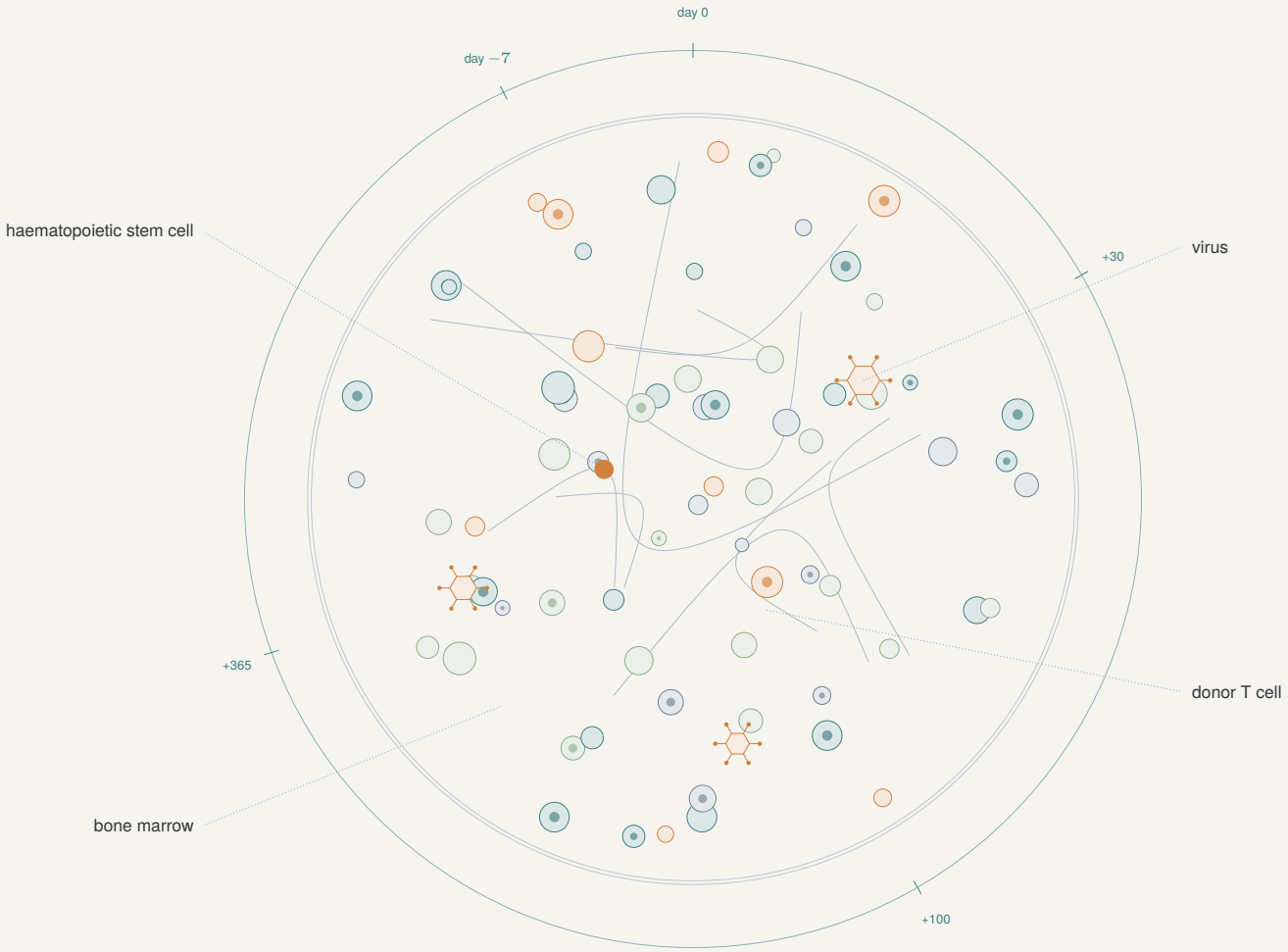
A CLINICAL COMPANION • OPEN ACCESS

Oncology and Stem Cell Transplantation for the Virologist

Haematology, cancer therapy, cellular therapy and the transplant journey — with a focus on viral infection



Saranga Sumathipala

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Oncology and Stem Cell Transplantation for the Virologist: A Clinical Companion

Saranga Sumathipala

First edition, October 2026

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Suggested citation. Sumathipala S. *Oncology and Stem Cell Transplantation for the Virologist: A Clinical Companion*. 1st ed. 2026. Open access, CC BY 4.0.

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About this book

This book is written for a medical virologist who works with infections in cancer patients and wants to understand the patients themselves: how their blood and immune systems work, what their cancers are, what their treatments do to them, and — in most detail — what happens to a patient having a haematopoietic stem cell (bone marrow) transplant. It is written as notes with a clinical slant. There are no questions or exercises.

How the book is organised

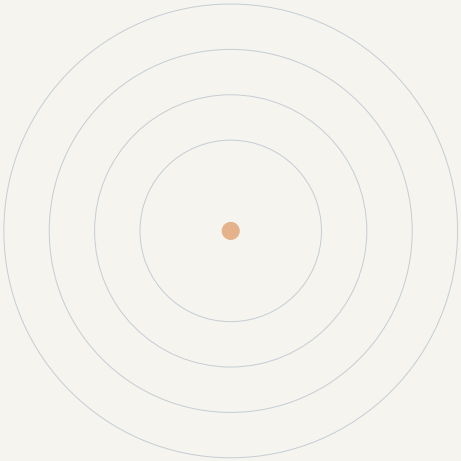
Part	Content
I. Foundations	Blood formation and the blood count; the immune system; how cancer develops; how cancer is diagnosed, classified and staged
II. Haematological malignancies	Acute leukaemias; myelodysplasia and myeloproliferative disorders; lymphomas and CLL; myeloma; non-malignant marrow diseases
III. Solid tumours	What a virologist needs to know about common solid cancers
IV. Treatment and its consequences	Chemotherapy; radiotherapy and surgery; targeted, antibody and immune therapies; CAR-T cells; supportive care; oncological emergencies
V. Immunosuppression and infection	The "net state of immunosuppression"; viral infections in non-transplant cancer patients
VI. Haematopoietic stem cell transplantation	Everything from patient selection and donor choice to conditioning, engraftment, GVHD, immune reconstitution, infections, other complications, relapse, late effects and the daily life of a transplant unit
Appendices	Abbreviations, laboratory values, drug glossary, grading systems, references

References. Numbers in square brackets, e.g. [1], refer to the reference list at the end. The single most useful companion is the open-access *EBMT Handbook* (2024) [1], which covers every aspect of transplantation in depth and is free to download.

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PART I

Foundations



Chapter 1 — Haematopoiesis, the bone marrow and the blood count

Every blood cell comes from a small population of haematopoietic stem cells (HSCs) in the bone marrow. Cancer treatment and stem cell transplantation are, at heart, interventions on this system: chemotherapy damages it, transplantation replaces it, and most infections in these patients follow from its failure.

1.1 Where blood is made

- In adults, blood is made in the marrow of the **axial skeleton**: pelvis, vertebrae, sternum, ribs, skull and proximal long bones. In children, marrow throughout the long bones is active.
- The marrow is a soft tissue between bony trabeculae. It contains haematopoietic cells, fat, and a **stromal niche** (endothelial cells, mesenchymal stromal cells, osteoblasts) that holds stem cells in place and controls their behaviour through signals such as CXCL12 (SDF-1) acting on the CXCR4 receptor on stem cells. This CXCL12–CXCR4 axis is the target of plerixafor, used to mobilise stem cells into the blood for collection (Chapter 22).
- **Cellularity** falls with age (roughly 100 minus age, in per cent). After chemotherapy or transplant conditioning the marrow becomes empty ("aplastic") and fatty; recovery is seen as regeneration of haematopoietic islands.

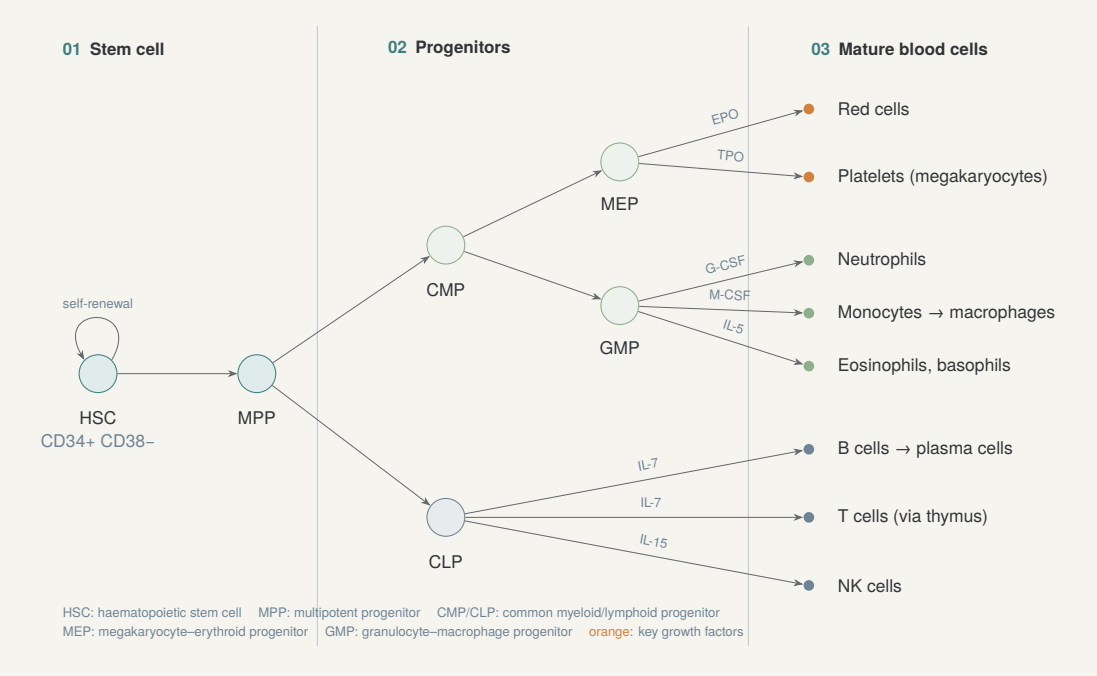


Figure 1: Haematopoiesis. A small pool of self-renewing stem cells gives rise to all blood lineages through progressively restricted progenitors; growth factors (orange) drive each lineage.

1.2 The haematopoietic hierarchy

- **Haematopoietic stem cells** are rare (about 1 in 10,000–100,000 marrow cells), mostly quiescent, able to **self-renew** and to produce all blood lineages. They carry the surface marker **CD34** (with CD90, lacking CD38) — CD34 counts are used to measure the dose of a stem cell graft.
- They give rise to **multipotent progenitors**, which split into:
  - the **common myeloid progenitor** → granulocytes (neutrophils, eosinophils, basophils), monocytes/macrophages, dendritic cells, red cells, megakaryocytes/platelets;
  - the **common lymphoid progenitor** → B cells, T cells (after migration to the thymus), NK cells, some dendritic cells.

- Production is controlled by **growth factors**: G-CSF (neutrophils), GM-CSF, erythropoietin (red cells), thrombopoietin (platelets and stem cells), IL-7 (lymphocytes), and others. Recombinant G-CSF (filgrastim, pegfilgrastim) is used to shorten neutropenia and to mobilise stem cells.

Why this matters for the virologist

- Most viral infections in cancer patients reflect failure of the **lymphoid** arm (T cells especially), which recovers much more slowly than the myeloid arm after treatment or transplant (Chapter 29).
- Some viruses target haematopoiesis directly: **parvovirus B19** infects erythroid progenitors (pure red cell aplasia in immunocompromised patients); **CMV**, **HHV-6** and **EBV** can suppress marrow function or cause haemophagocytosis.

1.3 Life span and kinetics

Cell	Normal blood count (adult, approx.)	Life span in blood	Implication
Neutrophils	2.0–7.5 $\times 10^9$/L	About 6–10 hours in blood (a few days in tissues)	Counts fall within days of marrow damage
Lymphocytes	1.5–4.0 $\times 10^9$/L	Weeks to decades (memory cells)	Long-lived memory cells survive some treatments; regeneration is slow
Monocytes	0.2–0.8 $\times 10^9$/L	1–3 days in blood, then tissue macrophages	First cells to recover after transplant
Platelets	150–400 $\times 10^9$/L	7–10 days	Thrombocytopenia follows marrow damage within a week or two
Red cells	Hb 130–170 g/L (men), 120–150 g/L (women)	About 120 days	Anaemia develops slowly; transfusion often needed during intensive therapy

Normal values vary by laboratory, age, sex and ethnicity — for example, **Duffy-null associated neutrophil count** (common in people of African and Middle Eastern ancestry) gives lower normal neutrophil counts without infection risk.

1.4 The full blood count in cancer care

- **Absolute neutrophil count (ANC).** The most important number for infection risk. Neutropenia: $< 1.5 \times 10^9$/L; **severe neutropenia** $< 0.5 \times 10^9$/L; **profound** $< 0.1 \times 10^9$/L. Risk of serious bacterial and fungal infection rises steeply with depth and duration — especially below 0.5 for more than 7–10 days [8].
- **Absolute lymphocyte count (ALC)** and **CD4 count.** Low counts after chemotherapy, steroids, purine analogues (fludarabine), alemtuzumab, ATG or transplant predict viral and *Pneumocystis* infection risk.
- **Platelets.** $< 10 \times 10^9$/L (or < 20 with fever or bleeding) usually triggers prophylactic transfusion; procedures such as lumbar puncture or bronchoscopy need higher counts.
- **Haemoglobin.** Transfusion thresholds are usually 70–80 g/L.
- **Blood film.** Shows blasts (leukaemia), dysplasia (myelodysplasia), left shift or toxic granulation (infection, G-CSF), fragmented red cells (thrombotic microangiopathy), atypical lymphocytes (viral infection, including EBV), and haemophagocytosis features.

1.5 How chemotherapy affects the count: the nadir

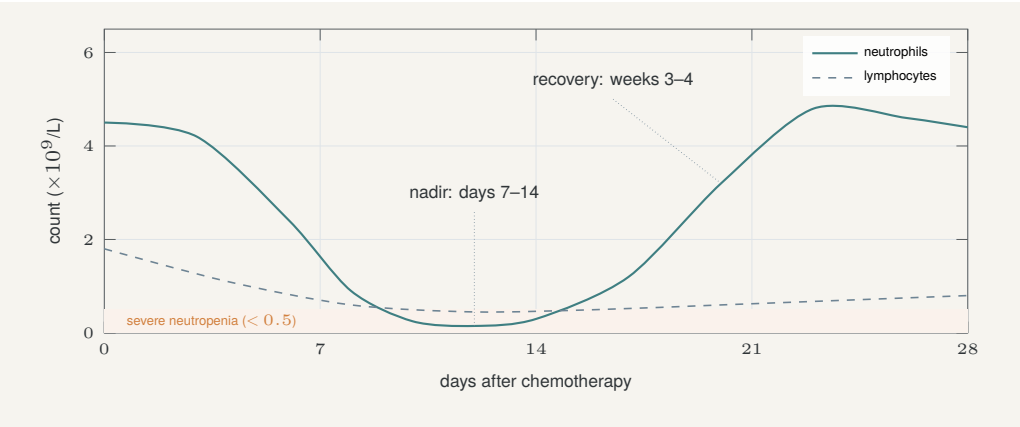


Figure 2: The neutrophil nadir after a typical cycle of chemotherapy. Lymphocytes recover far more slowly, which is why viral and *Pneumocystis* risk outlasts neutropenia.

- After a cycle of conventional chemotherapy, the neutrophil count usually reaches its lowest point (**nadir**) about 7–14 days after treatment and recovers by 3–4 weeks.
- Intensive leukaemia induction or transplant conditioning produces **profound neutropenia** for 2–4 weeks or longer.
- **Platelets** follow a similar course, slightly later; **lymphocytes** may stay low for months.
- G-CSF shortens neutropenia by a few days but does not prevent it.

1.6 The bone marrow examination

- **Aspirate:** liquid marrow smeared on slides — morphology (cell types, blasts, dysplasia), and samples for flow cytometry, cytogenetics and molecular tests.
- **Trephine biopsy:** a core of bone and marrow — cellularity, architecture, fibrosis, infiltration by lymphoma or carcinoma, granulomas.
- **Indications in oncology:** diagnosis of leukaemia, myelodysplasia, myeloma and lymphoma staging; response assessment; unexplained cytopenias after treatment; suspected marrow infection (e.g. mycobacteria, *Leishmania*, *Histoplasma*, parvovirus B19).

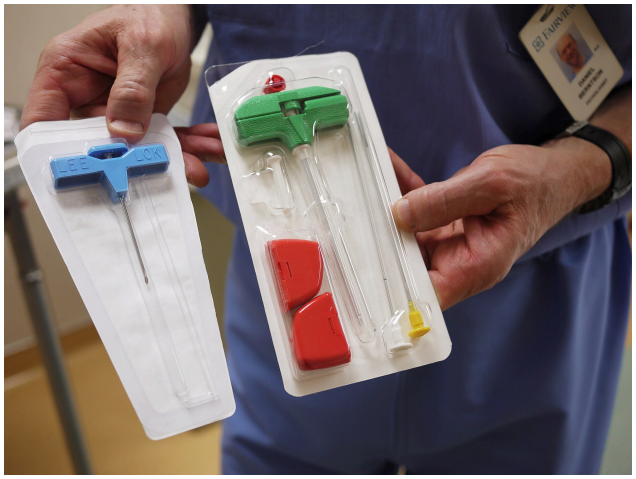


Figure 3: Bone marrow aspiration and trephine biopsy needles. Image: Thirteen Of Clubs from Minneapolis, CC BY-SA 2.0, via Wikimedia Commons.

