Secondary immunodeficiency (SID) associated with haematopoietic stem cell transplantation (HSCT)

SECONDARY
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Principles of HSCT and its clinical indications

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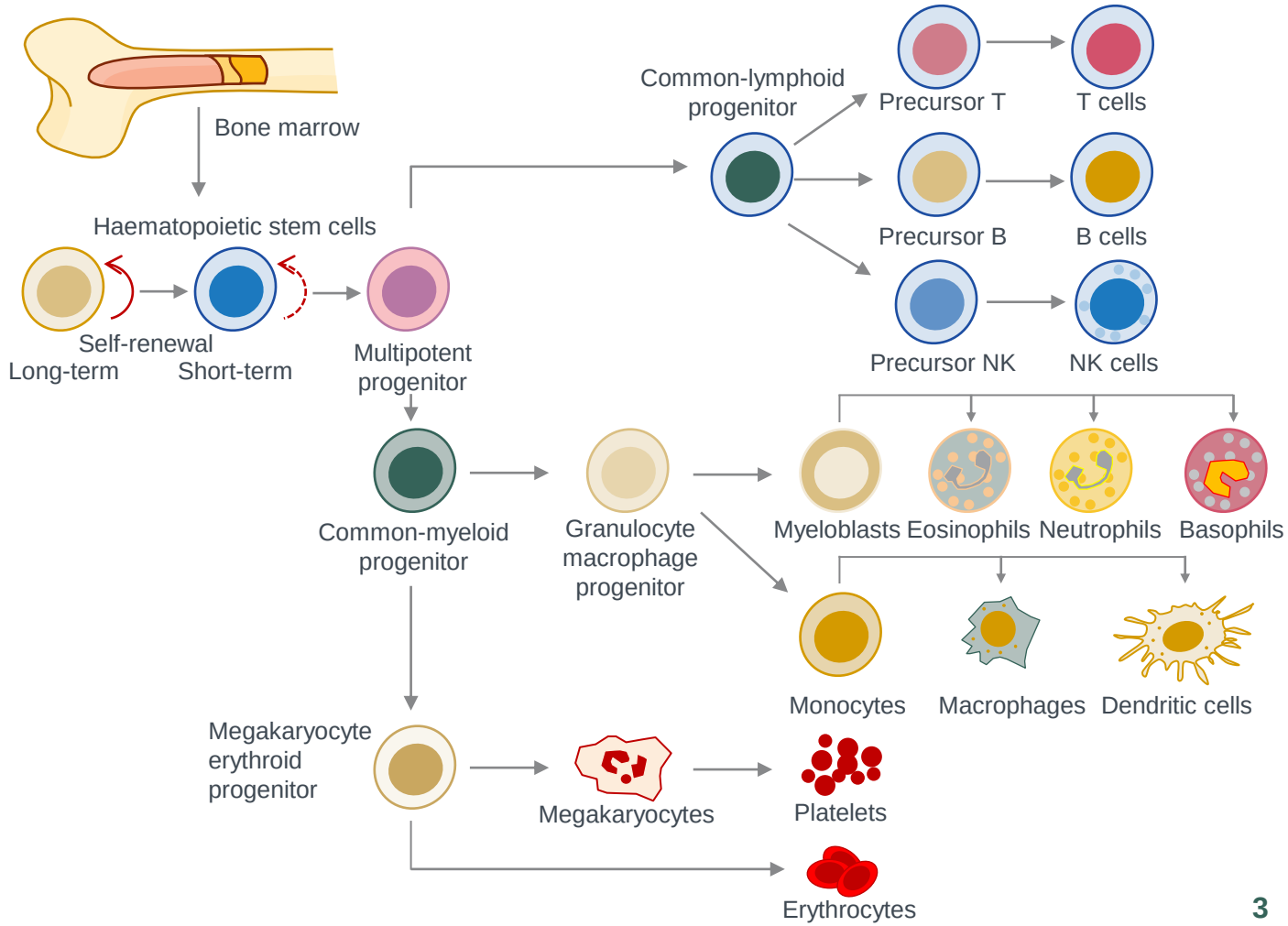
The importance of haematopoietic stem cells (HSCs) in the formation of blood cellular components

- Haematopoiesis is defined as *a continuous process of blood-cell production occurring through the orchestrated proliferation, self-renewal and differentiation of haematopoietic stem cells (HSCs)*.[1]
- Throughout life, all blood cell lineages derive solely from HSCs.[1]

The hierarchical system of normal haematopoiesis[2]



HSC: haematopoietic stem cell.

1. Mendelson, A. and Frenette, PS., Nat Med. 2014; 20:833-46,
2. Adapted from Zhang, P. et al., Stem Cell Res Ther. 2019; 10:327.

What is haematopoietic stem cell transplantation (HSCT)?

SECONDARY IMMUNE DEFICIENCY

- Sometimes also referred to as bone marrow transplantation.[1]
- HSCT is the infusion of HSCs to re-establish haematopoietic function in patients with a damaged or defective bone marrow or immune system.[1,2]
  - Patients with malignant haematopoietic diseases require HSCT to rescue their bone marrow from the toxic effects of high-dose chemotherapy and exploit the graft-versus-leukemia effect against residual disease.
  - In non-malignant diseases, the goal of HSCT is to replace genetically defective stem cells or failing haematopoiesis.
- Stem cells for HSCT are usually derived from bone marrow, peripheral blood or umbilical cord blood.[1]

Over 40,000 HSCTs are carried out in Europe each year.[3]

HSC: haematopoietic stem cell; HSCT: haematopoietic stem cell transplantation.

1. Saria, MG. and Gosselin-Acomb, T., Clin J Oncol Nurs. 2007; 11:53–63,
2. Mosaad, YM., Immunol Invest. 2014; 43:858–87,
3. Passweg, JR. et al., Bone Marrow Transplant. 2016; 51:786–92.

HSCT is categorised by the donor source

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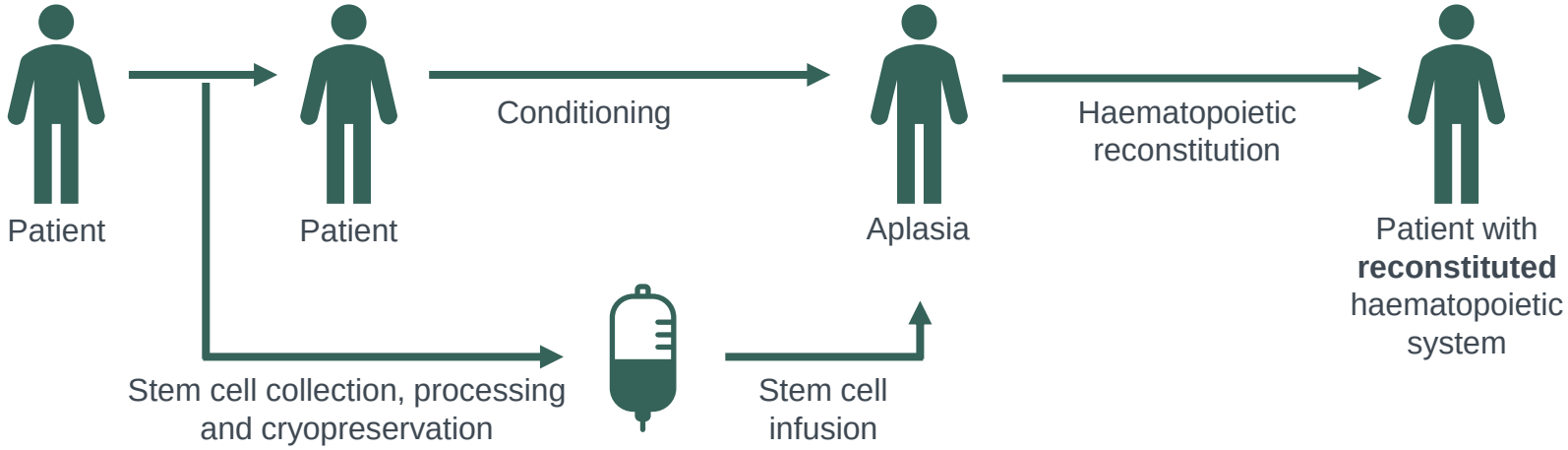
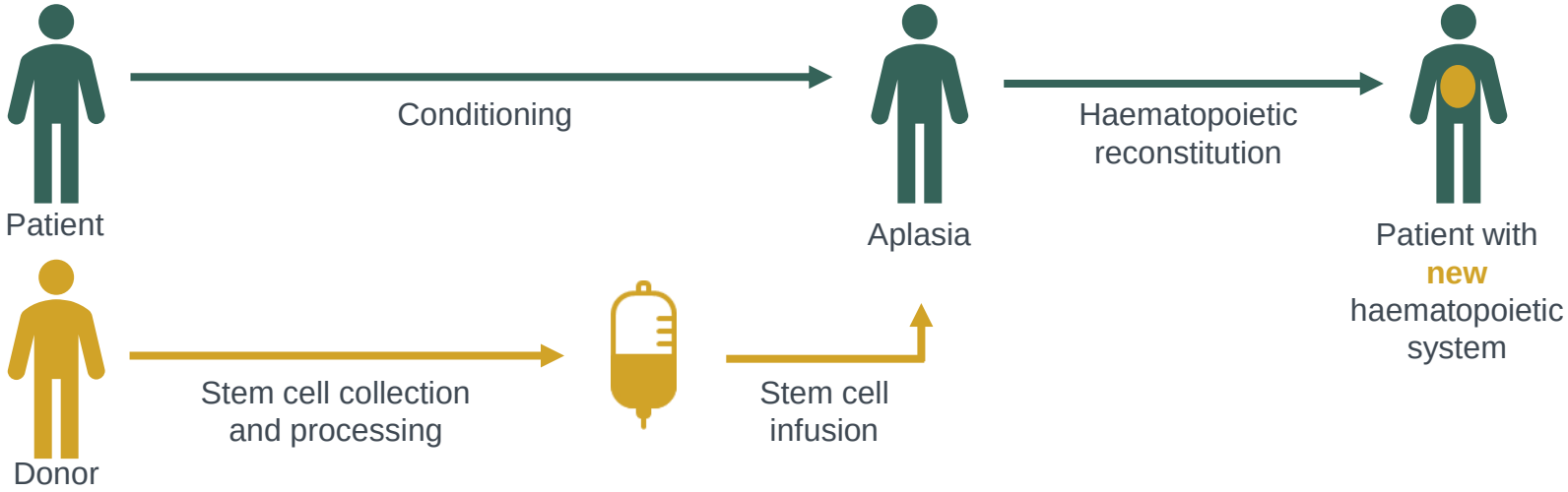
Autologous
From the patient's own peripheral blood.



