturation associated with PAP in patients with ADA deficiency
- Evaluate lymphocyte subsets, including T-cell CD45RA/RO determined by using flow cytometry, to confirm the initial flow cytometry done by the screening program
- Blood chemistries, albumin, liver function tests, and total bilirubin
- PCR or antigen tests for HIV, HSV, EBV, HepB, parvovirus B19, adenovirus, respiratory viruses, and rotaviruses; do not rely on serologic tests; serial maternal serology and/or PCR might suffice to rule out some of the above
- Quantitative immunoglobulins: IgG (reflects maternal transfer to baby, must be drawn before IVIG administration), IgA, IgM, and IgE
- Lymphocyte proliferation to PHA: send large enough sample to account for low lymphocyte count and inform the testing laboratory of the infant's low T-cell count
- ADA and PNP enzyme and purine metabolites (unless there is a family history or strong suspicion of another genotype)
- Maternal chimerism studies by DNA testing of polymorphic alleles
- Molecular diagnosis directed by sex and lymphocyte profile (T^-B^+ or T^-B^- and whether NK cells are present); sequence single leading candidate gene or panel of SCID genes
- SNP array (or other copy number DNA array) preferred over chromosome 22 fluorescence *in situ* hybridization for infants with cardiac anomalies or any features suggesting DiGeorge syndrome
- Unless concern for radiation-sensitive SCID exists,* perform a chest radiograph to document whether the thymus is visible and view lung parenchyma and osseous structures (In asymptomatic infants imaging can be deferred until documenting central venous line placement.)

HepB, Hepatitis B; *HSV*, herpes simplex virus; *IVIG*, intravenous immunoglobulin.
*Microcephaly and bird-like facial appearance; infants with Navajo background.

Evaluation and management of non-SCID TCL (persistently <1500 CD3 T cells)

Figure 2. *(from Dorsey 2017)*



Sample requirements for initial investigations

Sample type	Volume	Tube	Special requirements
Full blood count	250 uL	Micro-EDTA	Local laboratory
Serum IgG, IgA, IgM	0.5-1 mL	Micro-plain serum	Local laboratory
CMV PCR on whole blood	1.2 mL	Micro-EDTA	Local laboratory
Lymphocyte phenotype (+/- naïve/memory T¶)	500 uL	Micro-EDTA or heparin	Local laboratory or LabPlus, Auckland
Lymphocyte proliferation to PHA	1 mL	Micro-heparin	Local laboratory or LabPlus, Auckland
Tissue typing for class 1 & class 2	1 mL	2 x micro-EDTA	Dedicated tubes & NZBS tissue typing form¥

For all tests work with local laboratory to ensure minimum blood volumes are used.

¶ If not already performed or if repeat indicated.

¥ Liaise with bone marrow transplant team Starship Hospital.

References

1. Gaspar HB, Qasim W, Davies EG, Rao K, Amrolia PJ and Veys P. How I treat severe combined immunodeficiency Blood 2013 122:3749-3758; https://doi.org/10.1182/blood-2013-02-380105
2. Thakar MS, Hintermeyer MK, Gries MG, Routes JM and Verbsky JW. A Practical Approach to Newborn Screening for Severe Combined Immunodeficiency Using the T Cell Receptor Excision Circle Assay. Front. Immunol. 2017 8:1470. https://doi.org/10.3389/fimmu.2017.01470
3. Dorsey, MJ, Dvorak, CC, Cowan, MJ, and Puck JM. Treatment of Infants Identified by Newborn Screening for Severe Combined Immunodeficiency. J Allergy Clin Immunol. 2017 Mar; 139(3): 733-742. https://doi.org/10.1016/j.jaci.2017.01.005