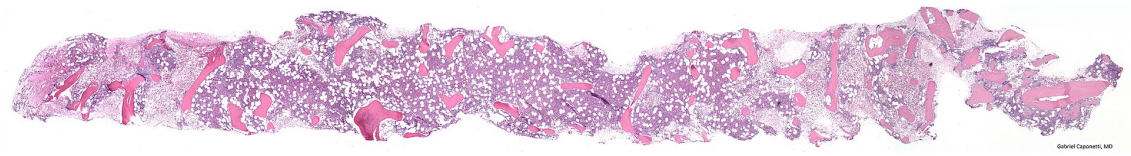


Figure 4: Bone marrow trephine biopsy (H&E): bony trabeculae with haematopoietic marrow between them. Image: Gabriel Caponetti, CC BY 3.0, via Wikimedia Commons.

Chapter 2 — The immune system as it matters in cancer patients

Infection risk depends on which part of the immune system is broken. This chapter summarises the components and what happens when each fails; Chapter 17 applies this to the patient in front of you.

2.1 Barriers

- **Skin** and **mucosae** (mouth, gut, airways, urinary tract) are the first defence. Chemotherapy and radiotherapy cause **mucositis** — ulceration of the mouth and gut lining — which lets oral and gut bacteria (viridans streptococci, Gram-negative rods, anaerobes, *Candida*) enter the blood.
- **Central venous catheters** breach the skin and cause line infections (coagulase-negative staphylococci, *S. aureus*, Gram-negative rods, *Candida*).
- **Surgery, tumour obstruction** (bile duct, ureter, bronchus) and **radiation fibrosis** create stagnant spaces that become infected.

2.2 Innate immunity

Component	Role	Failure in cancer care	Infections that follow
Neutrophils	Phagocytose and kill bacteria and fungi	Chemotherapy, marrow infiltration, conditioning	Bacteraemia (Gram-negative and Gram-positive), invasive candidiasis and aspergillosis
Monocytes/macrophages	Phagocytosis, antigen presentation, granuloma formation	Purine analogues, steroids, hairy cell leukaemia (monocytopenia)	Mycobacteria, *Listeria*, endemic fungi
NK cells	Kill virus-infected and tumour cells without prior sensitisation	Early after transplant they recover quickly and help control CMV	Herpesviruses
Complement	Opsonisation, lysis of encapsulated bacteria	Rarely affected by treatment; eculizumab-type drugs block it	*Neisseria*
Spleen	Filters blood; clears encapsulated bacteria	Splenectomy; functional hyposplenism after radiotherapy or chronic GVHD	Pneumococcus, *Haemophilus influenzae*, meningococcus, *Capnocytophaga*, babesiosis, malaria

2.3 Adaptive immunity

- **T cells** (CD4 helper and CD8 cytotoxic) recognise peptides presented by HLA molecules. They are essential for controlling **intracellular** pathogens: herpesviruses (CMV, EBV, VZV, HSV, HHV-6), adenovirus, polyomaviruses (BK, JC), respiratory viruses, *Pneumocystis*, mycobacteria, *Listeria*, *Toxoplasma*, *Cryptococcus*, endemic fungi.
- **B cells** make **antibodies**. Loss of B cells or antibody (rituximab, CD19/BCMA CAR-T, bispecific antibodies, CLL, myeloma) leads to infections with **encapsulated bacteria**, recurrent sinopulmonary infection, enteroviruses, norovirus persistence, poor vaccine responses and **hepatitis B reactivation**.
- **Memory.** Prior immunity to herpesviruses (seropositivity) is held by memory T cells. When those cells are destroyed (by ATG, alemtuzumab, transplant conditioning), latent viruses reactivate.

- **Thymus.** New naïve T cells are made in the thymus, which shrinks with age. In adults, T-cell recovery after transplant depends initially on expansion of mature T cells from the graft, and only later (and incompletely) on thymic output (Chapter 29).

2.4 Measuring immune function in practice

Test	What it shows	Typical use
Neutrophil count	Phagocyte number	Febrile neutropenia, prophylaxis decisions
Lymphocyte subsets (CD3, CD4, CD8, CD19, CD16/56)	T, B and NK numbers	Post-transplant and post-CAR-T monitoring; *Pneumocystis* and VZV prophylaxis decisions
Immunoglobulins (IgG, IgA, IgM)	Antibody levels	CLL, myeloma, after rituximab or CAR-T; immunoglobulin replacement decisions
Vaccine-specific antibodies	Functional antibody response	Revaccination after transplant
CMV-specific T-cell assays (e.g. interferon-gamma release)	Virus-specific cellular immunity	Predicting CMV control; deciding prophylaxis duration (in some centres)

Chapter 3 — How cancer develops

Cancer is a disease of genes: accumulated mutations and other changes in a cell's DNA free it from the controls that normally limit growth, survival and spread. Understanding the mechanisms explains both the targeted drugs used today and the link between viruses and cancer.

3.1 Oncogenes and tumour suppressor genes

- **Oncogenes** are normal genes (proto-oncogenes) that, when activated by mutation, amplification or translocation, push the cell to grow. Examples: *KRAS*, *BRAF*, *EGFR*, *HER2/ERBB2*, *MYC*, and the *BCR::ABL1* fusion of chronic myeloid leukaemia. One activated copy is enough (dominant).
- **Tumour suppressor genes** normally restrain growth or repair DNA. Both copies usually have to be lost (the "two-hit" hypothesis). Examples: *TP53*, *RB1*, *APC*, *BRCA1/2*, *PTEN*.
- **DNA repair defects** (mismatch repair deficiency, *BRCA*) raise the mutation rate and create many mutated proteins — which is why such tumours often respond to immune checkpoint inhibitors.
- **Epigenetic changes** (DNA methylation, histone modification) silence genes without changing their sequence; azacitidine and decitabine (hypomethylating agents) reverse some of these changes in myeloid cancers.

3.2 The hallmarks of cancer

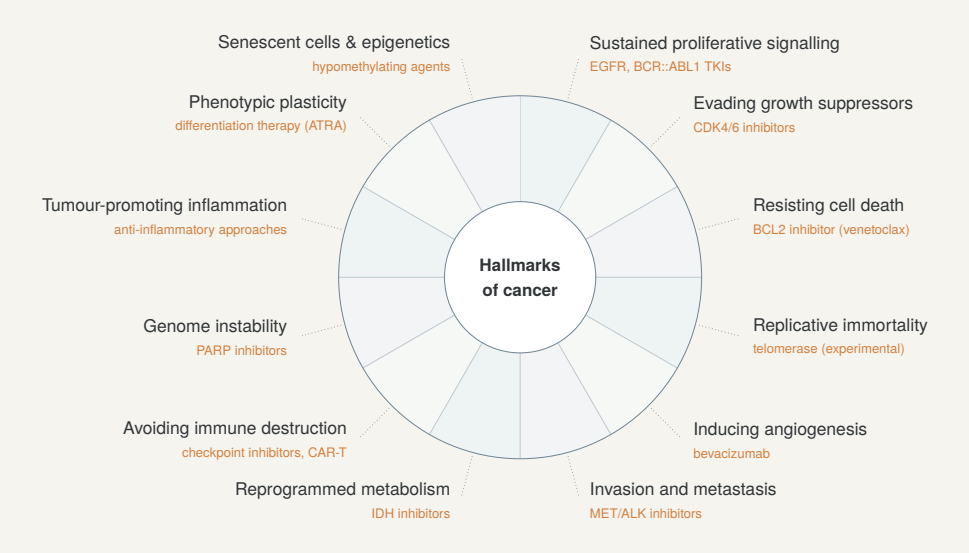


Figure 5: The hallmarks of cancer (after Hanahan 2022 [2]), each with an example of a drug class that targets it (orange).

Hanahan and Weinberg grouped the capabilities that cancer cells acquire into "hallmarks", updated in 2022 [2]. Each hallmark is now the target of drug classes — for example, angiogenesis (bevacizumab), avoiding immune destruction (checkpoint inhibitors), resisting cell death (venetoclax), and sustained proliferative signalling (tyrosine kinase inhibitors).

3.3 Clonal evolution

- A cancer starts as one clone and evolves into many **subclones** with different mutations. Treatment selects resistant subclones — the reason for combination therapy and for relapse.
- **Clonal haematopoiesis** (e.g. *DNMT3A*, *TET2* mutations in blood cells of older people) is a pre-malignant state; it can be transmitted with a donor graft and rarely leads to donor-derived leukaemia.

- **Minimal (measurable) residual disease (MRD)** — tiny numbers of cancer cells detectable only by flow cytometry or molecular methods after treatment — predicts relapse and increasingly guides decisions such as whether to transplant.

3.4 Viruses and cancer

Roughly 10–15% of human cancers worldwide are caused by infectious agents, mostly viruses [3]. For a virologist, this is the natural bridge into oncology.

Virus	Cancers	Mechanism in brief	Clinical relevance
EBV	Burkitt lymphoma, Hodgkin lymphoma (subset), nasopharyngeal carcinoma, post-transplant lymphoproliferative disorder (PTLD), some T/NK lymphomas, gastric carcinoma (subset)	Latent genes (EBNAs, LMP1, LMP2A) drive B-cell proliferation and survival	EBV DNA load monitors PTLD risk after transplant and nasopharyngeal carcinoma burden
HPV (high-risk types 16, 18 and others)	Cervical, anal, oropharyngeal, vulval, vaginal and penile cancers	E6 degrades p53; E7 inactivates Rb	Screening, vaccination; HPV-positive oropharyngeal cancer has a better prognosis
HBV, HCV	Hepatocellular carcinoma; HCV also B-cell lymphoma	Chronic inflammation, regeneration, integration (HBV)	Antiviral therapy reduces risk; HBV reactivation during chemotherapy
HHV-8 (KSHV)	Kaposi sarcoma, primary effusion lymphoma, multicentric Castleman disease	Viral cyclin, vFLIP, vIL-6	HIV and transplant-associated
HTLV-1	Adult T-cell leukaemia/lymphoma	Tax and HBZ proteins	Endemic regions; screening of donors
Merkel cell polyomavirus	Merkel cell carcinoma	Integrated virus expresses truncated large T antigen	Responds to checkpoint inhibitors
HIV (indirect)	Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer and others	Immunodeficiency allows oncogenic viruses to act	“AIDS-defining” cancers

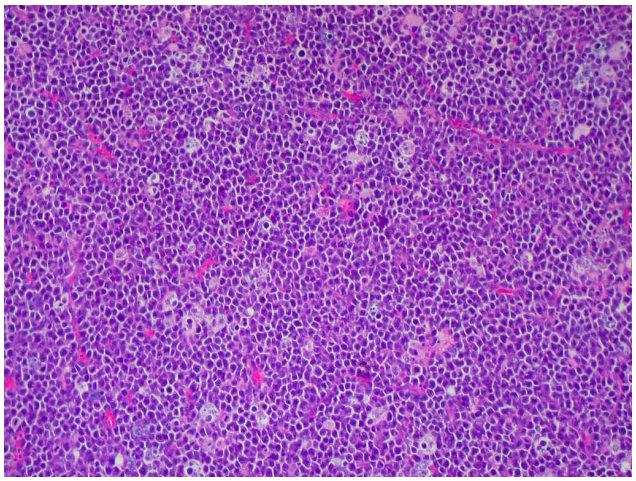


Figure 6: Burkitt lymphoma (H&E): sheets of tumour cells with interspersed macrophages (the “starry sky” pattern). Endemic Burkitt lymphoma is EBV-associated. Image: Ed Uthman from Houston, TX, USA, CC BY 2.0, via Wikimedia Commons.

Chapter 4 — The pathology of cancer

Pathologists diagnose cancer, define its type and extent, and provide the biomarkers that select treatment. Reading a pathology report is a core skill for anyone working with cancer patients.

4.1 From specimen to diagnosis

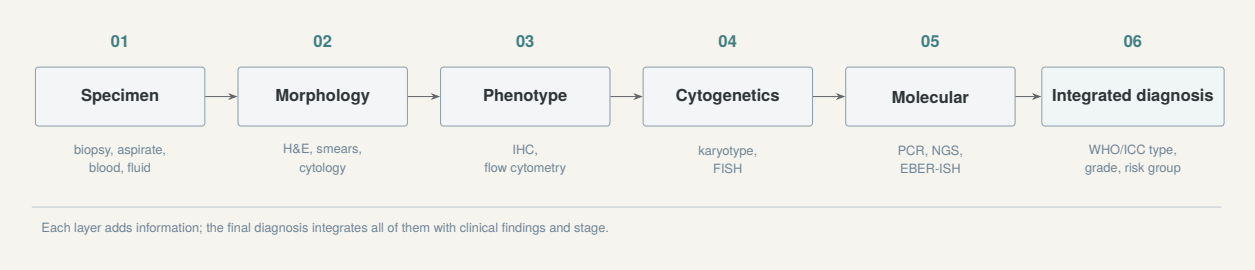


Figure 7: From specimen to diagnosis: the layered work-up of a suspected cancer.

Method	What it tells you	Examples
Morphology (H&E stain, blood/marrow smears)	Cell appearance, architecture, invasion	Carcinoma vs lymphoma; blast percentage
Immunohistochemistry (IHC)	Proteins in tissue sections	Lineage (CD20 for B cells, cytokeratins for carcinoma); prognostic and predictive markers (ER, HER2, PD-L1, Ki-67)
Flow cytometry	Surface and intracellular markers on single cells	Leukaemia and lymphoma immunophenotype; MRD; lymphocyte subsets
Cytogenetics (karyotype, FISH)	Chromosome number and structure	t(9;22) *BCR::ABL1*; t(15;17) in acute promyelocytic leukaemia; del(17p)
Molecular genetics (PCR, NGS)	Mutations, fusions, expression	*FLT3*, *NPM1*, *IDH1/2* in AML; *EGFR*, *ALK* in lung cancer; *BRAF* in melanoma
In situ hybridisation	Nucleic acid in tissue	EBER (EBV-encoded RNA) for EBV-positive lymphoma and PTLD; HPV
Cytology	Cells from fluids and fine-needle aspirates	Pleural effusion, lymph node aspirates

The **WHO Classification of Tumours** (5th edition) is the international standard; for haematological cancers it is published as separate myeloid [4] and lymphoid [5] classifications, alongside the closely related International Consensus Classification.

4.2 Grade and stage

- **Grade** describes how abnormal the cells look and how fast they divide (e.g. low vs high grade; Gleason score in prostate; Nottingham grade in breast).
- **Stage** describes how far the cancer has spread. Solid tumours use **TNM**: T (size/extent of primary tumour), N (regional lymph nodes), M (distant metastasis), combined into stages I–IV.
- **Lymphomas** use the Lugano (Ann Arbor-based) staging: stage I (one node region), II (two or more on one side of the diaphragm), III (both sides), IV (extranodal spread such as marrow or liver); “B symptoms” (fever, drenching sweats, weight loss).

- **Leukaemias** are not staged in the same way; risk is defined by genetics and response (e.g. European LeukemiaNet risk groups for AML [6]).
- **Myeloma** uses the Revised International Staging System (R-ISS), based on albumin, β2-microglobulin, LDH and high-risk cytogenetics.

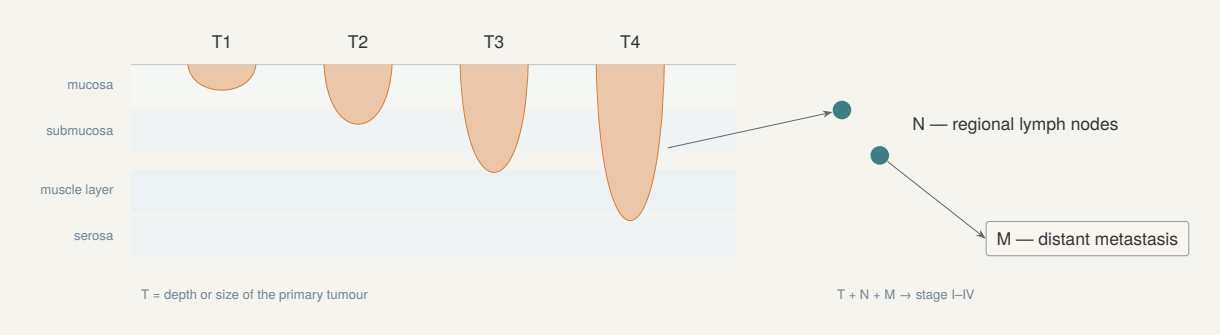


Figure 8: TNM staging of a solid tumour. Deeper invasion (T), nodal spread (N) and distant metastasis (M) combine into an overall stage.

4.3 Performance status and fitness

- **ECOG performance status:** 0 = fully active; 1 = restricted in strenuous activity; 2 = ambulatory and self-caring, up and about > 50% of the day; 3 = limited self-care, in bed or chair > 50%; 4 = completely disabled.
- **Karnofsky score** (100 to 0, in steps of 10) is used in transplant ($\geq$ 70–80% usually required).
- Fitness for intensive treatment combines performance status, age, organ function and comorbidities — formalised for transplant by the HCT-CI score (Chapter 20).

4.4 Reading a pathology report: what to look for

1. **Diagnosis** — tumour type and subtype (WHO terminology).
2. **Grade** and **stage** elements (size, depth, margins, lymph nodes).
3. **Biomarkers** — IHC, FISH, molecular results that predict response to targeted therapy or immunotherapy.
4. **Viral markers** where relevant — EBER, HPV/p16, HHV-8 (LANA), and viral cytopathic effect.
5. **Infection in the specimen** — granulomas, fungal hyphae, viral inclusions (e.g. CMV "owl's eye" inclusions; adenovirus "smudge" cells), which may be reported incidentally.