Allogeneic
From another person, related or unrelated, who has been selected based on HLA-matching and other factors.



HLA: human leukocyte antigen; HSCT: haematopoietic stem cell transplantation.
Saria, MG. and Gosselin-Acomb, T. Clin J Oncol Nurs. 2007; 11:53–63.

HSCT is indicated for a wide range of diseases

Selected indications shown

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Autologous

- Haematologic malignancies.
  - Multiple myeloma.
  - Lymphoma.
- Autoimmune diseases.
  - i.e. Systemic sclerosis or multiple sclerosis.

Allogeneic

- Haematologic malignancies.
  - Leukaemia.
  - T-cell lymphoma.
  - Myelodysplastic syndrome.
- Inherited disorders.
  - Primary immunodeficiencies, thalassemia, sickle cell disease, metabolic diseases.
- Bone marrow failure syndromes.

For further information on chronic lymphocytic leukaemia and multiple myeloma please see https://www.secondaryimmunodeficiency.com/

HSCT: haematopoietic stem cell transplantation.

Snowden, JA. et al., Bone Marrow Transplant. 2022; 57:1217–39.

Immune reconstitution and secondary immunodeficiency (SID) after HSCT

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Immune reconstitution after HSCT

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Immune reconstitution after HSCT is a critical process to **prevent infections and malignancy relapse**.[1,2]

It is a gradual process by which the patient's immune system **regains its normal function** over time.[1]

Immune reconstitution involves the recovery of **neutrophils, monocytes, antigen-presenting cells, T cells, B cells, and NK cells**.[1,3,4]

HSCT: haematopoietic stem cell transplantation; NK: natural killer.

1. Elfeky, R. et al., Exp Rev Clin Immunol. 2019; 15:735-51, 2. Servais, S. et al., Biol Blood Marrow Transplant. 2014; 20:507-17,
3. de Koning, C. et al., Biol Blood Marrow Transplant. 2019; 25:819-26, 4. Velardi, E. et al., Nat Rev Immunol. 2021; 21:277-91.

The major immune cell types follow a predictable kinetic pattern of recovery after HSCT

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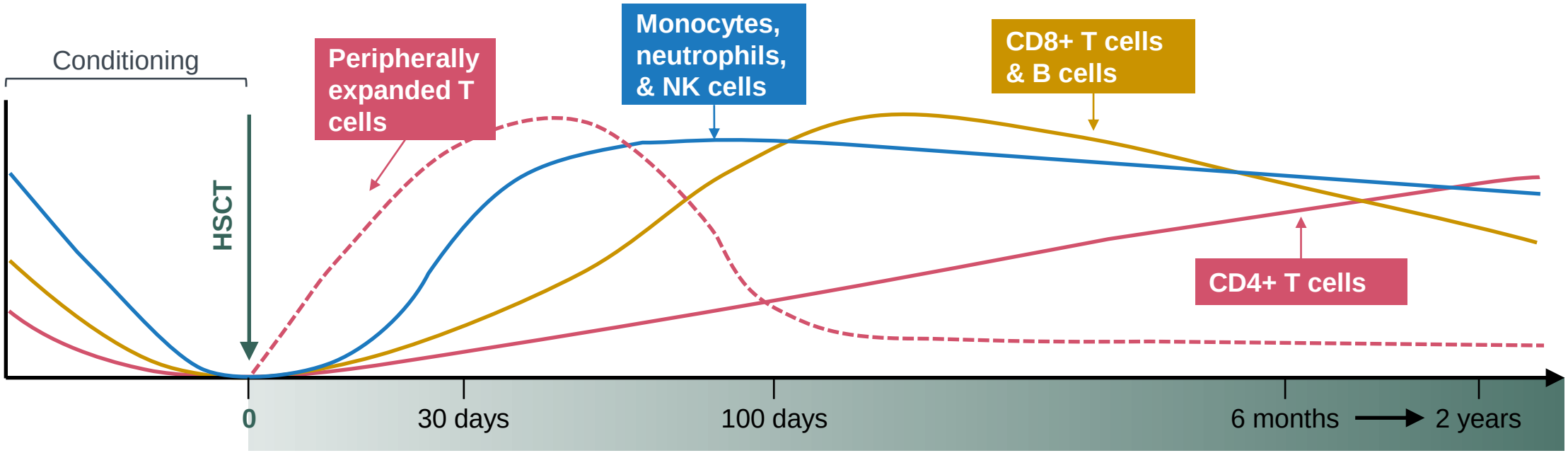
Allogeneic HSCT [1]



Autologous HSCT

- Immune reconstitution after autologous HSCT is significantly faster than for allogeneic HSCT.[2]

HSCT: haematopoietic stem cell transplantation; NK: natural killer.

1. Adapted from Velardi, E. et al., Nat Rev Immunol. 2021; 21:277-91, 2. Champlin, R., Selection of Autologous or Allogeneic Transplantation. In: Kufe, DW. et al., Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003.

Factors affecting immune reconstitution

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Pre-transplant factors[1]

- **Age.**
- Comorbidities.
- Prior treatment.
- Underlying disease.

Transplant factors[1]

- **Conditioning intensity.**
- **HLA matching.**
- **T-cell depletion.**
- Donor source.
- Graft manipulation.
- Stem cell dose and product composition.

Post-transplant interventions[1]

- **Immunosuppression**.
- Donor lymphocyte and other cell infusions.
- IgG.[2]

Post-transplant events[1]

- **GvHD.**
- Rejection.
- Infections: CMV, Epstein-Barr virus, varicella zoster virus, fungus, others.
- Relapse.

Autologous HSCT[3]

- Immune reconstitution after autologous HSCT is not impaired by factors such as graft-rejection, immunosuppression and GvHD. A more rapid reconstitution results in a generally lower risk of infection.

CMV: cytomegalovirus; GvHD: graft-versus-host disease; HLA: human leukocyte antigen; HSCT: haematopoietic stem cell transplantation; IgG: immunoglobulin G.

1. Stern, L. et al., Front Immunol. 2018; 9:1672, 2. Gaytán-Morales, JF. et al., Bol Med Hosp Infant Mex. 2021; 78:191-9,
3. Champlin, R., Selection of Autologous or Allogeneic Transplantation. In: Kufe, DW. et al., Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003.

A focus on two major factors affecting immune reconstitution after HSCT

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Conditioning regimen[1,2]

High-dose chemotherapy and/or radiation therapy before HSCT can affect immune reconstitution by damaging the bone marrow microenvironment, thymus and other lymphoid tissues.

GvHD[3,4]

Following allogenic HSCT, donor-derived T cells can be activated by residual host-derived antigen-presenting cells which can escalate into GvHD, a life-threatening condition.

Acute GvHD (usually *occurring within the first 100 Days after transplant*) substantially decreases thymic output and thus recovery of CD4+ T cells and diversified T cell repertoires.

Both acute and chronic GvHD (usually *occurring beyond 100 Days after transplant*) have been associated with delayed B cell reconstitution.

A reduction or lack of B cell precursors in the bone marrow has been observed in patients with GvHD.

GvHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation.

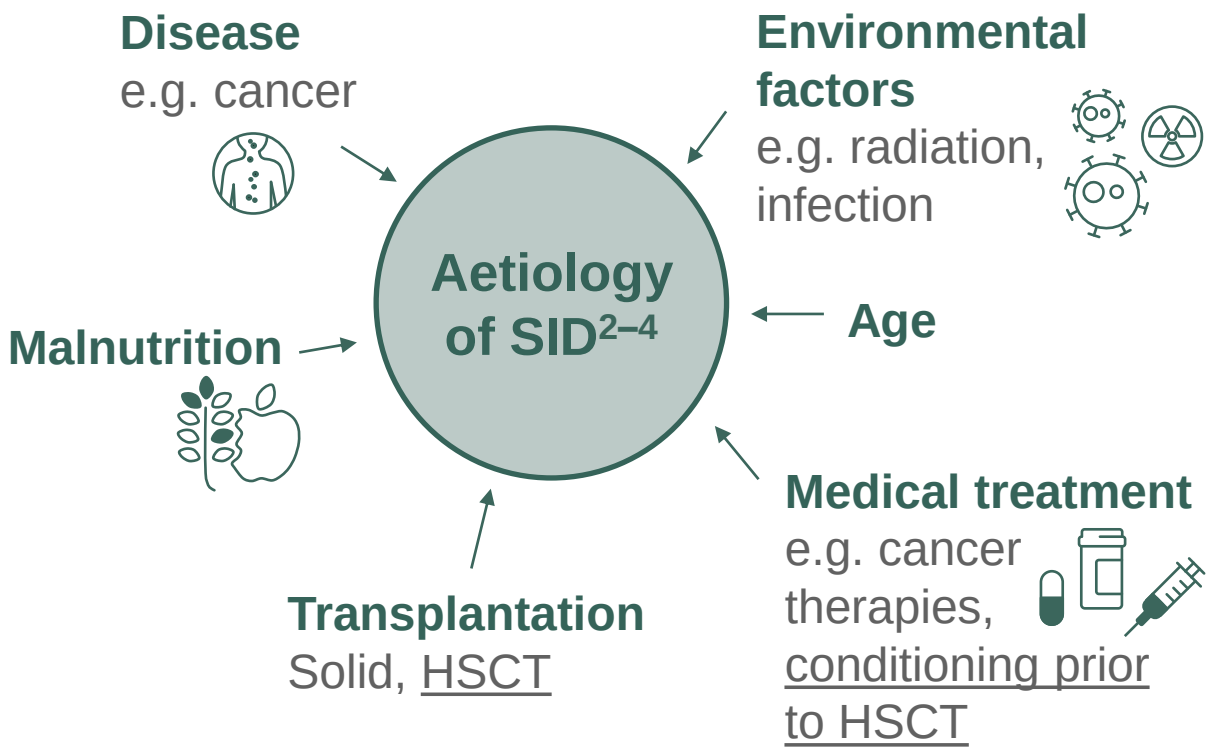
1. Shao, L. et al., Transl Cancer Res. 2013; 2:397-411, 2. Głowala-Kosińska, M. et al., Biol Blood Marrow Transplant. 2016; 22:834-42,
3. Ogonek, J. et al., Front Immunol. 2016; 7:507, 4. Velardi, E. et al., Nat Rev Immunol. 2021; 21:277-91.

HSCT can lead to secondary immune deficiency (SID)

SECONDARY IMMUNE DEFICIENCY

SID is defined as *the transient or persistent impairment of the cellular or humoral components of the immune system, caused by extrinsic factors, leading to increased risk of infection*.[1]

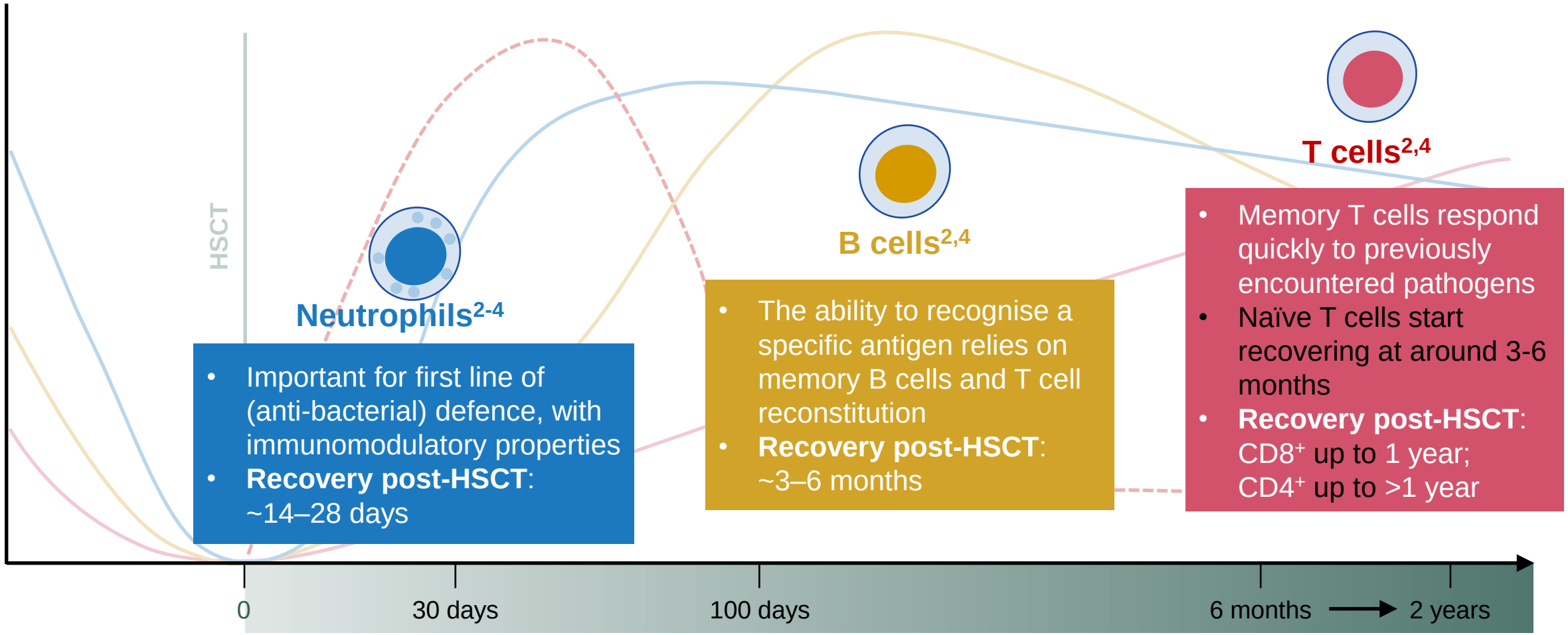
Timely diagnosis, ongoing monitoring, and prophylactic therapy are needed for SID management.[1]



HSCT: haematopoietic stem cell transplantation; SID: secondary immune deficiency.

1. Cem Ar, M. et al., Leukemia Research. 2023; 133:107365, 2. Tuano KS. et al., Ann Allergy Asthma Immunol. 2021 Dec;127(6):617-626, 3. Shah N. et al., Crit Rev Oncol Hematol. 2023; 181:103896, 4. Heck, C. et al., Fronts Immunol. 2021; 12:736137.

Main cell types contributing to SID after allogeneic-HSCT



HSCT: haematopoietic stem cell transplantation; SID: secondary immune deficiency.

1. Adapted from Velardi, E. et al., Nat Rev Immunol. 2021; 21:277-91, 2. Stern, L. et al., Front Immunol. 2018; 9:1672,
3. Tecchio, C. and Cassatella, MA., Cell Mol Immunol. 2021; 18:905-18, 4. Tomblyn, M. et al., Biol Blood Marrow Transplant. 2009; 15:1143-1238.

Potential biomarkers for humoral immune reconstitution[1-4]

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Predicting infection risk

There are no ideal biomarkers to predict infection risk caused by incomplete humoral IR, because long-lived plasma cells can produce IgG without specific antibody responses.

Potential biomarkers

- Serum IgG levels.*
- Peripheral blood B cell numbers.*
- $CD4^+$ T-cell counts (needed for effective B-cell function).

Evaluating humoral IR

Biomarkers can be complemented with infection history and specific antibody response to pneumococcal vaccine.

* Normal serum IgG and total B-cell numbers may not be suitable markers of humoral immune reconstitution as long-lived plasma cells can survive and generate IgG without inducing specific antibody responses.

IgG: immunoglobulin G; IR: immune reconstitution.

1. Otani, IM. et al., J Allergy Clin Immunol. 2022;149(5):1525-1560, 2. van der Maas, NG., et al., Front Immunol. 2019 Apr 12;10:782,
3. Cavazzana-Calvo, M. et al., Curr Opin Immunol. 2009 Oct;21(5):544-8, 4. Storek, J. et al., Expert Opin Biol Ther. 2008; 8:583-97.