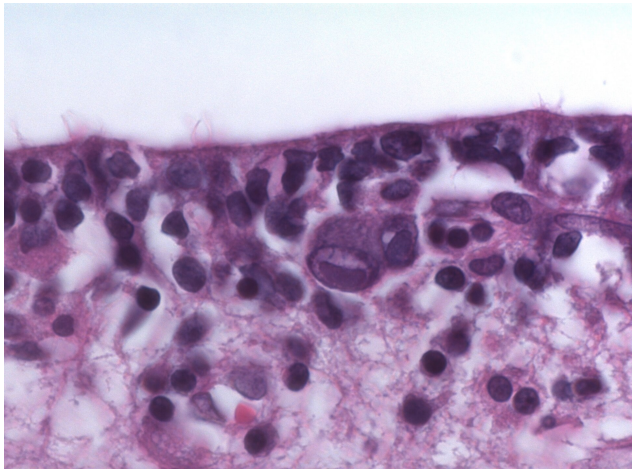
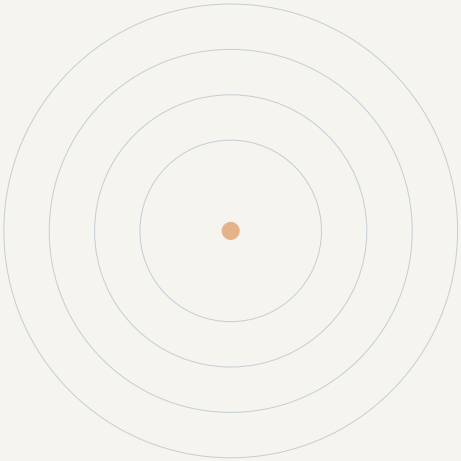


Figure 9: Cytomegalovirus inclusions ("owl's eye" intranuclear inclusions) in brain tissue, H&E. Image: Jensflorian, CC BY-SA 4.0, via Wikimedia Commons.

PART II

Haematological Malignancies



Chapter 5 — Acute leukaemias

Acute leukaemias are cancers of immature blood cells (blasts) that fill the marrow, stop normal blood production and spill into the blood. They are the commonest reason for allogeneic stem cell transplantation, and their treatment produces the deepest and longest neutropenia in oncology.

5.1 Acute myeloid leukaemia (AML)

- **Who:** median age at diagnosis about 68 years; incidence rises steeply with age. Risk factors: prior chemotherapy or radiotherapy ("therapy-related"), myelodysplasia, benzene, Down syndrome, inherited predisposition (e.g. *DDX41*, *RUNX1*).
- **Presentation:** symptoms of marrow failure — fatigue (anaemia), infection (neutropenia), bleeding or bruising (thrombocytopenia); sometimes gum infiltration, skin lesions (leukaemia cutis), very high white count with leukostasis.
- **Diagnosis:** $\geq$ 20% blasts in blood or marrow (or a defining genetic abnormality at lower blast counts), with flow cytometry, cytogenetics and molecular testing [4,6].
- **Risk groups (ELN 2022) [6]:**
  - *Favourable* — e.g. t(8;21), inv(16), *NPM1* mutation without *FLT3*-ITD, in-frame bZIP *CEBPA* mutation.
  - *Intermediate* — e.g. *NPM1* with *FLT3*-ITD, normal karyotype without favourable mutations.
  - *Adverse* — e.g. complex or monosomal karyotype, *TP53*, -7, *KMT2A* rearrangements, myelodysplasia-related gene mutations.

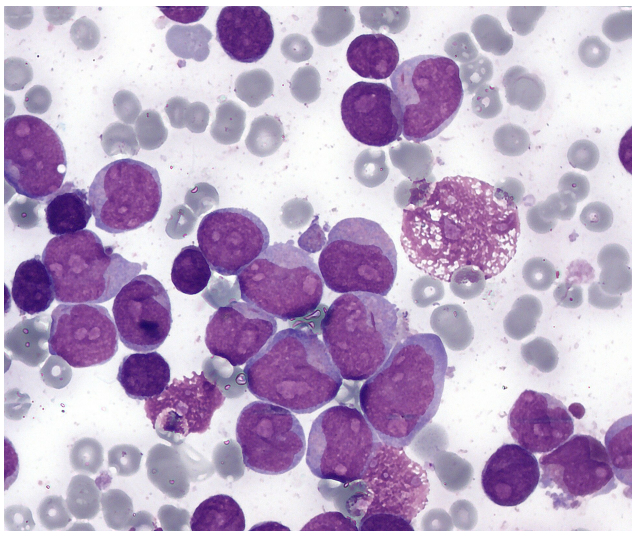


Figure 10: Myeloid leukaemia: a smear dominated by immature myeloid cells. Image: Makysm, CC0, via Wikimedia Commons.

Treatment in outline

Phase	Typical regimens	What it does to the patient
Induction (fit patients)	"7+3": cytarabine for 7 days + an anthracycline (daunorubicin or idarubicin) for 3 days; plus targeted drugs (midostaurin or quizartinib for *FLT3*; gemtuzumab ozogamicin for CD33-positive favourable/intermediate disease); CPX-351 for therapy- or MDS-related AML	3–4 weeks of profound neutropenia; mucositis; high risk of bacteraemia and invasive aspergillosis; antifungal prophylaxis (posaconazole) is standard

Phase	Typical regimens	What it does to the patient
Consolidation	High- or intermediate-dose cytarabine; or allogeneic transplant in first remission for intermediate/adverse risk	Repeated neutropenic periods
Less-intensive treatment (older or unfit)	Azacitidine or decitabine + venetoclax; low-dose cytarabine	Prolonged cytopenias; infections common in early cycles
Maintenance	Oral azacitidine; FLT3 inhibitors after transplant	
Relapsed disease	Salvage chemotherapy; targeted agents (gilteritinib for *FLT3*; ivosidenib/enasidenib/olutasidenib for *IDH1/2*; menin inhibitors for *KMT2A*/*NPM1*); transplant	

Outcome: cure in roughly 40% of younger adults; much lower in older patients and adverse-risk disease.

5.2 Acute promyelocytic leukaemia (APL)

- A distinct AML subtype with **t(15;17)** forming *PML::RARA*.
- Presents with **disseminated intravascular coagulation (DIC)** — early death from bleeding is the main danger; it is a medical emergency treated as soon as suspected.
- Treated with **all-trans retinoic acid (ATRA) + arsenic trioxide**, usually without conventional chemotherapy in standard-risk disease; cure rates above 90%.
- **Differentiation syndrome** (fever, breathlessness, pulmonary infiltrates, weight gain, renal impairment) can mimic infection; treated with dexamethasone.

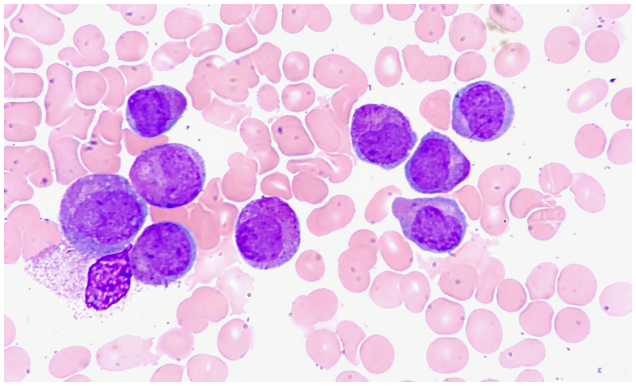


Figure 11: Acute promyelocytic leukaemia, marrow aspirate: abnormal, heavily granulated promyelocytes. Image: Ed Uthman from Houston, TX, USA, CC BY 2.0, via Wikimedia Commons.

5.3 Acute lymphoblastic leukaemia (ALL)

- Commonest childhood cancer (peak 2–5 years); a second peak in older adults.
- **B-ALL** (about 75–85%) and **T-ALL**. Genetic subtypes drive risk: hyperdiploidy and *ETV6::RUNX1* (favourable in children); **Philadelphia chromosome** t(9;22) *BCR::ABL1* (common in adults) and Ph-like ALL; *KMT2A* rearrangements in infants.
- **Treatment:** multi-agent protocols over 2–3 years — induction (steroids, vincristine, asparaginase, ± anthracycline), consolidation, CNS-directed therapy (intrathecal methotrexate), delayed intensification, and long maintenance (oral mercaptopurine and methotrexate). Tyrosine kinase inhibitors (imatinib, dasatinib, ponatinib) for Ph-positive ALL. Antibody-based

drugs: **blinatumomab** (CD19×CD3 bispecific T-cell engager) and **inotuzumab ozogamicin** (CD22 antibody–drug conjugate). **CD19 CAR-T** for relapsed or refractory disease (Chapter 14).

- **Infection relevance:** high-dose steroids and prolonged lymphopenia → *Pneumocystis* (cotrimoxazole prophylaxis), VZV, fungal infection; asparaginase toxicities (pancreatitis, thrombosis) mimic infection.
- **Outcome:** cure in about 90% of children; 40–60% in adults (higher with modern antibody and TKI regimens). MRD guides intensification and transplant decisions.

Chapter 6 — Myelodysplastic syndromes, myeloproliferative neoplasms and CML

6.1 Myelodysplastic syndromes (MDS)

- Clonal disorders of older adults with **ineffective haematopoiesis**: cytopenias, dysplastic cells, and a risk of progression to AML.
- Risk stratified by IPSS-R or the molecular IPSS-M (blasts, karyotype, cytopenias, mutations such as *TP53*, *SF3B1*).
- **Treatment:** supportive care (transfusion, iron chelation, erythropoiesis-stimulating agents, luspatercept); lenalidomide for del(5q); **hypomethylating agents** (azacitidine, decitabine) for higher-risk disease; **allogeneic transplant** is the only cure.
- **Infection relevance:** neutrophils may be present but dysfunctional; iron overload predisposes to some infections (e.g. mucormycosis, *Yersinia*).

6.2 Myeloproliferative neoplasms (MPN)

- **Polycythaemia vera** (*JAK2* V617F), **essential thrombocythaemia** and **primary myelofibrosis** (*JAK2*, *CALR*, *MPL*).
- **Myelofibrosis** causes marrow fibrosis, massive splenomegaly and cytopenias; treated with JAK inhibitors (ruxolitinib, fedratinib, pacritinib, momelotinib) and, in fit higher-risk patients, allogeneic transplant (with a high risk of graft failure because of fibrosis and splenomegaly).
- **Infection relevance of ruxolitinib:** reduced T-cell and NK function → **herpes zoster**, HBV reactivation, tuberculosis, *Pneumocystis*, and rarely PML.

6.3 Chronic myeloid leukaemia (CML)

- Caused by the **Philadelphia chromosome**, t(9;22), forming the *BCR::ABL1* fusion tyrosine kinase.
- Usually presents in **chronic phase** with high white cell count and splenomegaly; untreated, progresses to blast phase.
- **Tyrosine kinase inhibitors** (imatinib, dasatinib, nilotinib, bosutinib, ponatinib, asciminib) have transformed it into a chronic disease with near-normal life expectancy. Response is monitored by quantitative RT-PCR of *BCR::ABL1* transcripts on the International Scale — a molecular test familiar to virologists.
- Transplant is now reserved for TKI failure or blast phase.

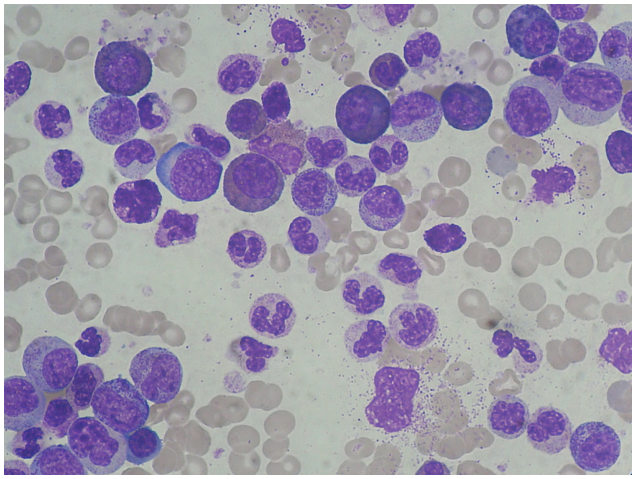


Figure 12: Chronic myeloid leukaemia, blood film: increased granulocytes at all stages of maturation. Image: Paulo Henrique Orlandi Mourao, CC BY-SA 3.0, via Wikimedia Commons.

Chapter 7 — Lymphomas and chronic lymphocytic leukaemia

Lymphomas are cancers of lymphocytes, mostly of B cells. They are classified by the WHO into many entities [5]; a few account for most cases.

7.1 Hodgkin lymphoma

- Young adults and older adults; characteristic **Reed–Sternberg cells** (CD30+, CD15+) in a background of reactive inflammatory cells. EBV is present in a subset (mixed cellularity type, HIV-associated cases).
- **Treatment:** ABVD or escalated BEACOPP-type chemotherapy, PET-guided, ± radiotherapy; brentuximab vedotin (anti-CD30 antibody–drug conjugate) and checkpoint inhibitors (nivolumab, pembrolizumab) in advanced or relapsed disease; **autologous transplant** for relapse.
- Cure in more than 80%.

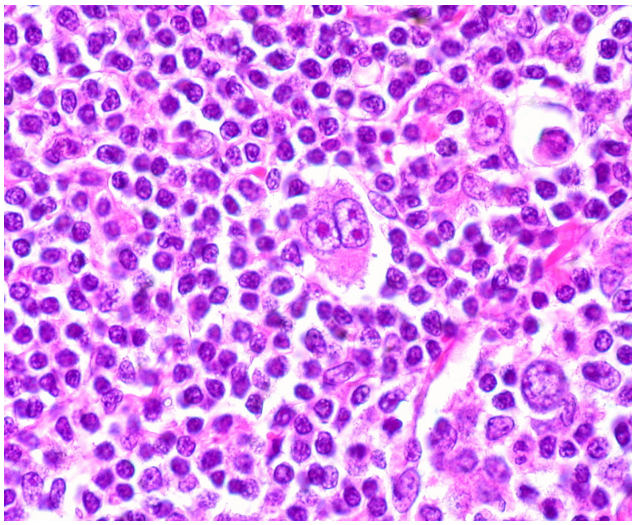


Figure 13: A Reed–Sternberg cell in Hodgkin lymphoma: a large binucleate cell with prominent nucleoli. Image: Ed Uthman, MD, CC BY-SA 2.0, via Wikimedia Commons.

7.2 Non-Hodgkin lymphomas (NHL)

Type	Behaviour	Standard treatment (outline)	Infection points
Diffuse large B-cell lymphoma (DLBCL)	Aggressive; commonest NHL	R-CHOP or Pola-R-CHP; CAR-T or bispecific antibodies for relapse; autologous transplant in selected relapse	**Rituximab → HBV reactivation** (screen HBsAg and anti-HBc); hypogammaglobulinaemia
Follicular lymphoma	Indolent; relapsing	Watch-and-wait; rituximab ± chemotherapy (bendamustine); maintenance rituximab; bispecifics, CAR-T	Bendamustine → prolonged CD4 lymphopenia (VZV, *Pneumocystis*, CMV)
Mantle cell lymphoma	Variable; often aggressive	Chemo-immunotherapy, BTK inhibitors, autologous transplant, CAR-T	BTK inhibitors → fungal infections, bleeding

Type	Behaviour	Standard treatment (outline)	Infection points
Burkitt lymphoma	Very aggressive; MYC translocation; EBV in endemic form	Intensive short-course chemotherapy with CNS prophylaxis	High risk of **tumour lysis syndrome**
Marginal zone lymphomas	Indolent; some linked to chronic infection (*H. pylori* gastric MALT; HCV splenic MZL)	Treat the infection (eradication therapy; HCV antivirals); rituximab	Antiviral therapy of HCV can induce lymphoma regression
T-cell lymphomas (e.g. peripheral T-cell, ALCL, ATLL)	Mostly aggressive	CHOP-based, brentuximab for CD30+; transplant	HTLV-1 in adult T-cell leukaemia/lymphoma; strongyloides screening
Primary CNS lymphoma	Aggressive	High-dose methotrexate-based regimens; autologous transplant	EBV-positive in immunocompromised patients
Post-transplant lymphoproliferative disorder (PTLD)	Spectrum from polyclonal to monoclonal	Reduce immunosuppression; rituximab; chemotherapy; EBV-specific T cells	See Chapter 32

7.3 Chronic lymphocytic leukaemia (CLL)

- Commonest adult leukaemia in Western countries; accumulation of mature-appearing CD5+ B cells in blood, marrow and nodes; “smudge cells” on the blood film.
- Staged by Binet or Rai; risk by *TP53* status, *IGHV* mutation status and complex karyotype [7].
- **Treatment:** time-limited **venetoclax + obinutuzumab** or venetoclax + ibrutinib, or continuous **BTK inhibitors** (ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib); chemo-immunotherapy now rarely used.
- **Infection relevance:** CLL itself causes **hypogammaglobulinaemia** and T-cell dysfunction even before treatment. Recurrent bacterial chest infections, poor vaccine responses (including COVID-19), herpes zoster, and severe or prolonged respiratory virus infections are common. **Richter transformation** (to DLBCL) can mimic infection with fever and rapidly growing nodes.

Chapter 8 — Plasma cell disorders

8.1 Multiple myeloma

- Malignant plasma cells in the marrow producing a monoclonal protein (paraprotein). Features: **CRAB** — hyperCalcaemia, Renal impairment, Anaemia, Bone lesions; plus myeloma-defining events ($\geq 60\%$ marrow plasma cells, free light chain ratio ≥ 100, > 1 focal MRI lesion).
- **Treatment** (fit patients): induction with a quadruplet such as daratumumab + bortezomib + lenalidomide + dexamethasone, followed by **high-dose melphalan with autologous stem cell transplant**, then lenalidomide maintenance. Relapse: other proteasome inhibitors (carfilzomib), pomalidomide, anti-CD38 antibodies (daratumumab, isatuximab), **BCMA- or GPRC5D-directed CAR-T cells and bispecific antibodies** (teclistamab, elranatamab, talquetamab).
- **Infection relevance:** functional hypogammaglobulinaemia (normal antibodies suppressed), steroids, proteasome inhibitors (**VZV reactivation — aciclovir prophylaxis standard with bortezomib/carfilzomib**), anti-CD38 drugs (reduced NK cells), and particularly **BCMA bispecifics**, which cause profound hypogammaglobulinaemia and high rates of viral and bacterial infection; immunoglobulin replacement is often used.