A deeper look at B cell reconstitution after HSCT

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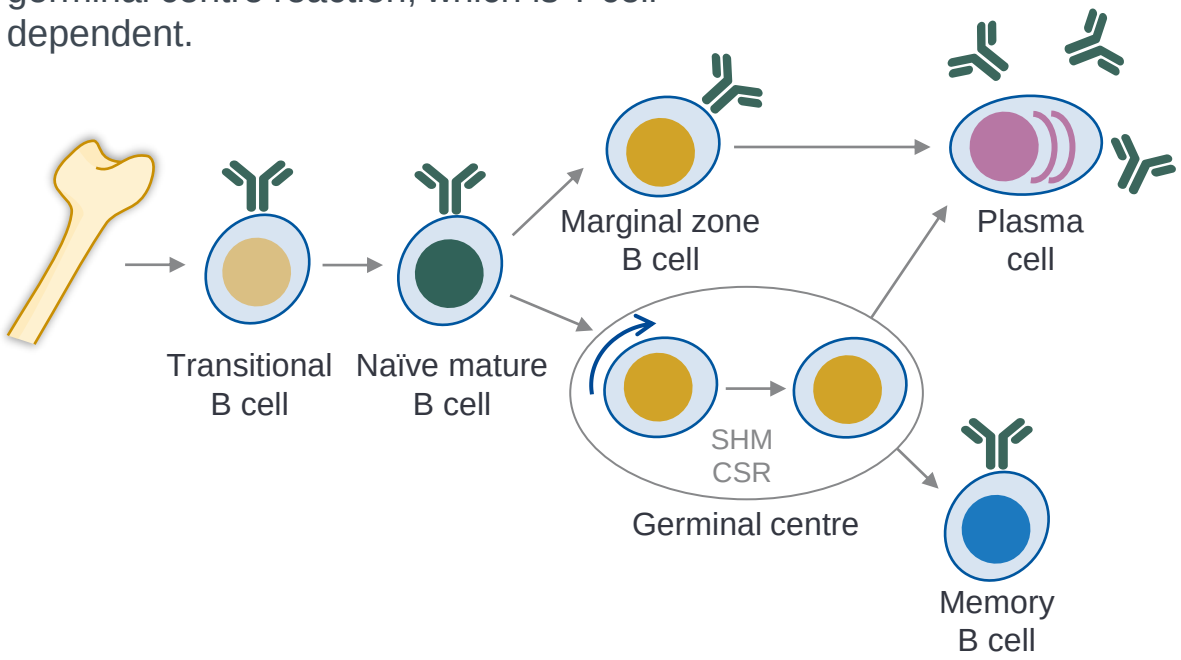
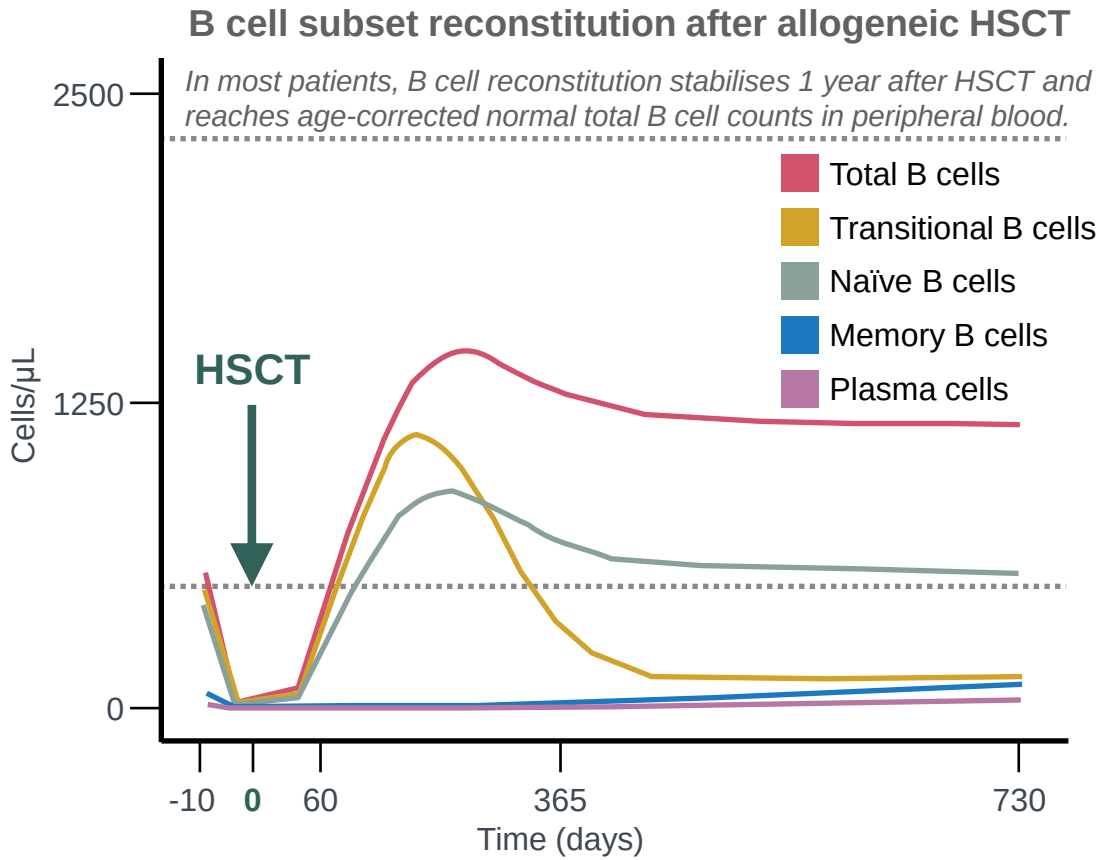
Peripheral B cell development

Mature B lymphocytes can differentiate into memory B cells and may undergo isotype switching as well as affinity maturation in a germinal centre reaction, which is T cell dependent.





Compared to other haematopoietic cell lines, B cell reconstitution – especially of memory B cells – occurs relatively late after HSCT.

CSR: class-switch recombination; HSCT: haematopoietic stem cell transplantation; SHM: somatic hypermutation.
Adapted from Van der Maas, NG. et al., Front Immunol. 2019; 10:782.

Several factors can delay B-cell reconstitution after HSCT

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- Stem cell source[1]
  - Different sources have varying kinetics of B cell recovery with cord blood being superior to bone marrow or peripheral blood stem cells.
- Reduced intensity conditioning[1]
  - This method can lead to increased rates of graft rejection and suboptimal B cell function.
- Total body irradiation[1]
  - May delay B cell reconstitution.
- Serotherapy[1]
  - Some agents used to reduce risk of graft rejection and acute GvHD target B cells.
- Rituximab[1,2]
  - This drug, used to mitigate EBV reactivation, depletes B cells.
- Immunosuppressive therapies[3]
  - Purine analogues (i.e. fludarabine) inhibit B cell proliferation
  - Steroids can reduce naïve B cells.
- GvHD[1*]
  - Higher grades of acute GvHD seem to be associated with more extensively impaired humoral immunity, due to both GvHD itself and associated immunosuppressive therapies.
  - Chronic GVHD leads to reduced numbers of B cell progenitors and unswitched memory B cells.

* Only valid for allogeneic HSCT.
EBV: Epstein-Barr virus; GvHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation.
1. Van der Maas, NG. et al., Front Immunol. 2019; 10:782, 2. Burns, D. et al., Bone Marrow Transplant. 2016; 51:825-32, 3. Patel, SY. et al., Front Immunol. 2019; 10:33.

Impaired B cell function and secondary antibody deficiency (SAD)

SECONDARY IMMUNE DEFICIENCY

Allogeneic HSCT can result in significant impairment of B cell function, including reduced antibody production and impaired memory B cell generation.[1]

B cell impairment can lead to SID, particularly secondary antibody deficiency (SAD).[2,3]

GvHD* can further impair B cell function and exacerbate SAD, as it affects the bone marrow microenvironment, leading to a reduced number and function of B cells and plasma cells.[3]

Immunosuppressive therapy for GvHD* contributes to SAD.[3]

SAD can result in an increased risk of infections and the need for prophylactic antibiotics and immunoglobulin replacement therapy.

* Only valid for allogeneic HSCT.

GvHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation; SAD: secondary antibody deficiency; SID: secondary immune deficiency.

1. Van der Maas, NG. et al., Front Immunol. 2019; 10:782, 2. Barrow, M. et al., Front Immunol. 2022; 13:928062, 3. Patel, SY. et al., Front Immunol. 2019; 10:33.

HSCT complications: A focus on infection

SECONDARY IMMUNE DEFICIENCY

Allogeneic HSCT is associated with multiple complications, mainly related to conditioning and immunosuppression

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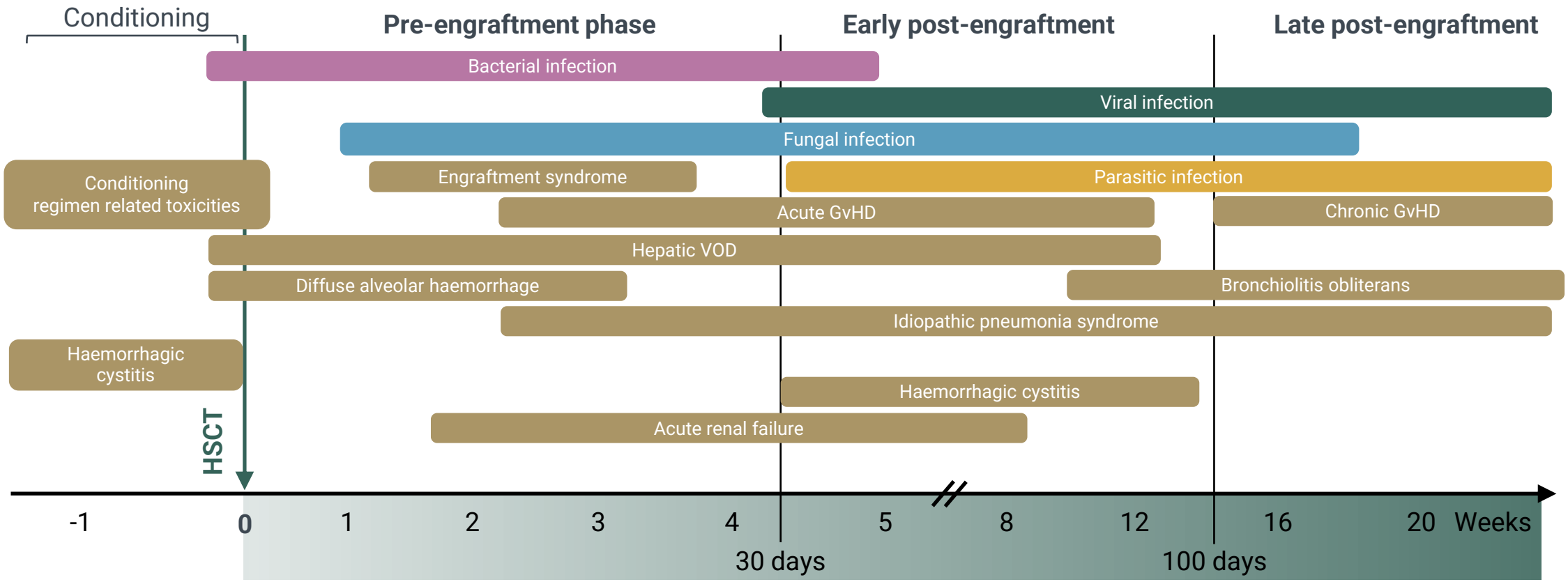
Chronology of possible haematopoietic stem cell transplant complications



GvHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation; VOD: veno-occlusive disease.
Adapted from Saria, MG. and Gosselin-Acomb, TK., Clin J Oncol Nurs. 2007; 11:53–63.

Infection remains a substantial cause of death after HSCT in adults

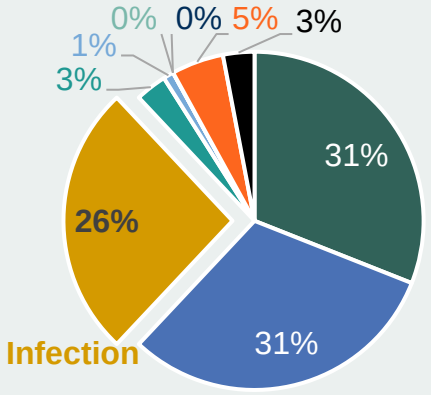
2018–2020

Autologous HSCT*

Total transplants: 29,748

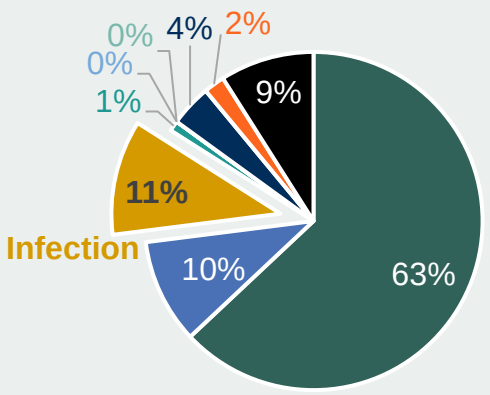
Died <100 days post-HSCT

n (%)♣: 508 (1.7)



Died ≥100 days post-HSCT‡

3,741 (12.6)

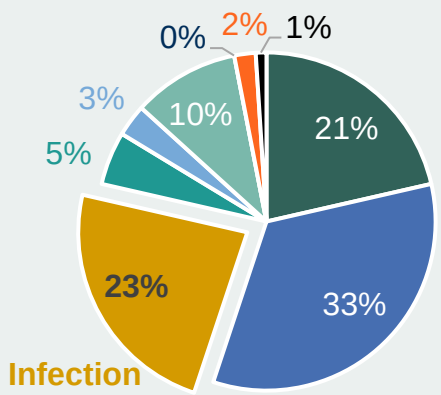


Allogeneic HSCT*♦

Total transplants: 19,042

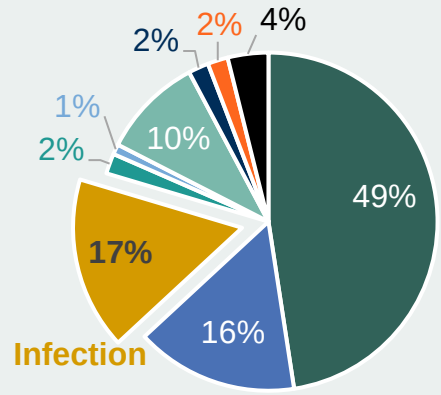
Died <100 days post-HSCT

n (%)♣: 1,502 (7.9)



Died ≥100 days post-HSCT‡

1,207 (28.4)

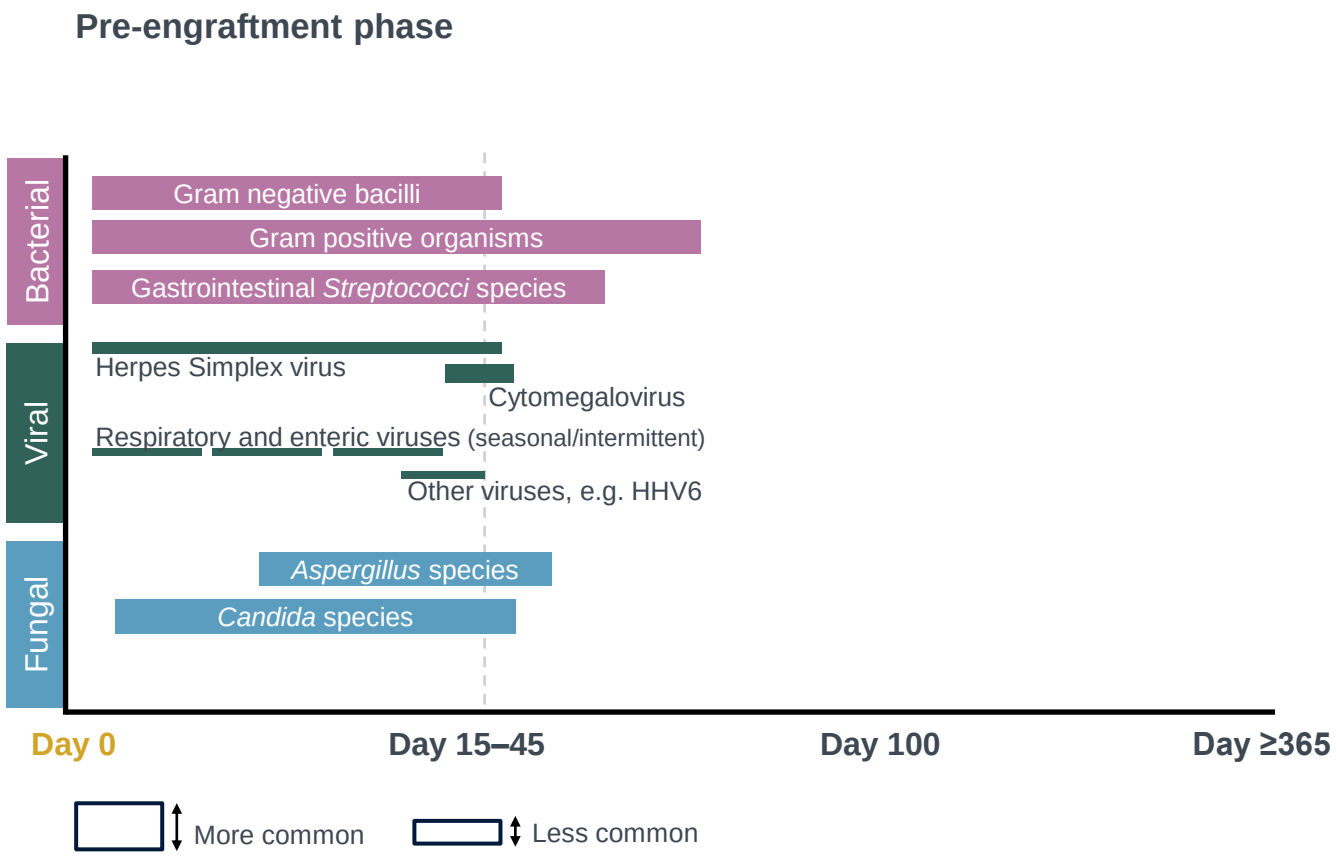


Primary disease | Organ failure | Infection | Haemorrhage | Graft rejection | GvHD | Malignancy after HSCT | Other | Not reported

* As data is shown to 0 decimal place total percent may not equal 100%; ♦ Includes ≥2 HLA antigen mismatch donors; ‡ 3-year mortality; of total transplants; ♣ % of total transplants in adults in the USA, 2018-2020. GvHD: graft-versus-host disease; HLA: human leukocyte antigen; HSCT: haematopoietic stem cell transplantation.