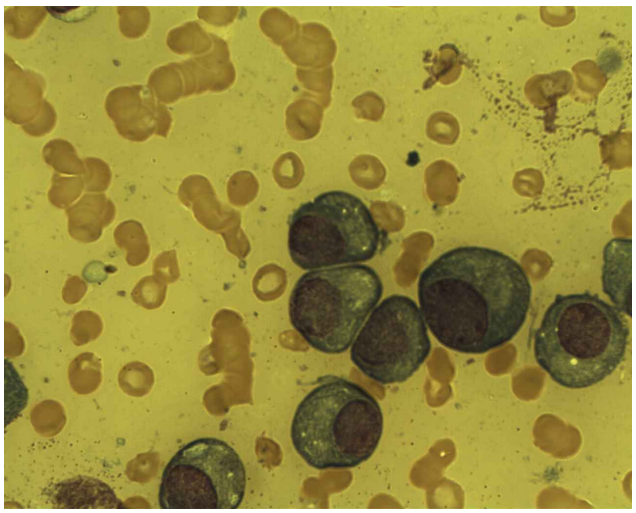


Figure 14: Plasma cells in the bone marrow of a patient with multiple myeloma. Image: Dr Osaro Erhabor, CC BY-SA 3.0, via Wikimedia Commons.

8.2 Related disorders

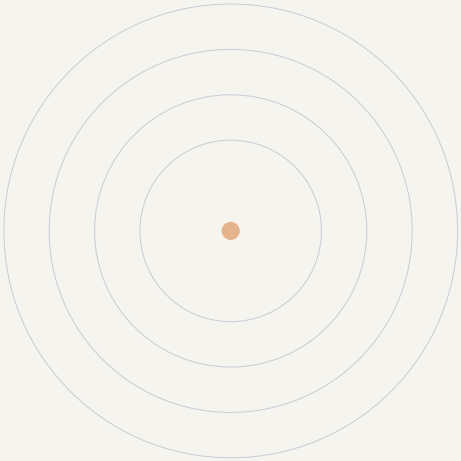
- **MGUS** (monoclonal gammopathy of undetermined significance) — precursor; monitored.
- **AL amyloidosis** — light chain deposits in heart, kidney, nerves; treated with myeloma-type therapy and sometimes autologous transplant.
- **Waldenström macroglobulinaemia** — IgM paraprotein, hyperviscosity; BTK inhibitors.

Chapter 9 — Non-malignant marrow and immune disorders treated by transplant

Disease	Problem	Role of transplant
Severe aplastic anaemia	Immune destruction of stem cells → pancytopenia	Matched sibling transplant first-line in younger patients; otherwise ATG + ciclosporin + eltrombopag
Paroxysmal nocturnal haemoglobinuria	Complement-mediated haemolysis	Complement inhibitors; transplant rarely
Sickle cell disease, thalassaemia major	Defective haemoglobin	Allogeneic transplant (curative); gene therapy (autologous, gene-modified stem cells)
Inborn errors of immunity (e.g. SCID, chronic granulomatous disease, Wiskott–Aldrich)	Defective immune cells	Transplant or gene therapy replaces the immune system
Haemophagocytic lymphohistiocytosis (familial)	Uncontrolled immune activation	Transplant after control of inflammation
Inherited marrow failure (Fanconi anaemia, dyskeratosis congenita)	DNA repair or telomere defects	Transplant with reduced-toxicity conditioning
Severe autoimmune disease (multiple sclerosis, systemic sclerosis)	Autoreactive immune system	Autologous transplant “resets” immunity in selected patients

PART III

Solid Tumours



Chapter 10 — Solid tumours: what the virologist needs to know

Solid tumour patients are seen by virologists mainly for viral reactivation during chemotherapy or immunotherapy, for vaccine questions, and for virus-associated cancers. Infection risks are generally lower than in haematological cancers, except during intensive chemotherapy, after major surgery, with obstruction, or with high-dose steroids.

10.1 Common cancers and their treatment

Cancer	Key facts	Main treatments	Infection-related points
Breast	Subtypes by ER/PR/HER2; often curable	Surgery, radiotherapy, chemotherapy (anthracyclines, taxanes), endocrine therapy, anti-HER2 drugs, CDK4/6 inhibitors	Neutropenia with dose-dense regimens; lymphoedema cellulitis
Lung	Non-small cell (adenocarcinoma, squamous) and small cell	Surgery, radiotherapy, chemotherapy, targeted drugs (EGFR, ALK), checkpoint inhibitors	Post-obstructive pneumonia; radiation pneumonitis mimics infection; immune-related pneumonitis
Colorectal	Many curable with surgery	Surgery, FOLFOX/FOLFIRI chemotherapy, anti-EGFR/VEGF antibodies	Anastomotic leaks, abscesses; fluoropyrimidine mucositis and diarrhoea
Prostate	Often indolent	Surveillance, surgery, radiotherapy, androgen deprivation	Low infection risk
Head and neck	HPV-positive oropharyngeal cancer increasing	Surgery, chemoradiotherapy, cetuximab, checkpoint inhibitors	Severe mucositis; aspiration pneumonia
Hepatocellular carcinoma	Mostly on cirrhosis from HBV, HCV, alcohol, metabolic disease	Resection, transplant, ablation, atezolizumab–bevacizumab	Manage underlying HBV/HCV
Cervical, anal	HPV-driven	Chemoradiotherapy, surgery	HPV vaccination and screening
Brain tumours (glioma)	Dexamethasone commonly used	Surgery, radiotherapy, temozolomide	Steroids + temozolomide → lymphopenia, *Pneumocystis*
Sarcomas, germ cell tumours, paediatric solid tumours	Intensive chemotherapy	Multi-agent chemotherapy; autologous transplant in some (neuroblastoma, germ cell relapse)	Neutropenia similar to leukaemia therapy
Melanoma, renal cancer	Highly immunogenic	Checkpoint inhibitors; targeted drugs (BRAF/MEK; VEGF TKIs)	Steroids for immune-related adverse events → opportunistic infections

10.2 Treatment intent

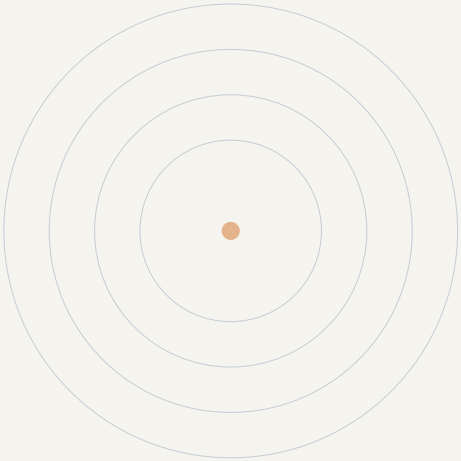
- **Curative** (radical) treatment aims for cure; toxicity is accepted.
- **Adjuvant** treatment follows surgery to remove micrometastases; **neoadjuvant** treatment precedes surgery to shrink the tumour.

- **Palliative** treatment aims to control disease and symptoms; quality of life dominates decisions.

Knowing the intent helps when discussing the risks of an antiviral or a delay in chemotherapy.

PART IV

Treatment and Its Consequences



Chapter 11 — Chemotherapy

Cytotoxic chemotherapy kills dividing cells. It cannot tell a cancer cell from a dividing normal cell, so it damages the tissues that renew fastest — marrow, gut lining, hair follicles, gonads — and these toxicities shape the infection risk of every patient who receives it.

11.1 How chemotherapy works

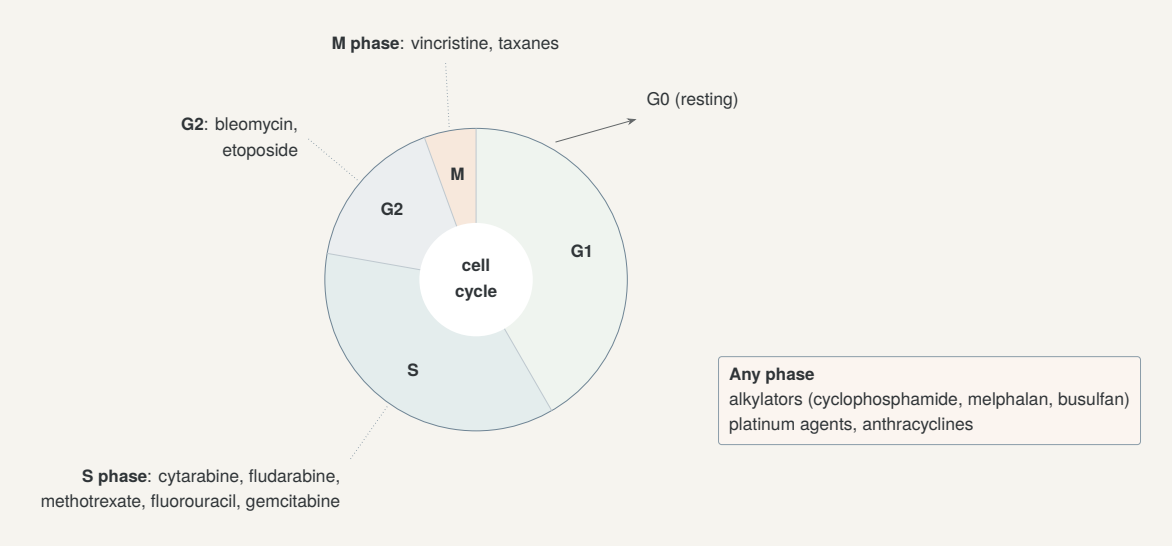


Figure 15: Where chemotherapy acts in the cell cycle. Phase-specific drugs hit dividing cells; alkylators, platinum agents and anthracyclines damage DNA in any phase.

- **Cell-cycle-specific** drugs act in one phase: antimetabolites in S phase (cytarabine, methotrexate, fluorouracil, gemcitabine, fludarabine); vinca alkaloids and taxanes in M phase.
- **Cell-cycle-non-specific** drugs damage DNA at any time: alkylating agents (cyclophosphamide, melphalan, busulfan, bendamustine, temozolomide), platinum agents (cisplatin, carboplatin, oxaliplatin), anthracyclines (doxorubicin, daunorubicin, idarubicin).
- Drugs are combined to attack different pathways and limit resistance (e.g. R-CHOP: rituximab, cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine [Oncovin], prednisolone).
- **Dose intensity** matters: delays or dose reductions because of infection can reduce cure rates — one reason virologists are asked whether chemotherapy can safely proceed.

11.2 Drug classes and their toxicities

Class	Examples	Main toxicities	Infection and virology points
Alkylating agents	Cyclophosphamide, ifosfamide, melphalan, busulfan, bendamustine, chlorambucil, temozolomide	Myelosuppression, mucositis (melphalan), haemorrhagic cystitis (cyclophosphamide, ifosfamide — prevented by mesna), infertility, secondary leukaemia, SOS/VOD (busulfan)	Bendamustine and temozolomide cause prolonged CD4 lymphopenia; early haemorrhagic cystitis must be distinguished from BK virus cystitis

Class	Examples	Main toxicities	Infection and virology points
Antimetabolites — purine analogues	Fludarabine, cladribine, pentostatin, clofarabine	Profound, prolonged T-cell lymphopenia; myelosuppression; neurotoxicity	*Pneumocystis*, VZV, CMV, *Listeria*, mycobacteria; irradiated blood products to prevent transfusion-associated GVHD
Antimetabolites — pyrimidine analogues	Cytarabine, fluorouracil, capecitabine, gemcitabine, azacitidine, decitabine	Myelosuppression; mucositis; diarrhoea (fluorouracil); cerebellar toxicity and conjunctivitis (high-dose cytarabine)	High-dose cytarabine → viridans streptococcal bacteraemia; DPYD deficiency → severe fluoropyrimidine toxicity
Antifolates	Methotrexate, pemetrexed	Mucositis, myelosuppression, renal and liver toxicity (high dose; folinic acid rescue, glucarpidase)	Methotrexate retention in effusions prolongs toxicity
Anthracyclines	Doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone	Myelosuppression, mucositis, cardiotoxicity (cumulative dose), extravasation injury	
Topoisomerase inhibitors	Etoposide, irinotecan, topotecan	Myelosuppression, diarrhoea (irinotecan)	
Microtubule agents	Vincristine, vinblastine, paclitaxel, docetaxel	Neuropathy, constipation/ileus (vincristine), myelosuppression (taxanes)	Azole antifungals increase vincristine neurotoxicity (drug interaction)
Platinum agents	Cisplatin, carboplatin, oxaliplatin	Nephrotoxicity, ototoxicity, neuropathy, nausea	Nephrotoxicity adds to that of antivirals (foscarnet, cidofovir)
Others	Asparaginase, bleomycin, hydroxycarbamide	Pancreatitis, thrombosis, liver toxicity (asparaginase); lung fibrosis (bleomycin)	
Corticosteroids	Dexamethasone, prednisolone, methylprednisolone	Hyperglycaemia, myopathy, mood change, adrenal suppression	Broad immunosuppression: *Pneumocystis* (risk rises at $\geq$ 20 mg prednisolone daily for $\geq$ 4 weeks), fungi, herpesviruses, HBV reactivation, strongyloides hyperinfection

11.3 Common toxicities in practice

- **Myelosuppression** (Chapter 1.5) — the dominant toxicity.
- **Mucositis** — painful ulceration of mouth and gut, peaking 7–14 days after treatment; causes bacteraemia, need for opioids and parenteral nutrition. **HSV reactivation** can worsen oral mucositis — aciclovir prophylaxis is standard in intensive regimens for HSV-seropositive patients.
- **Nausea and vomiting** — managed with 5-HT3 antagonists (ondansetron), NK1 antagonists (aprepitant), dexamethasone, olanzapine.
- **Neutropenic enterocolitis (typhlitis)** — necrotising inflammation of the caecum during neutropenia; abdominal pain, fever, diarrhoea; risk of perforation.
- **Organ toxicities** — cardiac (anthracyclines, trastuzumab), lung (bleomycin, busulfan), liver

(asparaginase, methotrexate), kidney (cisplatin, methotrexate, ifosfamide), nerves (vinca alkaloids, platinum, taxanes).

- **Late effects** — infertility, second cancers (therapy-related myeloid neoplasms), cardiomyopathy.

11.4 Chemotherapy and viral reactivation

Virus	Treatments that commonly cause reactivation	Prevention
HBV	Anti-CD20 antibodies (rituximab, obinutuzumab) — highest risk; high-dose steroids; anthracyclines; transplant; TKIs; checkpoint inhibitors; CAR-T	Screen all patients (HBsAg, anti-HBc ± anti-HBs). HBsAg-positive → antiviral prophylaxis (entecavir or tenofovir). HBsAg-negative, anti-HBc-positive on anti-CD20 or transplant → prophylaxis; on lower-risk therapy → HBV DNA monitoring or prophylaxis [16]
HCV	Rituximab; transplant	Treat HCV with direct-acting antivirals before or during chemotherapy where possible
HSV	Intensive chemotherapy, transplant	Aciclovir/valaciclovir prophylaxis for seropositive patients
VZV	Proteasome inhibitors, purine analogues, transplant, CAR-T, high-dose steroids	Aciclovir/valaciclovir prophylaxis; recombinant zoster vaccine when appropriate
CMV	Alemtuzumab, transplant, high-dose steroids; occasionally intensive chemotherapy	Monitoring in high-risk settings; letermovir after allogeneic transplant
Hepatitis E	Any profound immunosuppression	Chronic HEV in immunosuppressed — reduce immunosuppression; ribavirin

Chapter 12 — Radiotherapy and surgery

12.1 Radiotherapy

- Ionising radiation damages DNA; tumour cells repair less well than normal tissue. Doses are measured in **gray (Gy)** and given in **fractions** (e.g. 60 Gy in 30 fractions) to spare normal tissue.
- **Modern techniques:** intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT, few large fractions), proton therapy, brachytherapy (internal sources).
- **Total body irradiation (TBI)** is used in transplant conditioning (Chapter 23).
- **Acute effects** (within weeks): skin reactions, mucositis (head and neck), oesophagitis, diarrhoea, cystitis, marrow suppression when large marrow volumes are treated.
- **Late effects** (months to years): fibrosis, radiation pneumonitis (1–6 months after chest radiotherapy — mimics infection: cough, breathlessness, ground-glass changes confined to the radiation field), cardiac disease, second cancers, hypothyroidism, hyposplenism (spleen in the field).
- **Radiation recall:** inflammation in a previously irradiated area triggered by later drugs.

12.2 Surgery

- Curative resection, staging, debulking, palliation (bypass, stenting), and placement of venous access devices.
- **Infection relevance:** surgical site infection, anastomotic leaks, abscesses, prosthetic material, splenectomy (encapsulated bacteria), and catheter-related infections.

Chapter 13 — Targeted therapy, antibodies and immunotherapy

Modern cancer drugs target specific molecules on or in cancer cells, or harness the immune system. Many affect immune cells as well, and each class has its own infection signature — this chapter is especially relevant to virology consultations.