Adapted from Bolon, YT. et al., Current use and outcome of hematopoietic stem cell transplantation in the USA: CIBMTR summary slides, 2022, available at: https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports, last accessed 03 August 2023.

Infection and allogeneic HSCT[1,2]: Pre-engraftment

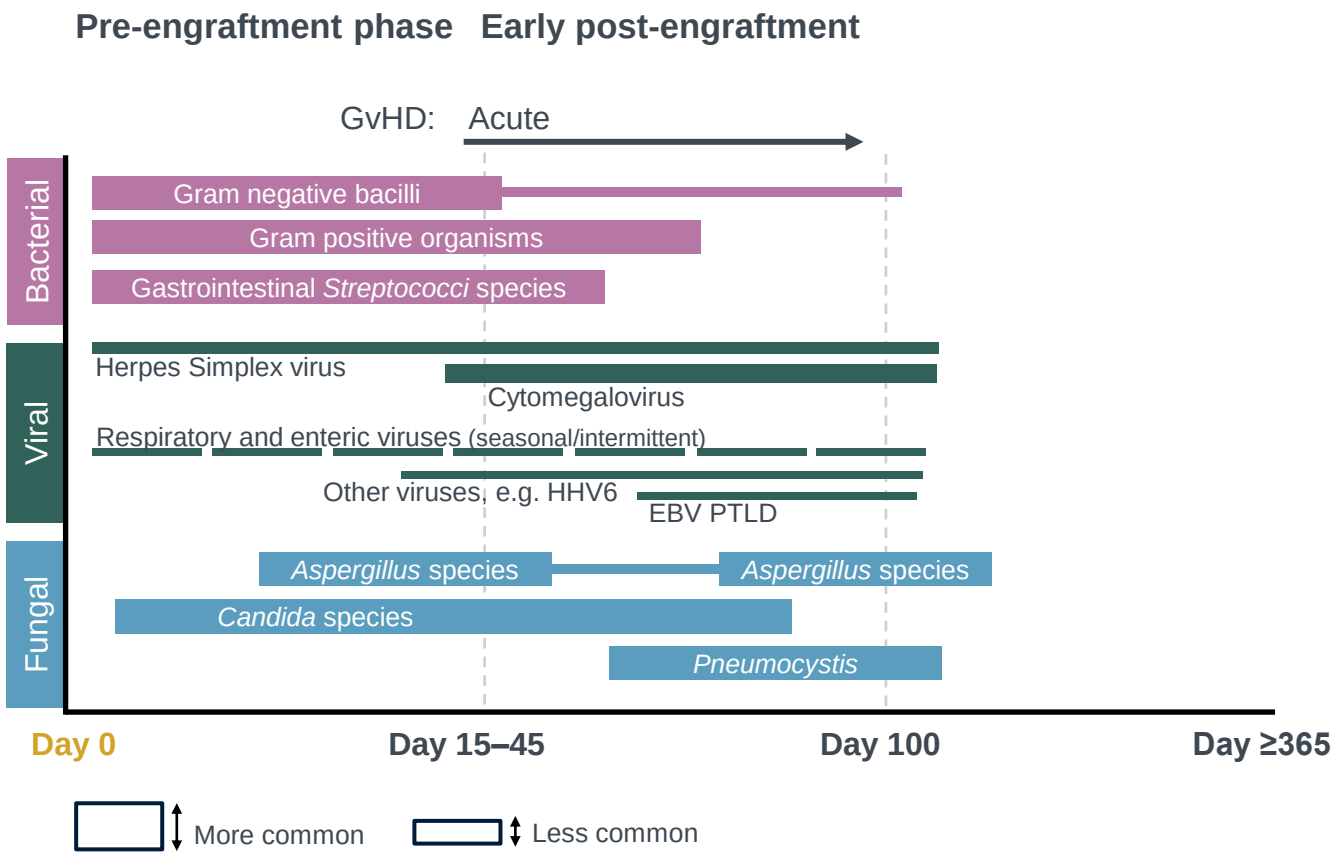


Bacterial infections, such as bloodstream infections, are more common during the pre-engraftment period than viral and fungal infections.

GvHD: graft-versus-host disease; HHV: human herpesviruses; HSCT: haematopoietic stem cell transplantation.

1. Adapted from Tomblyn, M. et al., Biol Blood Marrow Transplant. 2009; 15:1143-238, 2. Mehta, RS. and Rezvani, K., Virulence. 2016; 7:901-16.

Infection and allogeneic HSCT[1,2]: Early post-engraftment



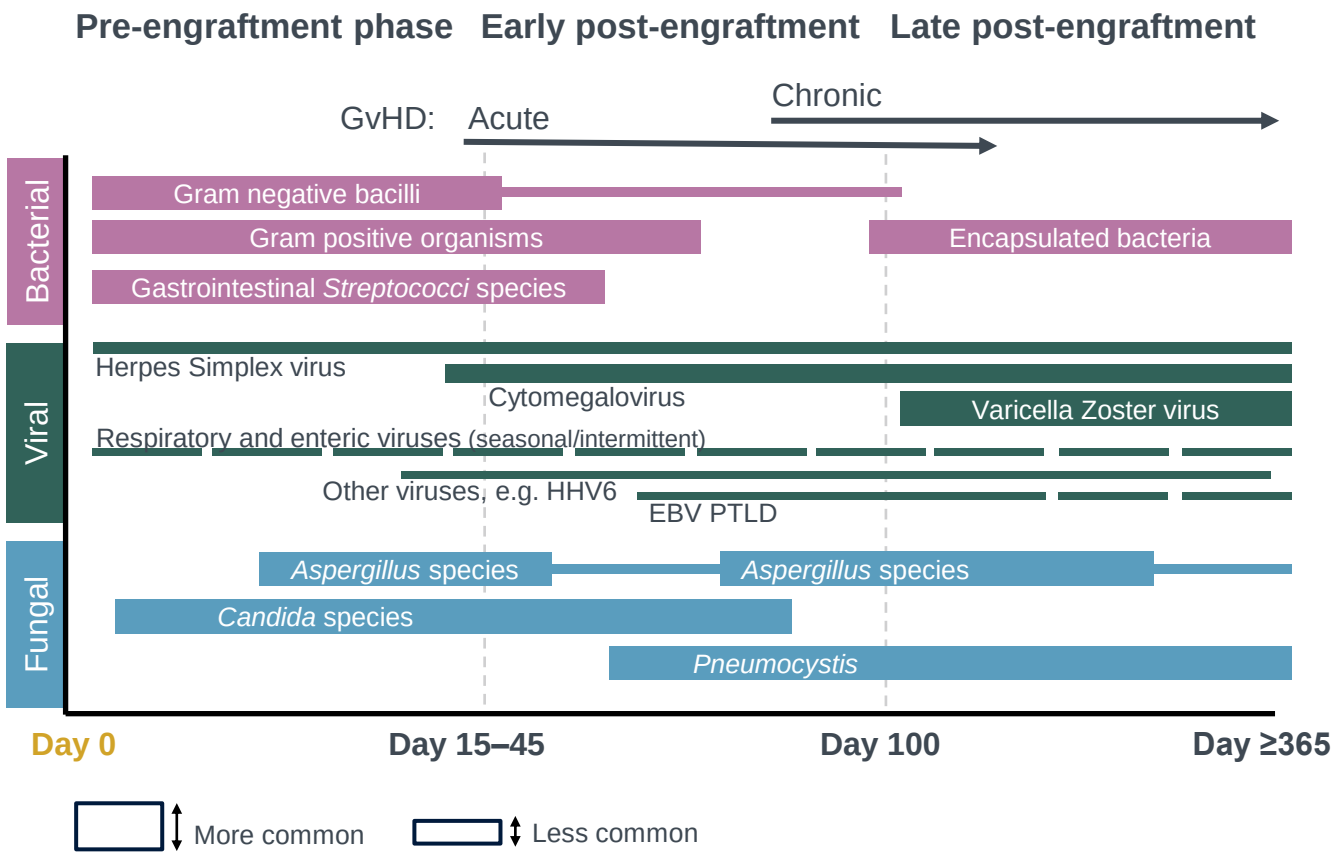
Patients remain at risk for:

- Viral infections, such as CMV, EBV, and adenovirus infections.
- Bacterial infections - although less common - can still occur, especially in patients with GvHD.
- Fungal infections can also occur during this period, especially in patients with GvHD and those receiving immunosuppressive therapy.

CMV: cytomegalovirus; EBV: Epstein-Barr virus; GvHD: graft-versus-host disease; HHV: human herpesviruses; HSCT: haematopoietic stem cell transplantation; PTLD: posttransplant lymphoproliferative disease.

1. Adapted from Tomblyn, M. et al., Biol Blood Marrow Transplant. 2009; 15:1143-238, 2. Mehta, RS. and Rezvani, K., Virulence. 2016; 7:901-16.

Infection and allogeneic HSCT[1,2]: Late post-engraftment



- Patients remain at risk for bacterial, fungal and viral infections, especially if they have chronic GvHD, are a recipient of alternative donor HSCT, or are still receiving immunosuppressive therapy.[1]
- *Pneumocystis jirovecii* pneumonia and encapsulated bacteria are a particular concern during this period, and prophylaxis is recommended for high-risk patients.[1-3]

EBV: Epstein-Barr virus; GvHD: graft-versus-host disease; HHV: human herpesvirus 6; HSCT: haematopoietic stem cell transplantation; PTLD: posttransplant lymphoproliferative disease.