13.1 Small-molecule targeted drugs

Target / class	Examples	Used in	Infection and virology points
BCR::ABL1 TKIs	Imatinib, dasatinib, nilotinib, ponatinib, asciminib	CML, Ph+ ALL	Dasatinib: pleural effusions, lymphocytosis; occasional HBV reactivation and CMV colitis
BTK inhibitors	Ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib	CLL, mantle cell, Waldenström	**Invasive aspergillosis and cryptococcosis** (early in therapy), *Pneumocystis*, HBV reactivation; bleeding; atrial fibrillation
BCL2 inhibitor	Venetoclax	CLL, AML	Tumour lysis syndrome; neutropenia; **strong CYP3A interaction with azole antifungals** — dose reduction needed
JAK inhibitors	Ruxolitinib, fedratinib	Myelofibrosis, GVHD	Herpes zoster, HBV, TB, *Pneumocystis*, PML
PI3K-delta inhibitors	Idelalisib	Indolent lymphoma (now limited)	**CMV reactivation**, *Pneumocystis* — prophylaxis and CMV monitoring recommended
FLT3 / IDH / menin inhibitors	Midostaurin, gilteritinib, quizartinib; ivosidenib, enasidenib; revumenib	AML	Differentiation syndrome (IDH, menin inhibitors) mimics infection
EGFR, ALK, BRAF/MEK, VEGF TKIs	Osimertinib, alectinib, dabrafenib/trametinib, sunitinib	Lung, melanoma, renal	Pneumonitis; pyrexia syndrome with dabrafenib/trametinib mimics infection
CDK4/6 inhibitors	Palbociclib, ribociclib	Breast	Neutropenia without much infection risk
PARP inhibitors	Olaparib	Ovarian, breast, prostate	Myelosuppression; rare MDS/AML
Immunomodulators (IMiDs)	Lenalidomide, pomalidomide, thalidomide	Myeloma, MDS, lymphoma	Neutropenia; thrombosis
Proteasome inhibitors	Bortezomib, carfilzomib, ixazomib	Myeloma	**VZV reactivation — aciclovir prophylaxis**

13.2 Monoclonal antibodies

Target	Examples	Effect on immunity	Infection and virology points
CD20 (B cells)	Rituximab, obinutuzumab, ofatumumab	B-cell depletion for 6–12 months; hypogammaglobulinaemia with repeated courses	**HBV reactivation** (the classic example; can be fatal); **PML** (JC virus); prolonged or chronic SARS-CoV-2, norovirus and enterovirus infection; poor vaccine responses; late-onset neutropenia
CD52 (lymphocytes)	Alemtuzumab	Profound T, B and NK depletion for months	CMV, adenovirus, EBV, *Pneumocystis*, fungi — CMV monitoring needed
CD38 (plasma cells, NK cells)	Daratumumab, isatuximab	NK and plasma-cell depletion; interference with blood bank testing	VZV, HBV reactivation, respiratory infections
CD30	Brentuximab vedotin (antibody–drug conjugate)	Neuropathy	PML (rare)
CD33, CD22	Gemtuzumab ozogamicin, inotuzumab ozogamicin	Myelosuppression	**SOS/VOD** risk, especially before transplant
HER2, EGFR, VEGF	Trastuzumab, cetuximab, bevacizumab	Little immune effect	Bevacizumab: wound healing, bowel perforation
SLAMF7	Elotuzumab	NK activation	Infections, herpes zoster
C5 complement	Eculizumab, ravulizumab	Blocks terminal complement	**Meningococcal infection** — vaccination and prophylaxis

13.3 Bispecific T-cell engagers

- Antibodies with one arm binding CD3 on T cells and the other a tumour antigen (CD19, CD20, BCMA, GPRC5D, DLL3). They bring T cells to tumour cells and activate them.
- **Examples:** blinatumomab (CD19, ALL); glofitamab, epcoritamab, mosunetuzumab (CD20, lymphoma); teclistamab, elranatamab (BCMA, myeloma); talquetamab (GPRC5D, myeloma); tarlatamab (DLL3, small cell lung cancer).
- **Toxicities:** cytokine release syndrome (usually milder than with CAR-T), neurotoxicity, cytopenias.
- **Infections:** target-cell depletion (B cells, plasma cells) → **profound hypogammaglobulinaemia**; high rates of bacterial and **viral** infections (respiratory viruses, CMV reactivation, adenovirus, PML), and *Pneumocystis*. Many centres give immunoglobulin replacement, *Pneumocystis* and VZV prophylaxis, and monitor CMV in selected patients.

13.4 Immune checkpoint inhibitors

- Antibodies blocking inhibitory receptors on T cells: **PD-1** (nivolumab, pembrolizumab, cemiplimab, dostarlimab), **PD-L1** (atezolizumab, durvalumab, avelumab), **CTLA-4** (ipilimumab, tremelimumab), **LAG-3** (relatlimab).
- They release the brakes on anti-tumour T cells, producing durable responses in melanoma, lung, renal, bladder, head and neck, Hodgkin lymphoma, MMR-deficient tumours and others.
- **Immune-related adverse events (irAEs)** can affect any organ: colitis, hepatitis, pneumonitis, endocrinopathies (thyroiditis, hypophysitis, adrenalitis, type 1 diabetes), dermatitis, myocarditis, nephritis, arthritis, neurological syndromes [11].
- **Infection relevance:**
  - Checkpoint inhibitors do not themselves cause much immunosuppression, but **treatment**

of irAEs with high-dose steroids, infliximab, vedolizumab or mycophenolate does — opportunistic infections (*Pneumocystis*, aspergillosis, CMV colitis) follow.
- **Infection must be excluded** before attributing symptoms to an irAE: CMV colitis can mimic or complicate immune colitis; viral hepatitis mimics immune hepatitis; respiratory infection mimics pneumonitis.
- In patients with chronic HBV, HCV or HIV, checkpoint inhibitors are generally safe with appropriate antiviral therapy.
- In **allogeneic transplant recipients**, checkpoint inhibitors can trigger severe GVHD.

13.5 Other cellular and immune therapies

- **Donor lymphocyte infusion** (Chapter 36), **virus-specific T cells** (Chapter 33), **tumour-infiltrating lymphocytes** (melanoma), **TCR-engineered T cells**, and **oncolytic viruses** (e.g. talimogene laherparepvec, a modified HSV-1 for melanoma — a live virus with biosafety implications, and detectable by HSV PCR from injected lesions).

Chapter 14 — CAR-T cell therapy

Chimeric antigen receptor (CAR) T cells are the patient's own T cells, genetically engineered to recognise a tumour antigen and kill the cells that carry it [12]. CAR-T therapy shares much with transplantation — apheresis, lymphodepleting chemotherapy, cytopenias, prolonged immune deficiency — and is usually delivered by transplant teams.

14.1 The CAR and the products

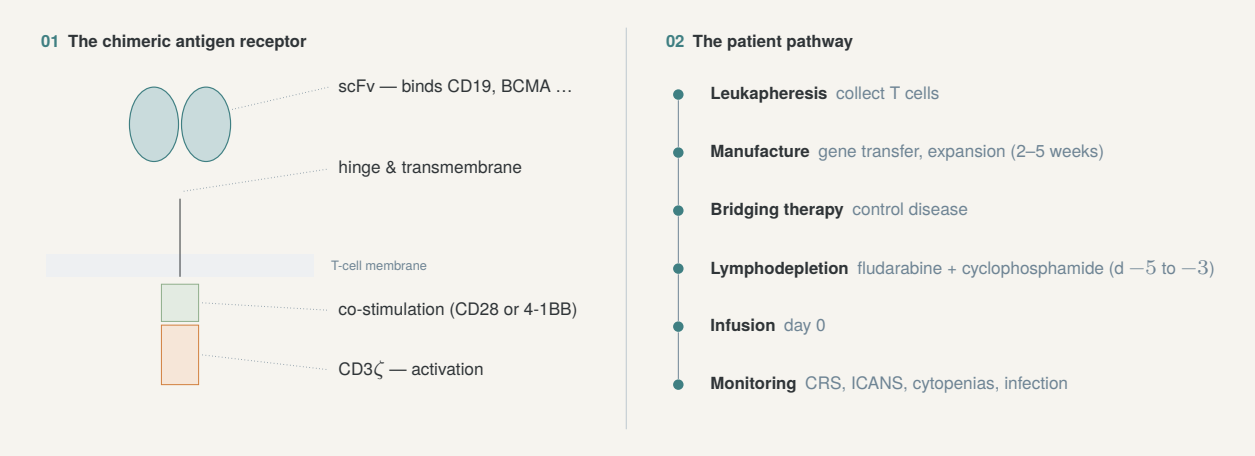


Figure 16: CAR-T cell therapy: structure of the receptor (left) and the steps from collection to infusion (right).

- A **CAR** joins an antibody-derived binding domain (single-chain variable fragment, scFv) to T-cell signalling domains: CD3ζ plus a **co-stimulatory domain** (CD28 or 4-1BB). The co-stimulatory domain affects expansion speed and persistence.
- The CAR gene is delivered by a **lentiviral or gammaretroviral vector** — so CAR-T products contain integrated vector sequences. This matters for some HIV nucleic acid tests, which can be falsely positive after CAR-T (cross-reactive lentiviral sequences); use an assay targeting a different region, or confirm with serology.

Target	Products (examples)	Diseases
CD19	Tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel, brexucabtagene autoleucel, obecabtagene autoleucel	B-ALL, DLBCL and other large B-cell lymphomas, follicular, mantle cell lymphoma
BCMA	Idecabtagene vicleucel, ciltacabtagene autoleucel	Myeloma
Emerging	CD22, GPRC5D, CD7; CAR-T for autoimmune disease (CD19) and solid tumours; allogeneic "off-the-shelf" products	

14.2 The patient pathway

1. **Referral and eligibility** — disease, fitness, organ function, infection screening (HIV, HBV, HCV serology and as for transplant).
2. **Leukapheresis** — the patient's T cells are collected.
3. **Manufacture** (about 2–5 weeks) — T-cell activation, gene transfer, expansion, quality testing (including replication-competent virus testing).
4. **Bridging therapy** — chemotherapy, radiotherapy or other drugs to control disease while waiting.
5. **Lymphodepleting chemotherapy** — usually **fludarabine + cyclophosphamide** on days −5 to −3; makes space and removes regulatory cells so CAR-T cells can expand.

6. **Infusion** (day 0).
7. **Close monitoring** — at least 7–14 days in or near hospital for cytokine release syndrome and neurotoxicity; patients must stay near the treatment centre for about 4 weeks.
8. **Long-term follow-up** — cytopenias, B-cell aplasia, infections, second cancers (including rare CAR-positive T-cell lymphomas) for 15 years under regulatory requirements.

14.3 Acute toxicities

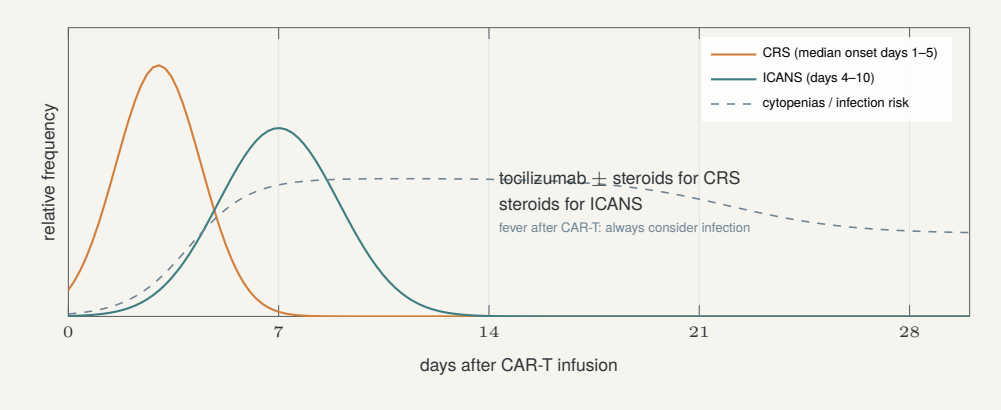


Figure 17: Typical timing of cytokine release syndrome, neurotoxicity and cytopenias after CAR-T infusion (schematic).

- **Cytokine release syndrome (CRS)** — fever, hypotension, hypoxia due to massive T-cell activation and cytokine release (IL-6, IFN-γ). Graded by ASTCT criteria [13]: grade 1 fever only; grade 2 hypotension not needing vasopressors and/or low-flow oxygen; grade 3 one vasopressor and/or high-flow oxygen; grade 4 multiple vasopressors and/or positive-pressure ventilation. Treated with **tocilizumab** (anti-IL-6 receptor) and steroids.
- **Immune effector cell-associated neurotoxicity syndrome (ICANS)** — confusion, word-finding difficulty, tremor, reduced consciousness, seizures, cerebral oedema; graded with the ICE score; treated with steroids (tocilizumab does not help ICANS).
- **Immune effector cell-associated HLH-like syndrome (IEC-HS)** — haemophagocytic picture with high ferritin.
- **CRS mimics sepsis.** Fever after CAR-T must be treated as possible infection — cultures and empirical antibiotics, particularly if neutropenic.

14.4 Cytopenias and immune deficiency after CAR-T

- **Immune effector cell-associated haematotoxicity (ICAHT)** — biphasic or prolonged cytopenias lasting weeks to months.
- **B-cell aplasia** (CD19 CAR-T) or **plasma-cell aplasia** (BCMA CAR-T) persists as long as CAR-T cells persist — a sign that the treatment is working — causing hypogammaglobulinaemia.
- **Infections** occur in about a third to a half of patients in the first year [14,15]: bacterial infections early (neutropenia), then respiratory viruses, herpesviruses (HSV, VZV; CMV reactivation especially after steroid use or BCMA products), HHV-6 (rare encephalitis), adenovirus, PML, *Pneumocystis* and invasive moulds (especially after steroids for toxicity).
- **Typical prevention:** aciclovir/valaciclovir (HSV/VZV) for at least a year; cotrimoxazole (*Pneumocystis*) from recovery of counts; antifungal prophylaxis in prolonged neutropenia or high-dose steroid use; immunoglobulin replacement for low IgG with infections (often routine after BCMA CAR-T); CMV monitoring in high-risk patients; revaccination from about 6–12 months.

Chapter 15 — Supportive care

Supportive care keeps patients alive through toxic treatment. Much of what happens on a haematology ward is supportive care.

15.1 Venous access

- **Peripherally inserted central catheters (PICC)**, **tunnelled central venous catheters** (Hickman lines — cuffed, tunnelled under the skin), and **implanted ports** (Portacath).
- Used for chemotherapy, blood products, antibiotics, parenteral nutrition and frequent blood sampling.
- **Complications:** line infections (exit site, tunnel, bloodstream), thrombosis, occlusion. Coagulase-negative staphylococci are the commonest organisms; *S. aureus*, *Pseudomonas*, *Candida* and non-tuberculous mycobacteria often require line removal.



Figure 18: A two-lumen tunnelled central venous catheter (Hickman line). Image: General Ludd, CC BY-SA 3.0, via Wikimedia Commons.

15.2 Blood transfusion

- **Red cells** for symptomatic anaemia (threshold Hb 70–80 g/L); **platelets** prophylactically below 10×10^9/L.
- **Irradiated** blood components prevent **transfusion-associated GVHD** (donor lymphocytes engrafting in a severely immunocompromised recipient). Indicated for transplant recipients, patients receiving purine analogues (fludarabine, cladribine, bendamustine), Hodgkin lymphoma, alemtuzumab/ATG, and CAR-T recipients around collection and infusion.
- **CMV-safe** components — leucodepleted (and in some countries CMV-seronegative) products reduce transfusion-transmitted CMV.
- **ABO-incompatible transplants** require careful choice of blood groups during the switch from recipient to donor blood group (Chapter 21).
- **Platelet refractoriness** — HLA antibodies may require HLA-matched platelets; fever, sepsis, splenomegaly and drugs also reduce increments.

15.3 Growth factors

- **G-CSF** (filgrastim, lenograstim, pegfilgrastim) reduces the duration of neutropenia and febrile neutropenia risk; used as primary prophylaxis when febrile neutropenia risk is $\geq 20\%$, after autologous transplant, and for stem cell mobilisation.

- **Erythropoiesis-stimulating agents** and **thrombopoietin receptor agonists** (eltrombopag, romiplostim) in selected settings.

15.4 Antimicrobial prophylaxis (overview)

Risk	Typical prophylaxis [9,35]
Expected profound neutropenia $>$ 7 days	Fluoroquinolone (in some centres) for bacterial prophylaxis
AML/MDS induction, allogeneic transplant with GVHD	Mould-active azole (posaconazole); otherwise fluconazole for yeasts
HSV-seropositive on intensive therapy	Aciclovir or valaciclovir
Lymphopenia, steroids, purine analogues, ALL, transplant	Cotrimoxazole for *Pneumocystis* (alternatives: pentamidine, atovaquone, dapsone)
HBV markers present	Entecavir or tenofovir, or HBV DNA monitoring
Hypogammaglobulinaemia with recurrent infections	Immunoglobulin replacement
Asplenia	Penicillin prophylaxis; vaccination

15.5 Nutrition, mouth care and symptom control

- Oral cryotherapy (ice chips) during melphalan reduces mucositis; palifermin in selected TBI regimens.
- Parenteral nutrition when mucositis or gut GVHD prevents eating — adds line infection risk.
- Pain control (opioids), antiemetics, management of diarrhoea (exclude *C. difficile*, norovirus, adenovirus, CMV, GVHD).
- **Neutropenic diet** restrictions are now relaxed in many centres; food hygiene remains important.

Chapter 16 — Oncological emergencies

16.1 Febrile neutropenia

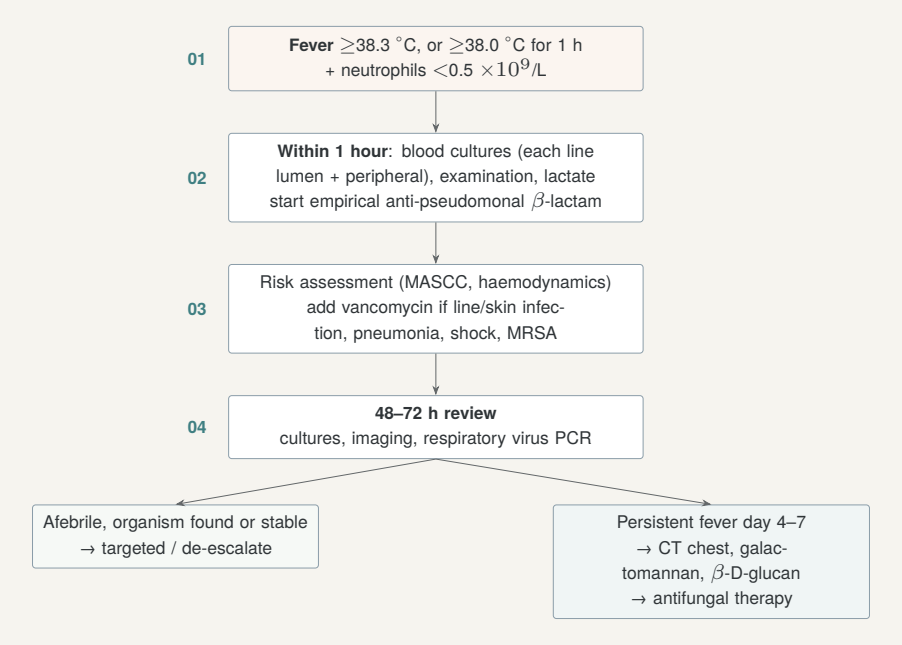


Figure 19: Febrile neutropenia: the first hours and days (after IDSA guidance [8]). Local protocols and resistance patterns determine the antibiotic choice.

- **Definition:** temperature $\geq 38.3\,^{\circ}\mathrm{C}$ once, or $\geq 38.0\,^{\circ}\mathrm{C}$ sustained over an hour, with neutrophils $< 0.5 \times 10^{9}/\mathrm{L}$ (or expected to fall below) [8].
- **A medical emergency:** give empirical broad-spectrum antibiotics (an anti-pseudomonal beta-lactam such as piperacillin–tazobactam or cefepime, or a carbapenem where resistance is likely) **within one hour**. Add vancomycin for line infection, skin/soft tissue infection, pneumonia, haemodynamic instability or known MRSA colonisation.
- **Investigations:** blood cultures (peripheral and each line lumen), urine, chest imaging, swabs of sites; respiratory virus PCR if respiratory symptoms; consider CMV and other viral testing in transplant recipients.
- **Risk stratification:** the MASCC score identifies low-risk patients suitable for oral or outpatient treatment.
- **Persistent fever** after 4–7 days of antibiotics → search for invasive fungal infection (CT chest, galactomannan, β-D-glucan) and consider empirical or pre-emptive antifungal therapy.
- **Fever is often not infection:** drugs (cytarabine, ATG, blood products), tumour fever, engraftment syndrome, CRS, GVHD, thrombosis. Only about a third of febrile neutropenia episodes have a documented infection.

16.2 Tumour lysis syndrome (TLS)

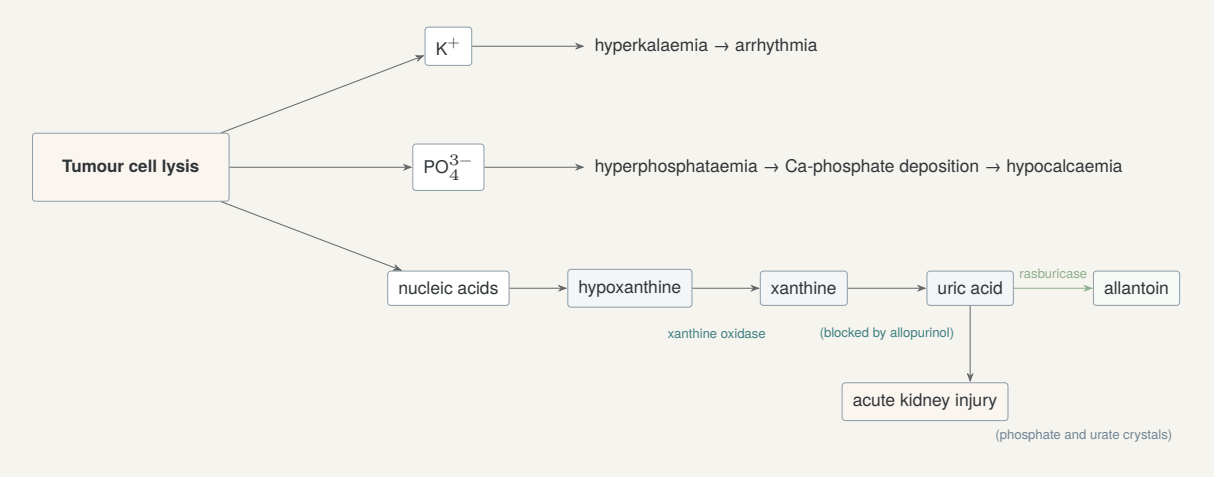


Figure 20: Tumour lysis syndrome. Released intracellular contents cause electrolyte disturbance and kidney injury; allopurinol and rasburicase act on the purine pathway [10].

- Rapid breakdown of tumour cells releases **potassium, phosphate and nucleic acids** (metabolised to **uric acid**). Results: hyperkalaemia (arrhythmia), hyperphosphataemia with secondary hypocalcaemia (tetany, seizures), hyperuricaemia, and **acute kidney injury** [10].
- **High-risk settings:** Burkitt lymphoma, ALL, AML with high white count, bulky lymphoma, venetoclax initiation in CLL.
- **Prevention:** intravenous hydration, allopurinol or **rasburicase** (contraindicated in G6PD deficiency), frequent electrolyte monitoring; dialysis if needed.

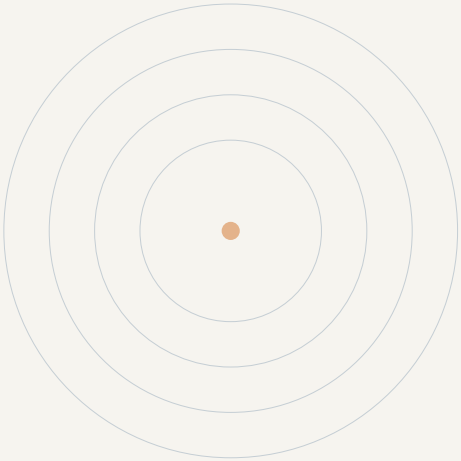
16.3 Other emergencies

Emergency	Cause	Key features	Management in brief
Hyperleukocytosis / leukostasis	Very high blast count (AML, ALL)	Hypoxia, confusion, visual disturbance	Urgent cytoreduction (hydroxycarbamide, chemotherapy), leukapheresis in selected cases; avoid red cell transfusion that raises viscosity
Disseminated intravascular coagulation	APL, sepsis	Bleeding, low fibrinogen and platelets	Treat cause (ATRA in APL); blood products
Hypercalcaemia of malignancy	PTHrP, bone metastases, myeloma	Confusion, dehydration, renal impairment	Fluids, bisphosphonate or denosumab
Spinal cord compression	Vertebral metastases, myeloma, lymphoma	Back pain, leg weakness, sphincter dysfunction	Urgent MRI, dexamethasone, radiotherapy or surgery
Superior vena cava obstruction	Mediastinal tumour, thrombosis around lines	Facial swelling, distended neck veins	Stenting, treatment of tumour
Hyperviscosity	Waldenström (IgM), myeloma	Bleeding, visual and neurological symptoms	Plasma exchange
Neutropenic sepsis	See above		

Emergency	Cause	Key features	Management in brief
Differentiation syndrome	ATRA/arsenic (APL), IDH and menin inhibitors	Fever, effusions, infiltrates, oedema	Dexamethasone; mimics infection
HLH (secondary)	Lymphoma, EBV, other infections, CAR-T	Fever, cytopenias, very high ferritin, splenomegaly	Treat trigger; steroids, etoposide, anakinra

PART V

Immunosuppression and Infection



Chapter 17 — The net state of immunosuppression

The infection risk of a cancer patient is not one thing. It is the sum of every defect present at that moment — barriers, neutrophils, T cells, antibodies, spleen — plus exposures and latent infections. Fishman's concept of the **"net state of immunosuppression"**, developed for organ transplantation [17], is the most useful way to think about any patient in this book.

17.1 Components of the net state

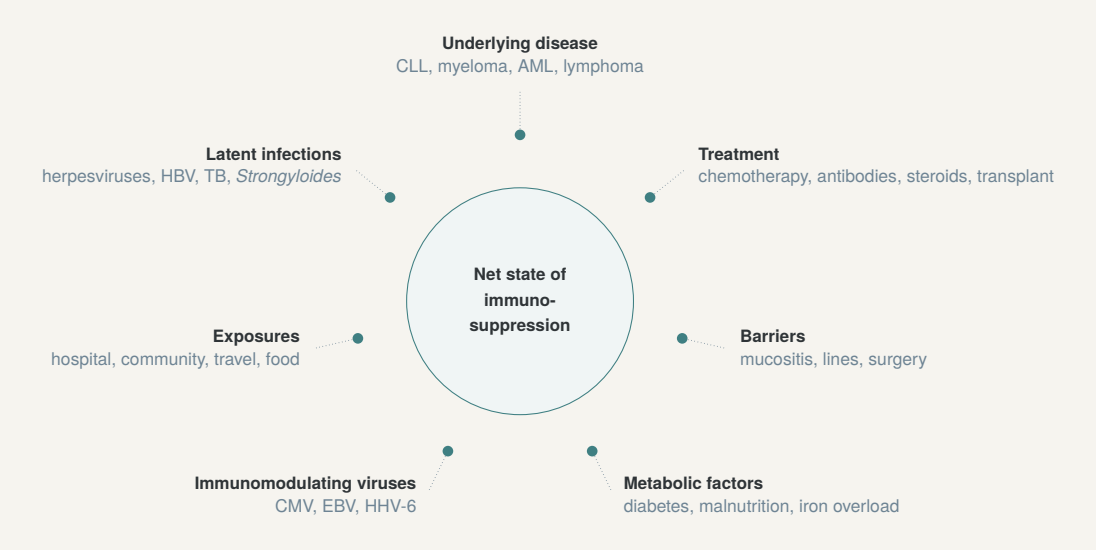


Figure 21: The net state of immunosuppression: infection risk is the sum of every factor present at a given time (after Fishman [17]).

1. **Underlying disease** — e.g. CLL (hypogammaglobulinaemia), myeloma, AML (neutropenia), Hodgkin lymphoma (T-cell dysfunction).
2. **Treatment** — dose, duration and sequence of chemotherapy, antibodies, steroids, radiotherapy, transplant.
3. **Barriers** — mucositis, lines, surgery, obstruction.
4. **Metabolic factors** — diabetes (steroids), malnutrition, uraemia, iron overload.
5. **Immunomodulating viruses** — CMV, EBV, HHV-6 and others themselves suppress immunity and predispose to bacterial and fungal infection.
6. **Exposures** — hospital water and air (*Legionella*, *Aspergillus*), community respiratory viruses, travel, food, pets, gardening.
7. **Latent infections** — herpesviruses, HBV, TB, *Strongyloides*, *Toxoplasma*, endemic fungi.

17.2 Matching defects to pathogens

Defect	Typical causes in oncology	Bacteria	Fungi	Viruses	Others
Neutropenia	Chemotherapy, conditioning, marrow infiltration	Enterobacterales, *Pseudomonas*, viridans streptococci, *S. aureus*, CoNS	*Candida*, *Aspergillus*, Mucorales, *Fusarium*	(HSV mucositis)	—
Barrier damage	Mucositis, lines, surgery	Gut flora, skin flora	*Candida*	HSV	—

Defect	Typical causes in oncology	Bacteria	Fungi	Viruses	Others
T-cell defects	Transplant, ATG, alemtuzumab, fludarabine, steroids, CAR-T	*Listeria*, *Nocardia*, *Legionella*, mycobacteria, *Salmonella*	*Pneumocystis*, *Cryptococcus*, endemic fungi, moulds	CMV, EBV, VZV, HSV, HHV-6, adenovirus, BK, JC, respiratory viruses	*Toxoplasma*, *Strongyloides*
B-cell / antibody defects	Rituximab, CAR-T, bispecifics, CLL, myeloma	Pneumococcus, *H. influenzae*, meningococcus	—	Enteroviruses, norovirus (chronic), SARS-CoV-2 (prolonged), HBV reactivation, JC (PML)	*Giardia*
Asplenia / hyposplenism	Splenectomy, splenic irradiation, chronic GVHD	Encapsulated bacteria, *Capnocytophaga*	—	—	*Babesia*, malaria

17.3 Risk tiers

Risk	Examples	Typical infection profile
Low	Standard-dose chemotherapy for solid tumours; endocrine therapy	Neutropenic bacterial infections only; viral infections as in the general population
Intermediate	Lymphoma chemo-immunotherapy, autologous transplant, myeloma therapy, CLL	Bacterial; HSV/VZV; HBV reactivation; respiratory viruses with more complications
High	AML/ALL induction, allogeneic transplant, CAR-T, alemtuzumab, prolonged high-dose steroids	Bacterial, fungal and the full range of viral and opportunistic infections

Chapter 18 — Viral infections in cancer patients outside transplantation

18.1 Hepatitis B reactivation

- **Mechanism:** immunosuppression lets HBV replicate from cccDNA in hepatocytes; when immunity returns (e.g. after rituximab or steroids are stopped), immune attack on infected hepatocytes causes hepatitis, sometimes fulminant [16].
- **Definitions:** rise in HBV DNA (e.g. $\geq$ 2 log above baseline, or new detection), or **reverse seroconversion** (HBsAg reappearing in an HBsAg-negative, anti-HBc-positive person).
- **Risk:** HBsAg-positive patients on anti-CD20 therapy or transplant have very high risk; HBsAg-negative, anti-HBc-positive patients have significant risk with anti-CD20 drugs and transplant.
- **Prevention:** universal screening before therapy; entecavir or tenofovir prophylaxis continued for at least 12–18 months after anti-CD20 therapy or longer after transplant; monitoring if not on prophylaxis. Prophylaxis is far more effective than treating reactivation once it has started.

18.2 Hepatitis C, hepatitis E and HIV

- **HCV:** chemotherapy can increase HCV RNA and hepatotoxicity; direct-acting antivirals are usually compatible with cancer treatment (check drug interactions).
- **HEV:** chronic hepatitis E (genotype 3, often foodborne) occurs in profoundly immunosuppressed patients; detected by HEV RNA (antibody tests unreliable); treated by reducing immunosuppression and with ribavirin.
- **HIV:** people with HIV are treated for cancer as other patients, with antiretroviral therapy continued; drug interactions (especially boosted regimens with chemotherapy and azoles) require pharmacist review. HIV is not a barrier to transplant or CAR-T.

18.3 Herpesviruses

Virus	Typical setting	Clinical features	Notes
HSV-1/2	Intensive chemotherapy, mucositis	Severe oral/oesophageal ulceration, rarely pneumonitis or hepatitis	Prophylaxis in seropositive patients
VZV	Myeloma (proteasome inhibitors), lymphoma, CLL, transplant, JAK inhibitors	Dermatomal or disseminated zoster; visceral zoster can present with abdominal pain before rash	Prophylaxis; recombinant zoster vaccine
CMV	Alemtuzumab, idelalisib, high-dose steroids, bispecifics; rarely conventional chemotherapy	Fever, cytopenias, hepatitis, colitis, pneumonitis, retinitis	Monitor in high-risk regimens; CMV colitis can mimic immune-related colitis
EBV	Fludarabine, alemtuzumab, ATG	EBV-driven lymphoproliferation (rare outside transplant)	
HHV-6	Mostly after transplant	Encephalitis, marrow suppression	Beware ciHHV-6



Figure 22: Herpes zoster (shingles) rash. Image: NIAID, CC BY 2.0, via Wikimedia Commons.

18.4 Respiratory viruses

- Influenza, RSV, parainfluenza, human metapneumovirus, rhinovirus, seasonal coronaviruses, adenovirus and SARS-CoV-2 cause more frequent **progression to lower respiratory tract disease**, longer shedding and higher mortality in haematology patients [42].
- Risk factors for progression: lymphopenia, neutropenia, recent transplant, steroids, older age, B-cell depletion.
- **Consequences for cancer care:** delays in chemotherapy or transplant; infection control (isolation, cohorting); antiviral treatment (oseltamivir for influenza; remdesivir and nirmatrelvir–ritonavir for SARS-CoV-2 — check interactions with ritonavir; ribavirin in selected RSV/parainfluenza cases in transplant recipients).
- **Prolonged SARS-CoV-2 infection** in B-cell-depleted patients can last months, with viral evolution; managed with combination antivirals and, where available, antibody products.

18.5 Other viruses

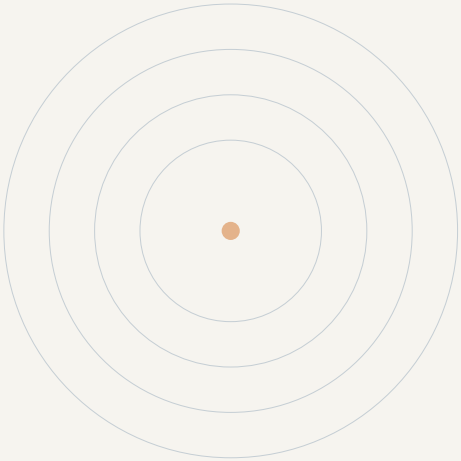
- **JC virus — progressive multifocal leukoencephalopathy (PML):** after rituximab, brentuximab, ruxolitinib, bendamustine, transplant. Diagnosed by MRI and JC virus PCR in CSF; no specific antiviral; immune reconstitution is the only effective treatment.
- **Parvovirus B19:** chronic anaemia (pure red cell aplasia) in patients unable to make antibody; treated with immunoglobulin.
- **Norovirus:** chronic diarrhoea for months in immunocompromised patients; mimics GVHD and drug toxicity.
- **Enteroviruses:** chronic meningoencephalitis in patients with antibody deficiency (after rituximab).
- **Adenovirus and BK virus:** mainly a transplant problem (Chapter 33).

18.6 Vaccination in cancer patients

- **Inactivated vaccines** (influenza, COVID-19, pneumococcal, recombinant zoster, hepatitis B) are safe; give ideally $\geq$ 2 weeks before chemotherapy or between cycles; responses are reduced, especially within 6 months of anti-CD20 therapy [18].
- **Live vaccines** (MMR, varicella, yellow fever, live zoster, oral typhoid, BCG) are contraindicated during and for a period after immunosuppressive treatment.
- **Household contacts** should be vaccinated (influenza, COVID-19; MMR and varicella are safe for contacts; avoid contact with nappies after rotavirus vaccination of infants).
- After transplant or CAR-T, patients need a full **revaccination** schedule (Chapter 37).

PART VI

Haematopoietic Stem Cell Transplantation



Chapter 19 — Overview of stem cell transplantation

Haematopoietic stem cell transplantation (HSCT, or HCT; still often called "bone marrow transplant") replaces a patient's blood-forming system. It lets doctors give doses of chemotherapy and radiation that would otherwise destroy the marrow permanently, and — in allogeneic transplants — it gives the patient a new immune system that can attack residual cancer [1,19].