1. Adapted from Tomblyn, M. et al., Biol Blood Marrow Transplant. 2009; 15:1143-238, 2. Mehta, RS. and Rezvani, K., Virulence. 2016; 7:901-16, 3. Maertens, JA. et al., J Antimicrob Chemother. 2016; 71:2397-404.

Strategies after HSCT to prevent infections

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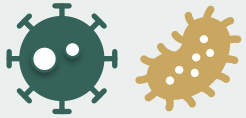
Antimicrobial prophylaxis[1-3]



Administering prophylactic antibiotics, antifungal and antiviral drugs can prevent infections during immunosuppression after HSCT.

Vaccination strategies[4]

Recipients of HSCT have an increased risk of infections compared with healthy individuals of the same age. Some of these infections are preventable by vaccination.

Immunoglobulin replacement therapy[5]

For patients with low immunoglobulin levels, immunoglobulin replacement can protect against certain infections.

HSCT: haematopoietic stem cell transplantation.

1. Mikulska, M. et al., J Infect. 2018; 76:20-37, 2. Maertens, JA. et al., J Antimicrob Chemother. 2018; 73:3221-30,
3. Ljungman, P. et al., Lancet Infect Dis. 2019; 19:e260-72, 4. Cordonnier, C. et al., Lancet Infect Dis. 2019; 19:e200-12,
5. Foster, JH. et al., Pediatr Blood Cancer. 2018; 65:e27348.

Guidelines for infection prophylaxis after HSCT

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Guidelines for infection prophylaxis after HSCT*

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European Conference on Infections in Leukaemia (ECIL) Guidelines

Prophylaxis	Population	Recommendations
Bacterial infections	Adult[1]	Antibacterial prophylaxis with fluoroquinolones for neutropenic patients with an expected length of neutropenia >7 days
	Paediatric[2]	No routine antibacterial prophylaxis
Fungal infections	Adult[3]	Fungal prophylaxis recommended and differs depending on treatment centre's incidence of mould infection
	Paediatric[4]	Strongly recommended in patients who are at high risk of developing invasive fungal diseases
Cytomegalovirus	Adult and paediatric[5]	Pre-emptive antiviral therapy based on detection of cytomegalovirus DNA (or antigen) in whole blood or plasma is effective for the prevention of cytomegalovirus disease
Pneumocystis jiroveci	Adult and paediatric[6]	Trimethoprim/sulfamethoxazole given up to 3 times a week, depending on the dose, is the drug of choice for primary prophylaxis
Vaccinations	Adult and paediatric[7]	Vaccination with inactivated vaccines from 3 months after transplant

* Table updated September 2023.

DNA: deoxyribonucleic acid; ECIL: European Conference on Infections in Leukaemia; HSCT: haematopoietic stem cell transplantation.

1. Bucaneve, G. et al., Eur J Cancer Suppl. 2007; Suppl 5:5-12, 2. Lehrnbecher, T. et al., Lancet Oncol. 2021; 22:e270-80, 3. Maertens, JA. et al., J Antimicrob Chemother. 2018; 73:3221-30, 4. Groll, AH. et al., Lancet Oncol. 2021; 22:e254-69, 5. Ljungman, P. et al., Lancet Infect Dis. 2019; 19:e260-72,
6. Maertens, JA. et al., J Antimicrob Chemother. 2016; 71:2397-404, 7. Cordonnier, C. et al., Lancet Infect Dis. 2019; 19:e200-12.

Immunoglobulin replacement therapy (IgRT) after HSCT

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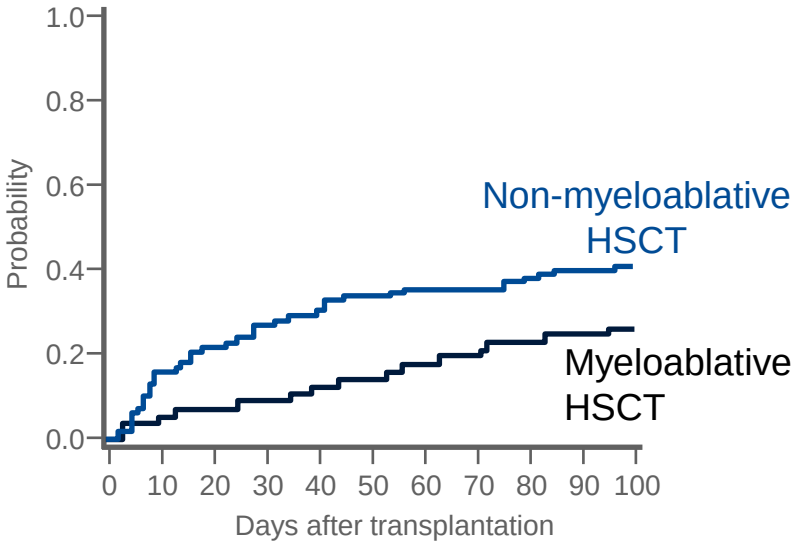
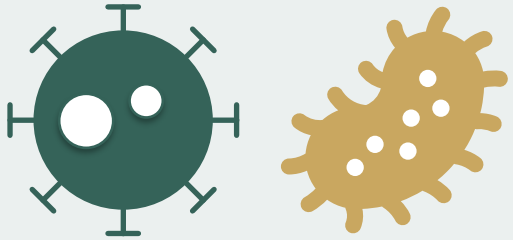
Despite use of antibiotic prophylaxis, the incidence of infection remains high

SECONDARY IMMUNE DEFICIENCY

Cumulative incidence of bacteraemia[1]



High incidence of bacteraemia in non-myeloablative and myeloablative HSCT with antibiotic prophylaxis during neutropenia, but without IgRT.



The increased risk of infection is thought to be due in part to low levels of immunoglobulins.[2]

IgRT

Prophylactic intravenous immunoglobulins are administered to patients after HSCT as **standard of care** to decrease infection risk.[2]

HSCT: haematopoietic stem cell transplantation; IgRT: immunoglobulin replacement therapy.

1. Junghanss, C. et al., Biol Blood Marrow Transplant. 2002; 8:512-20, 2. Foster, J. et al., Pediatr Blood Cancer. 2018; 65:e27348.

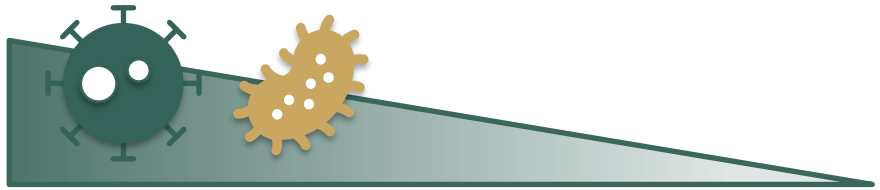
Scientific evidence for the use of IgRT after HSCT

SECONDARY IMMUNE DEFICIENCY

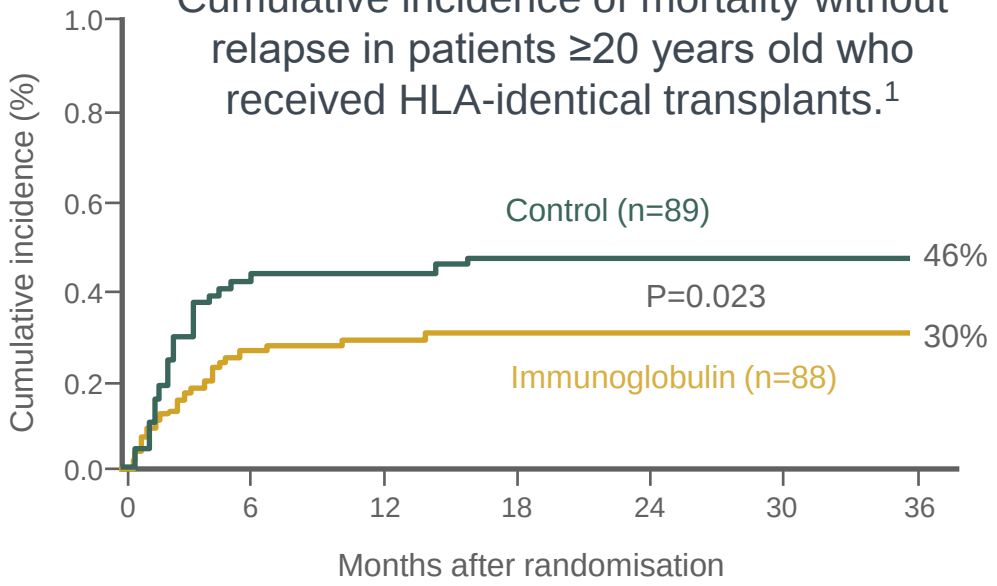
Studies have shown that prophylactic IgRT **can reduce** the incidence and **severity of infections** after HSCT.[1-3]

In 16 studies with 4462 patients, IgRT:[4]

- Reduced incidence of serious and moderate infection.
- Provided longer infection-free periods.
- Reduced morbidity compared with control groups.
- Reduced infection-related hospitalisations.*
- Showed a tolerable safety profile.