19.1 Two fundamentally different procedures

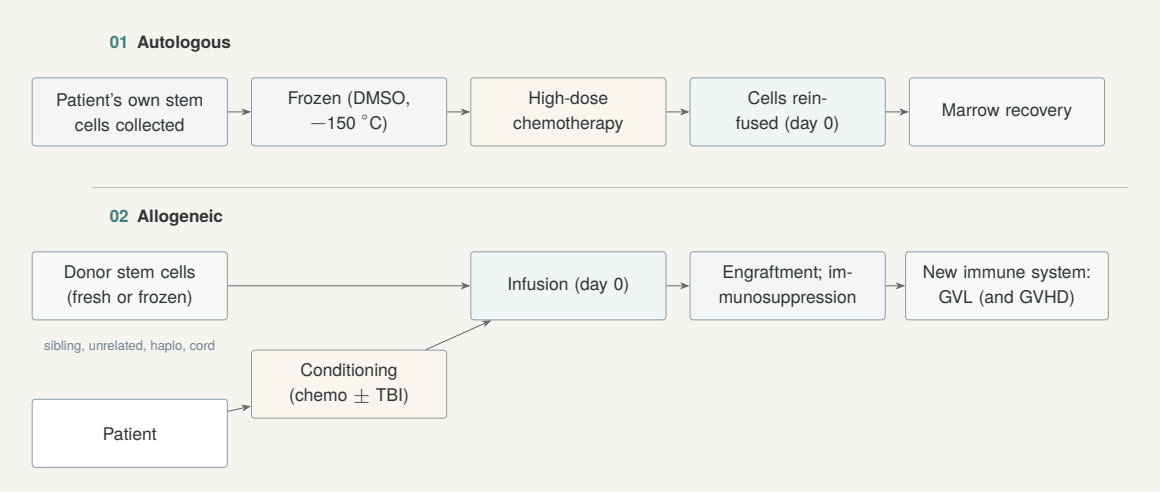


Figure 23: Autologous transplantation rescues the marrow after high-dose therapy; allogeneic transplantation replaces it and adds donor immunity.

	Autologous transplant	Allogeneic transplant
Source of stem cells	The patient's own, collected earlier and frozen	A donor: sibling, unrelated volunteer, haploidentical relative or cord blood
Main purpose	**Rescue** after high-dose chemotherapy (dose intensification)	**Replace** a diseased marrow and provide **graft-versus-leukaemia (GVL)** immunity
Main indications	Myeloma, relapsed chemosensitive lymphoma (DLBCL, Hodgkin), some mantle cell and T-cell lymphomas, germ cell tumours, neuroblastoma, AL amyloidosis, selected autoimmune diseases	AML, ALL, MDS, myelofibrosis, CML after TKI failure, selected lymphomas and CLL, aplastic anaemia, haemoglobinopathies, inborn errors of immunity
GVHD	No (except rare autologous GVHD-like syndromes)	Yes — major cause of illness and death
Immunosuppressive drugs after transplant	None	Yes, usually for 3–12 months or longer
Immune recovery	Faster (months)	Slower (1–2 years or more)
Viral infection risk	Moderate: HSV, VZV, respiratory viruses; CMV disease uncommon	High: CMV, EBV/PTLD, adenovirus, HHV-6, BK, respiratory viruses, VZV
Transplant-related mortality	Low (about 1–5%)	Higher (about 10–25% at 2 years, depending on patient and donor)

19.2 How a transplant cures cancer

1. **High-dose therapy** (conditioning) kills cancer cells more completely than standard doses.

2. **Graft-versus-leukaemia effect** (allogeneic only): donor T cells and NK cells recognise residual malignant cells as foreign — through minor histocompatibility antigens and mismatched HLA — and eliminate them. Evidence: lower relapse with GVHD, higher relapse with T-cell-depleted grafts or identical-twin donors, and remissions after donor lymphocyte infusion.
3. **Replacement** of a defective marrow or immune system (aplastic anaemia, haemoglobinopathies, immunodeficiencies).

The central tension of allogeneic transplantation is that the same donor immune cells that cause GVL also cause GVHD, while the drugs that prevent GVHD also impair GVL and anti-viral immunity.

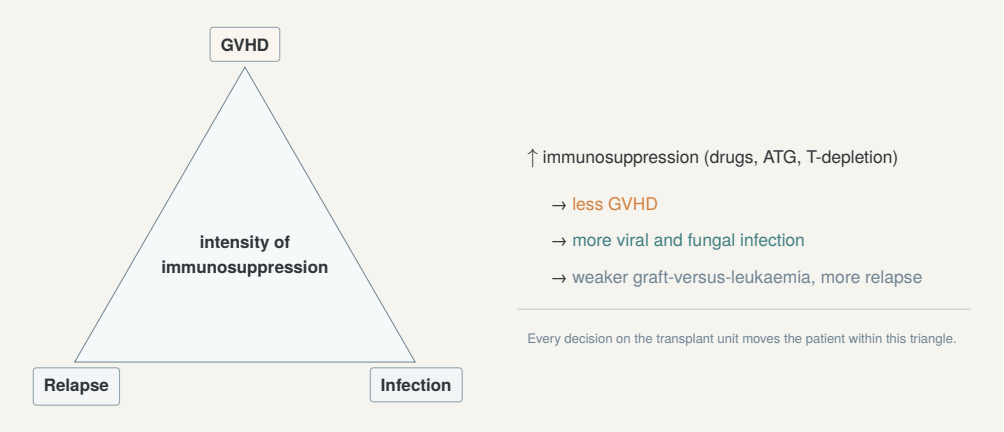


Figure 24: The central balance of allogeneic transplantation.

19.3 A short history

- **1950s:** experiments showing that marrow infusion rescues irradiated animals; first human attempts.
- **1957–1970s:** E. Donnall Thomas and colleagues in Seattle develop human marrow transplantation (Nobel Prize 1990). Discovery of HLA makes matched sibling transplants possible.
- **1968:** first successful transplants for severe combined immunodeficiency.
- **1980s:** unrelated donor registries (e.g. the US National Marrow Donor Program, 1986); first cord blood transplant (1988).
- **1990s:** peripheral blood stem cells replace marrow for most adult transplants; reduced-intensity conditioning extends transplant to older patients.
- **2000s–2010s:** post-transplant cyclophosphamide makes haploidentical transplantation widely available [23]; better antifungals and pre-emptive CMV strategies.
- **2017 onwards:** letermovir CMV prophylaxis [38]; ruxolitinib for steroid-refractory GVHD [31]; CAR-T cells; PTCy extended to unrelated donors [24].

19.4 Activity

Tens of thousands of transplants are performed each year in Europe alone, reported to the EBMT registry; more than half are autologous. The commonest indications are myeloma and lymphoma (autologous) and AML, MDS and ALL (allogeneic). Indications are graded by expert bodies — standard of care, clinical option, developmental, or generally not recommended — and updated regularly [20].

Chapter 20 — Assessing the patient

20.1 Is transplant indicated?

The transplant team weighs **disease risk** (chance of relapse without transplant) against **transplant risk** (chance of dying from the transplant). Examples:

- **AML in first remission:** allogeneic transplant recommended for adverse-risk disease, and for intermediate-risk or persistent MRD; usually not for favourable-risk disease with MRD clearance [6].
- **ALL:** for high-risk genetics, persistent MRD, or relapse.
- **Myeloma:** autologous transplant as part of first-line therapy in fit patients.
- **DLBCL:** autologous transplant for chemosensitive late relapse; CAR-T for early relapse or refractory disease.

20.2 Is the patient fit enough?

- **Performance status:** Karnofsky $\geq$ 70–80% (ECOG 0–1) usually required.
- **Age:** biological rather than chronological; reduced-intensity conditioning allows allogeneic transplant into the 70s.
- **HCT comorbidity index (HCT-CI) [21]:** scores conditions such as arrhythmia, cardiac disease, inflammatory bowel disease, diabetes, cerebrovascular disease, psychiatric disturbance, liver disease, obesity, prior infection requiring treatment, rheumatological disease, peptic ulcer, renal disease, lung function abnormalities, prior solid tumour, heart valve disease. Scores of 0, 1–2, and $\geq$ 3 predict increasing non-relapse mortality. **Infection requiring continued treatment at the time of transplant scores a point** — virologists' input on active infections feeds directly into this assessment.
- **Composite risk tools** combine disease (Disease Risk Index), comorbidity, age and donor factors (e.g. EBMT risk score).

20.3 Pre-transplant work-up

Area	Tests	Purpose
Disease status	Marrow, imaging, MRD	Confirm remission or response
Heart	ECG, echocardiogram (ejection fraction)	Anthracycline and conditioning toxicity
Lungs	Pulmonary function tests (FEV1, DLCO)	Predict pulmonary complications
Kidney, liver	Creatinine/eGFR, liver tests, liver imaging if iron overload or prior hepatitis	Drug dosing; SOS/VOD risk
Infection screening (recipient)	Serology: CMV IgG, EBV, HSV, VZV, HIV, HBV (HBsAg, anti-HBc, anti-HBs), HCV, HTLV-1/2, syphilis, *Toxoplasma*; *Strongyloides* serology if exposure; TB risk assessment (IGRA in selected patients); respiratory virus PCR if symptomatic; dental assessment; sinus imaging if symptomatic	Plan prophylaxis and monitoring; treat or defer for active infection [35]
Fertility	Discussion; sperm or egg/embryo cryopreservation	Conditioning usually causes infertility
Psychosocial	Carer availability, mental health, adherence	Transplant needs a carer and close follow-up
Venous access	Tunnelled central line	
Consent	Detailed discussion of risks and alternatives	

Active infection before transplant. Respiratory viruses (RSV, influenza, parainfluenza, hMPV, SARS-CoV-2) at the time of admission often lead to **postponement** of conditioning when possible, because progression to pneumonia during neutropenia is common and severe [42]. Invasive fungal infection is controlled before transplant with continued secondary prophylaxis.

Chapter 21 — HLA, donors and donor selection

21.1 HLA and why matching matters

- **HLA molecules** present peptides to T cells. Donor T cells recognise mismatched recipient HLA as foreign (GVHD); recipient T cells surviving conditioning recognise mismatched donor HLA (graft rejection).
- **Key loci** for donor selection: HLA-A, -B, -C, -DRB1 (the "8/8" match at high resolution), plus -DQB1 ("10/10") and -DPB1 (assessed for "permissive" or "non-permissive" mismatches) [22].
- Even fully HLA-matched sibling pairs differ in **minor histocompatibility antigens** (polymorphic peptides from other proteins, e.g. Y-chromosome antigens from a female donor to a male recipient) — enough to cause GVHD and GVL.

21.2 Inheritance

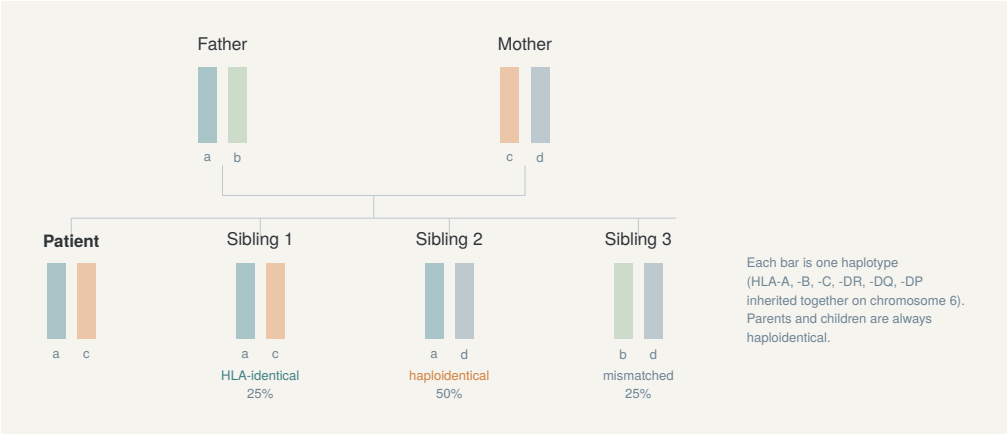


Figure 25: Inheritance of HLA haplotypes. Each sibling has a 25% chance of being an HLA-identical match.

HLA genes are inherited as a block (**haplotype**) from each parent. Each sibling has a **25%** chance of being an HLA-identical match, 50% of being haploidentical (half-matched), and 25% of being fully mismatched. Parents and children are always haploidentical.

21.3 Donor types

Donor	Availability	Advantages	Disadvantages
Matched sibling donor (MSD)	About 25–30% of patients	Fast; least GVHD; reference standard	Sibling may be older or have comorbidities
Matched unrelated donor (MUD, 8/8 or 10/10)	Depends on ancestry; high for people of European ancestry, much lower for many minority groups	Large registries (> 40 million volunteers worldwide)	Search and collection take weeks; more GVHD than MSD
Mismatched unrelated donor (MMUD, 7/8)	More often available		Higher GVHD and mortality; PTCy reduces the gap

Donor	Availability	Advantages	Disadvantages
Haploidentical related donor (parent, child, sibling, other relative)	Nearly all patients	Rapid; motivated donor; available for repeat donations (DLI)	Requires PTCy or intensive T-cell manipulation; donor-specific antibodies cause graft failure; more BK haemorrhagic cystitis, CMV, HHV-6
Umbilical cord blood	Banked units available immediately	Tolerates more HLA mismatch (4–6/8); low chronic GVHD; strong GVL	Low cell dose → slow engraftment; very slow immune recovery; **high viral infection risk** (CMV, HHV-6, adenovirus); no donor for DLI

21.4 Choosing among donors

Beyond HLA, transplant teams consider [22]:

- **Donor age** — younger donors give better survival (the strongest non-HLA factor for unrelated donors).
- **Donor sex** — female donors (especially multiparous) to male recipients carry more chronic GVHD.
- **CMV serostatus** — a seronegative recipient (R−) should ideally receive a graft from a seronegative donor (D−) to avoid primary infection; for seropositive recipients (R+) a seropositive donor can transfer CMV-specific immunity (benefit mainly shown with myeloablative conditioning).
- **ABO blood group** — major incompatibility (recipient has antibodies against donor red cells, e.g. O recipient, A donor) causes delayed red cell recovery and pure red cell aplasia; minor incompatibility (donor antibodies against recipient red cells) causes passenger lymphocyte haemolysis around days 5–15. Blood groups convert to the donor's group over weeks to months.
- **Donor-specific anti-HLA antibodies (DSA)** in the recipient — important for haplo and cord transplants; cause graft failure; desensitisation may be needed.
- **Donor health and infection markers** — donors are screened for HIV, HBV, HCV, HTLV, syphilis, CMV, and region-specific infections (e.g. *T. cruzi*, West Nile, Zika, malaria risk); donor HBV status and **donor-derived infections** must be assessed (e.g. anti-HBc-positive donors).

21.5 The search process

1. HLA typing of patient and siblings at diagnosis for anyone likely to need a transplant.
2. Preliminary unrelated donor and cord search through national registries and the World Marrow Donor Association network.
3. Confirmatory typing, donor medical assessment, and donor work-up; typically 4–12 weeks for unrelated donors.
4. Backup donor and haploidentical options identified in parallel.

Chapter 22 — Stem cell sources, mobilisation, collection and processing

22.1 Sources compared

Source	How collected	Cell dose (typical targets)	Engraftment	GVHD
Peripheral blood stem cells (PBSC)	G-CSF mobilisation then apheresis	CD34+ $\geq 2 \times 10^6$/kg minimum; 4–8 $\times$ 10^6/kg preferred for allogeneic	Fastest (neutrophils about day +12 to +18)	More chronic GVHD (more T cells)
Bone marrow	Multiple aspirations from posterior iliac crests under general anaesthesia	Total nucleated cells $\geq$ 2–3 $\times$ 10^8/kg	Slower (about day +18 to +25)	Less chronic GVHD — preferred for non-malignant diseases and children
Umbilical cord blood	Collected from the placenta after birth; frozen in public banks	Total nucleated cells $\geq$ 2.5–3 $\times$ 10^7/kg; CD34+ about 1–2 $\times$ 10^5/kg	Slowest (day +20 to +35)	Less chronic GVHD despite mismatch

22.2 Mobilisation and apheresis

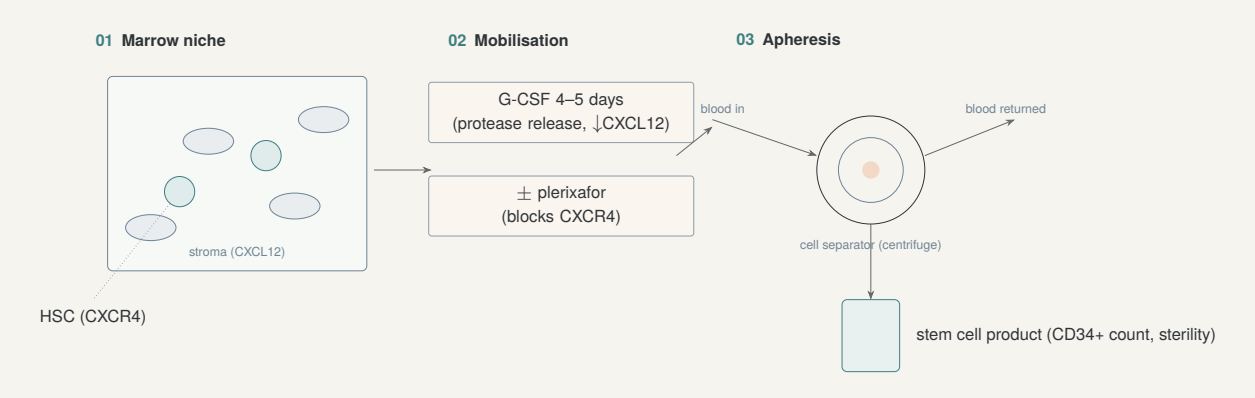


Figure 26: Peripheral blood stem cell mobilisation and collection. G-CSF (± plerixafor) releases CD34+ stem cells from the marrow niche into the blood, where apheresis collects them.