Cumulative incidence of mortality without relapse in patients ≥20 years old who received HLA-identical transplants.[1]



As HSCT and treatments for HSCT-related complications have evolved substantially over the past 30 years,[5] more robust and newer clinical data on the use of IgRT in patients after HSCT are urgently required.[2,6]

* In one study.

GvHD: graft-versus-host disease; HLA: human leukocyte antigen; HSCT: haematopoietic stem cell transplantation; IgRT: Immunoglobulin replacement therapy.

1. Sullivan, KM. et al., N Engl J Med. 1990; 323:705–12, 2. Ahn, H. et al., Transfusion. 2018; 58:2437–52, 3. Foster, J. et al., Pediatr Blood Cancer. 2018; 65:e27348;
4. Shah, N. et al., Crit Rev Oncol Hematol. 2023; 181:103896, 5. Granot N and Storb R., Haematologica 2020; 105:2716-2729;
6. Ohmoto A. et al., Bone Marrow Transplant 2022; 57:874-880.

Recommendations for IgRT in HSCT recipients

Publication year: Society/Group	Patients who should receive IgRT
2009: American Society for Blood and Marrow Transplantation (**ASBMT**)[1]	High-risk recipients who undergo unrelated HSCT with IgG <400 mg/dL
2017: Japan Society for Hematopoietic Cell Transplantation (**JSHCT**)[2]	Allogenic-HSCT recipients with pre-transplant IgG <400 mg/dL or with delayed immunoglobulin recovery
2018: American Society for Blood and Marrow Transplantation (**ASMBT**) and Canadian Blood and Marrow Transplant (**CBMT**)[3]	CBT recipients, children who undergo transplantation for inherited or acquired disorders associated with B cell deficiency, and chronic GvHD patients with recurrent sinopulmonary infections
2019: European Society for Blood and Marrow Transplantation (**EBMT**)[4]	Patients who underwent HSCT with IgG <400 mg/dL
2021: European expert consensus[5]	All allogenic-HSCT recipients (particularly patients with low IgG level (<400 mg/dL) or with GvHD on immunosuppressive treatment)
2021: U.S. National Comprehensive Cancer Network (**NCCN**)[6]	Allogenic-recipients who had recurrent infection with a serum IgG <400 mg/dL
2022: American Academy of Allergy Asthma & Immunology (**AAAAI**)[7]	Recipients with IgG <400 mg/dL who had bacteraemia or recurrent sinopulmonary infection

CBT: cord blood transplantation; GvHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation; IgG: immunoglobulin G; IgRT: immunoglobulin replacement therapy.

1. Tomblyn, M., et al. Biol Blood Marrow Transplant. 2009; 15:1143–238; 2. The Japan Society for Hematopoietic Cell Transplantation. Post-transplant infectious control guidelines (version 4.2017). https://www.jstct.or.jp/uploads/files/guideline/01_01_kansenkanri_ver04.pdf, last accessed 03 August 2023, 3. Bhella, S. et al., Biol Blood Marrow Transplant. 2018; 24:909–13, 4. Carreras, E. et al., The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. 7th ed. Cham: Springer; 2019. PMID:32091673, 5. Jolles, S. et al., Eur J Haematol. 2021; 106:439–49, 6. U.S. National Comprehensive Cancer Network, Guidelines for management of immunotherapy-related-toxicities - Version 2.2021, Guidelines Detail (nccn.org), last accessed 03 August 2023, 7. Otani, IM. et al., J Allergy Clin Immunol. 2022; 149:1525-60.

Harmonisation of clinical practice across Europe: European consensus statements on IgRT prophylaxis

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All patients undergoing allogeneic HSCT should be considered as candidates for IgRT.

Particularly in patients with low IgG levels (<400 mg/L) or with GvHD on immunosuppressive treatment.

When initiating IgRT*, the dose should be weight-based*.

In patients who are about to start IgRT, *both SCIg and IVIg should be discussed*.

Patients should be involved in the decision on the best route of administration.

In patients who require IgRT, *discontinuation should be considered after a clinically significant period without infections or if there is evidence of immunological recovery*.

For further information on the European expert consensus please see https://www.secondaryimmunodeficiency.com/expert-consensus/

GvHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation; IgG: immunoglobulin G; IgRT: immunoglobulin replacement therapy; IVIg: intravenous immunoglobulin; SCIg: subcutaneous immunoglobulin.

Jolles, S. et al., Eur J Haematol. 2021; 106:439–49.

European Medicines Agency: Recommendations for IgRT notably in SID

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Therapeutic indications for IVIg[1]

- Replacement therapy in adults, children, and adolescents (0–18 years) in:
  - PID with impaired antibody production.
  - SID in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure* or serum IgG level of <4 g/L.
- Measles pre-/post-exposure prophylaxis for susceptible adults, children and adolescents (0–18 years) in whom active immunisation is contraindicated or not advised.
- Immunomodulation in adults, children and adolescents (0–18 years) in:
  - Primary immune thrombocytopenia, in patients at high risk of bleeding or prior to surgery to correct the platelet count.
  - Guillain Barré syndrome.
  - Kawasaki disease (in conjunction with acetylsalicylic acid).
  - Chronic inflammatory demyelinating polyradiculoneuropathy.
  - Multifocal motor neuropathy.

Therapeutic indications for SCIg[2]

- Replacement therapy in adults, children, and adolescents (0–18 years) in:
  - PID with impaired antibody production.
  - Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed or are contraindicated.
  - Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma patients.
  - Hypogammaglobulinaemia in patients pre- and post- allogeneic HSCT.

* Failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.
HSCT: haematopoietic stem cell transplantation; IgG: immunoglobulin G; IgRT: Immunoglobulin replacement therapy; IVIg: intravenous immunoglobulin; PID: primary immunodeficiency syndromes; SCIg: subcutaneous immunoglobulin; SID: secondary immune deficiency.
1. Guideline on core SmPC for normal immunoglobulin for IVIg. Dec 2021, 2. Guideline on core SmPC for normal immunoglobulin for SCIg. Feb 2015.

Importance of monitoring HSCT patients

SECONDARY IMMUNE DEFICIENCY

Monitoring antibody levels is important to identify patients with SAD and in guiding the use of IgRT.[1,2]

Possible parameters to monitor humoral immune reconstitution:

- Serum immunoglobulin levels.[1]
- Specific antibody titres against common pathogens.[3]
- CD4 T cell number.[4]

HSCT: haematopoietic stem cell transplantation; IgRT: immunoglobulin replacement therapy; SAD: secondary antibody deficiency.

1. Jolles, S. et al., Eur J Haematol. 2021; 106:439–49, 2. Los-Arcos, I. et al., Infection. 2021; 49:215-1, 3. Meisel, R. et al., Blood. 2007; 109:2322-6, 4. Otani, IM. et al., J Allergy Clin Immunol. 2022; 149:1525-60.

Summary

SECONDARY IMMUNE DEFICIENCY

- HSCT is used to re-establish haematopoietic function in patients with a damaged or defective haematopoietic system.[1]
- **HSCT may result in prolonged secondary immunodeficiency.[2]**
- Immune reconstitution occurs faster after autologous HSCT compared to allogeneic HSCT.[3,4]
- **Immune reconstitution after allogeneic HSCT depends on a myriad of factors, e.g. donor source, age.[5,6]**
- Immune reconstitution is a critical process for preventing infections and disease relapse.[7,8]
- **Prophylactic IgRT can reduce the incidence and severity of infections after HSCT.[9-12]**
- HSCT patients with hypogammaglobulinaemia are candidates for IgRT.[13]
- The use of IgRT is generally considered beneficial, in patients with low IgG levels (<400 mg/L) or with GvHD on immunosuppressive treatment.[12]

GvHD: graft-versus-host disease; HSCT: haematopoietic stem cell transplantation; IgG: immunoglobulin G; IgRT: Immunoglobulin replacement therapy.

1. Saria, MG. and Gosselin-Acomb, T., Clin J Oncol Nurs. 2007; 11:53–63, 2. Barrow, M. et al., Front Immunol. 2022; 13:928062, 3. Wiegering, V. et al. J Pediatr Hematol Oncol. 2019 Jul;41(5):e302-e307, 4. Olkinuora, H. et al. Bone Marrow Transplantation. 2007;39(3):149-156, 5. Stern, L. et al., Front Immunol. 2018; 9:1672, 6. Gaytán-Morales, JF. et al., Bol Med Hosp Infant Mex. 2021; 78:191-9, 7. Mehta, RS. and Rezvani, K., Virulence. 2016; 7:901-16, 8. Elfeky, R. et al., Exp Rev Clin Immunol. 2019; 15:735-51, 9. Sullivan, KM. et al., N Engl J Med. 1990; 323:705–12, 10. Ahn, H. et al., Transfusion. 2018; 58:2437–52, 11. Foster, J. et al., Pediatr Blood Cancer. 2018; 65:e27348, 12. Shah, N. et al., Crit Rev Oncol Hematol. 2023; 181:103896, 13. Ohmoto A et al. Bone Marrow Transplant 2022; 57:874-880.