- **G-CSF** (filgrastim about 10 μg/kg/day for 4–5 days) loosens stem cell attachment in the marrow niche (protease release, reduced CXCL12), moving CD34+ cells into the blood.
- **Plerixafor** (CXCR4 antagonist) rapidly mobilises additional stem cells; used for poor mobilisers (often after lenalidomide, fludarabine or extensive chemotherapy).
- **Chemotherapy + G-CSF** mobilisation (e.g. cyclophosphamide) is used in some autologous settings to reduce tumour and collect during recovery.
- **Apheresis:** blood is drawn from one vein, centrifuged in a cell separator that collects the mononuclear layer containing stem cells, and returned through another; 2–4 blood volumes processed over 3–5 hours; often 1–2 days needed. Citrate anticoagulant can cause tingling (hypocalcaemia).
- **Peripheral CD34+ count** in blood on the morning of collection predicts yield.
- **Donor side effects:** bone pain from G-CSF, headache, rarely splenic rupture; marrow donors have anaesthetic risks and hip pain.

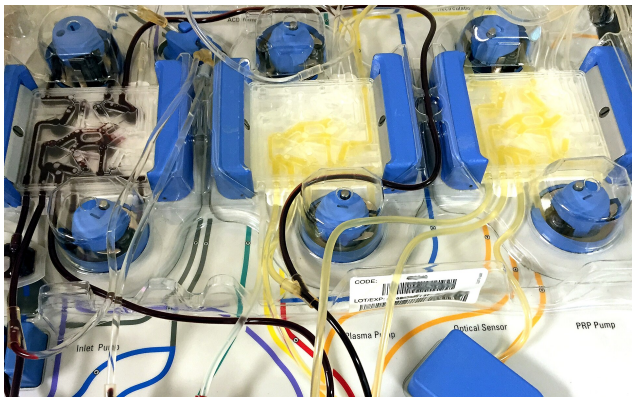


Figure 27: An apheresis cell separator of the type used to collect peripheral blood stem cells. Image: NIAID, CC BY 2.0, via Wikimedia Commons.

22.3 Processing, freezing and manipulation

- **Fresh grafts** (most allogeneic) are infused within 24–72 hours of collection.
- **Cryopreservation** (all autologous; some allogeneic) uses **DMSO** (dimethyl sulfoxide, usually 5–10%) as a cryoprotectant, controlled-rate freezing, and storage in liquid nitrogen vapour (below −150 °C).
- **Quality control:** CD34+ count, viability, sterility testing (bacterial and fungal cultures), and for cord blood HLA and identity confirmation.
- **Graft manipulation:**
  - **Red cell or plasma depletion** for ABO-incompatible grafts.
  - **T-cell depletion** to prevent GVHD: CD34+ selection, $\alpha\beta$ T-cell receptor/CD19 depletion (used in paediatric haplo transplants), CD45RA (naïve T-cell) depletion.
  - In vivo T-cell depletion with **ATG** or **alemtuzumab** (Chapter 26).
- T-cell depletion reduces GVHD but increases graft failure, relapse and — critically — **viral infections and EBV PTLD**, because the graft brings fewer virus-specific memory T cells.

Chapter 23 — Conditioning

Conditioning is the chemotherapy, with or without radiation, given in the days before the graft. Its purposes are to **kill residual disease**, to **suppress the recipient's immune system** so the graft is not rejected, and (traditionally) to **make space** in the marrow.

23.1 Intensity

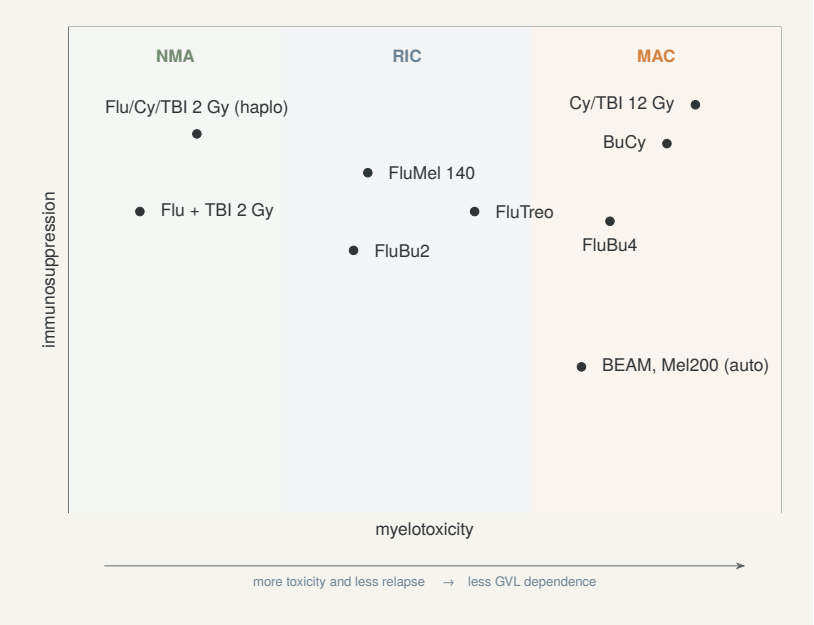


Figure 28: Conditioning regimens arranged by myelotoxicity and immunosuppression (schematic, after Bacigalupo [25]). Positions are approximate.

Conditioning regimens are classified by intensity [25]:

- **Myeloablative conditioning (MAC):** causes irreversible marrow aplasia; the patient would not recover without stem cell support. Examples: busulfan + cyclophosphamide (BuCy), cyclophosphamide + TBI 12–13.2 Gy (CyTBI), fludarabine + busulfan 4 days (FluBu4), treosulfan-based high-dose regimens.
- **Reduced-intensity conditioning (RIC):** lower doses; cytopenias substantial but shorter; relies more on GVL. Examples: fludarabine + melphalan 140 mg/m^2 (FluMel), fludarabine + busulfan 2 days (FluBu2), fludarabine + treosulfan.
- **Non-myeloablative (NMA):** minimal marrow toxicity, mainly immunosuppressive; e.g. fludarabine + 2 Gy TBI (Seattle regimen); fludarabine + cyclophosphamide + 2 Gy TBI in haplo transplants with PTCy.
- **Autologous high-dose regimens:** melphalan 200 mg/m^2 (myeloma); BEAM (carmustine, etoposide, cytarabine, melphalan) or similar for lymphoma; carmustine–thiotepa for CNS lymphoma.

MAC gives less relapse but more toxicity; RIC/NMA allow transplants in older or less fit patients at the cost of more relapse.

23.2 Main conditioning agents

Agent	Notes	Key toxicities
Total body irradiation (TBI)	Fractionated (e.g. 12 Gy in 6 fractions over 3 days) or low dose (2 Gy); penetrates sanctuary sites (CNS, testes); used in ALL	Mucositis, nausea, parotitis, pneumonitis, cataracts, infertility, growth and endocrine effects, second cancers
Busulfan	IV with **therapeutic drug monitoring** (area under the curve targeting)	Seizures (phenytoin or levetiracetam prophylaxis), **SOS/VOD**, mucositis, lung toxicity
Cyclophosphamide	120 mg/kg in MAC; also used after transplant (PTCy)	Haemorrhagic cystitis (mesna), cardiotoxicity, fluid retention
Fludarabine	Backbone of RIC; strongly lymphodepleting	Neurotoxicity (high doses), prolonged T-cell lymphopenia
Melphalan	140–200 mg/m^2	Severe mucositis, diarrhoea
Treosulfan, thiotepa	Alkylators with less liver toxicity (treosulfan) or CNS penetration (thiotepa)	Skin toxicity (thiotepa)
ATG (anti-thymocyte globulin)	Rabbit polyclonal antibodies against T cells, given days −3 to −1 (or around)	Fever, rigors, serum sickness; **in vivo T-cell depletion of both recipient and donor cells — delays antiviral immunity; increases EBV PTLD**
Alemtuzumab	Anti-CD52; used in some UK and paediatric protocols	Profound lymphodepletion; **high CMV and adenovirus reactivation**

23.3 The conditioning days

- Days are counted **relative to the day of stem cell infusion (day 0)**. Conditioning is days −7 to −1 (varies by regimen).
- During conditioning: hydration, antiemetics, seizure prophylaxis (busulfan), mesna (high-dose cyclophosphamide), drug levels (busulfan), start of GVHD prophylaxis (often calcineurin inhibitor from day −3 or −1), start of antimicrobial prophylaxis (aciclovir; antifungal; letermovir from day 0 to +28 for CMV-seropositive allogeneic recipients [38]).
- **Rest day(s)** may be built in before day 0 to allow drugs to clear.

Chapter 24 — Day 0 and the aplastic phase

24.1 Stem cell infusion

- The graft is infused through the central line like a blood transfusion, usually over 30 minutes to a few hours. It is undramatic compared with what precedes and follows it.
- **Cryopreserved grafts:** DMSO causes nausea, flushing, a garlic-like odour on the breath and body for a day or two, sometimes bradycardia, hypertension or allergic reactions; premedication with antihistamines and hydration.
- **ABO-incompatible grafts:** risk of haemolytic reactions; red cell or plasma depletion beforehand.
- Patients often call day 0 their "new birthday".

24.2 The aplastic period (about day 0 to engraftment)

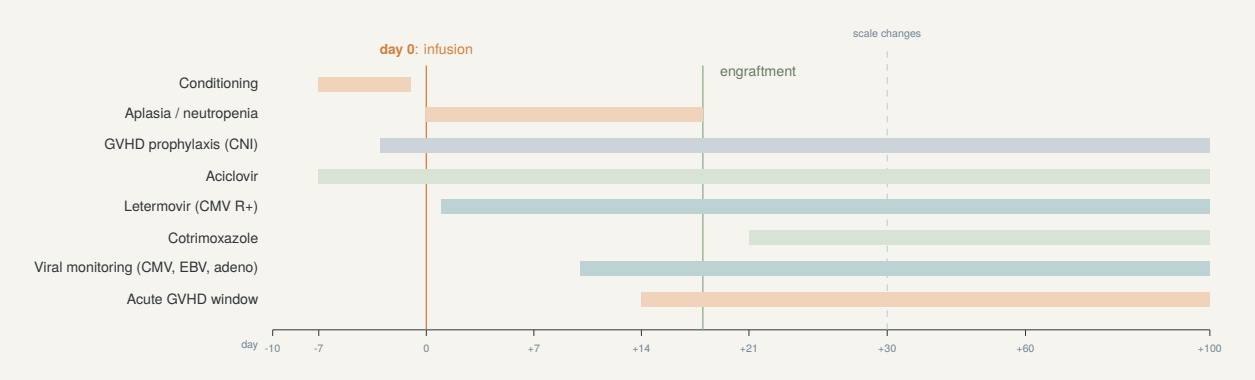


Figure 29: Timeline of a typical allogeneic transplant to day +100. Durations vary by protocol; the scale is compressed after day +30.

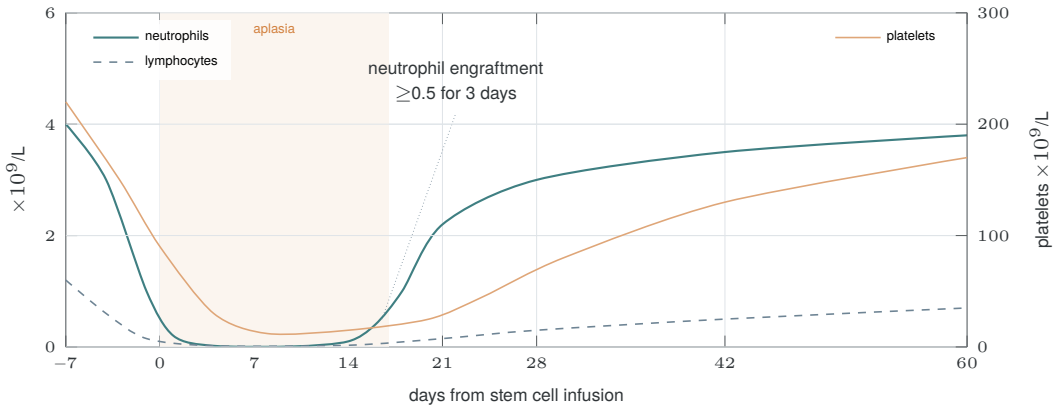


Figure 30: Blood counts around an allogeneic transplant (schematic). Neutrophils engraft first, platelets later, and lymphocytes take months to recover.

Problem	Timing	Clinical picture	Management
Pancytopenia	Day 0 to engraftment	Neutrophils < 0.1–0.5; transfusion-dependent	Red cells and platelets (irradiated); G-CSF in some protocols
Mucositis	Peaks days +5 to +12	Mouth ulcers, pain, inability to swallow, diarrhoea	Opioid infusions, parenteral nutrition, mouth care; **HSV prophylaxis**

Problem	Timing	Clinical picture	Management
Febrile neutropenia	Most patients	Fever; bacteraemia in 20–40%	Empirical antibiotics (Chapter 16)
Nausea, anorexia, diarrhoea	Throughout		Antiemetics; exclude infection (*C. difficile*, norovirus, adenovirus)
Fluid overload, weight gain	First weeks		Diuretics; watch for SOS/VOD
SOS/VOD	Usually by day +21	Weight gain, painful hepatomegaly, jaundice, ascites	Chapter 35
Early haemorrhagic cystitis	Within 72 hours of cyclophosphamide	Haematuria	Hydration, mesna; distinguish from later BK cystitis
Pre-engraftment infections		Bacteraemia, *Candida*, early moulds, HSV, respiratory viruses	Prophylaxis and empirical therapy

Protective environment: HEPA-filtered single rooms with positive pressure for allogeneic recipients (to reduce *Aspergillus* exposure), hand hygiene, restrictions on visitors with respiratory infections, food safety, no plants or flowers.

Chapter 25 — Engraftment, graft failure and chimerism

25.1 Engraftment

- **Neutrophil engraftment:** first of three consecutive days with ANC $\geq 0.5 \times 10^9$/L.
- **Platelet engraftment:** first of seven consecutive days with platelets $\geq 20 \times 10^9$/L without transfusion (some definitions use ≥ 50).
- **Typical timing:** autologous PBSC about day +10 to +14; allogeneic PBSC +14 to +21; bone marrow +18 to +25; cord blood +20 to +35. PTCy delays engraftment by a few days.
- Monocytes recover first; a rise in monocytes often heralds engraftment.
- **Engraftment syndrome** (fever, rash, capillary leak, pulmonary infiltrates) may occur around engraftment [26] — a diagnosis of exclusion of infection (Chapter 35).

25.2 Graft failure and poor graft function

- **Primary graft failure:** no neutrophil engraftment by day +28 (+42 for cord blood).
- **Secondary graft failure:** loss of graft after initial engraftment.
- **Poor graft function:** cytopenias despite full donor chimerism.
- **Causes:** low cell dose, HLA mismatch, **donor-specific antibodies**, inadequate immunosuppression, myelofibrosis/splenomegaly, **viral infections (CMV, HHV-6, parvovirus B19, adenovirus)**, drugs (ganciclovir, valganciclovir, mycophenolate, cotrimoxazole, linezolid), GVHD, relapse.
- **Management:** remove marrow-toxic drugs (e.g. switch ganciclovir to foscarnet), treat infections, G-CSF, thrombopoietin agonists, CD34+ selected "top-up" from the donor, or second transplant.

The virologist's role here is real: CMV, HHV-6 and parvovirus B19 testing are part of the work-up of poor graft function, and antiviral choices (ganciclovir vs foscarnet vs letermovir vs maribavir) are made with marrow toxicity in mind.

25.3 Chimerism

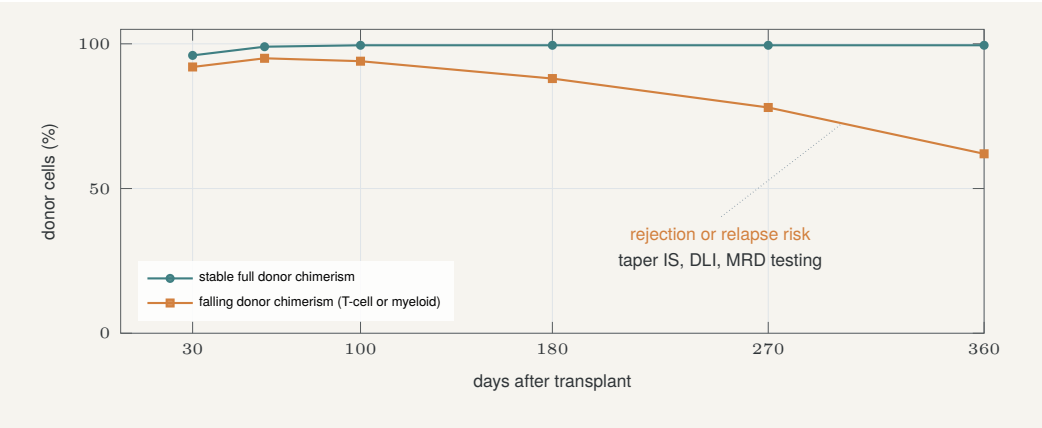


Figure 31: Chimerism monitoring. Falling donor chimerism, particularly in lineage-specific fractions, triggers action.

- Chimerism testing measures the proportion of donor and recipient DNA in blood or marrow, usually by short tandem repeat PCR (sensitivity 1–5%) or by qPCR/ddPCR/NGS for higher sensitivity.
- **Lineage-specific chimerism** (sorted T cells and myeloid cells) is more informative: falling donor T-cell chimerism suggests rejection risk; rising recipient myeloid cells suggest relapse.
- **Typical schedule:** around day +30, +60, +100, then periodically; more often after RIC.
- **Mixed chimerism** may be managed by tapering immunosuppression or giving donor lymphocyte infusion (Chapter 36).

Chapter 26 — GVHD prophylaxis and the immunosuppressive drugs

Every allogeneic transplant recipient (except identical twins) receives drugs to prevent GVHD. These drugs are the main reason for the prolonged T-cell immunodeficiency that underlies viral infections — and many of them interact with antimicrobials.

26.1 Standard prophylaxis platforms

Platform	Components	Typical use
Calcineurin inhibitor + methotrexate	Ciclosporin or tacrolimus from day −3/−1; methotrexate days +1, +3, +6 (± +11)	Classic for MSD and MUD with myeloablative conditioning
Calcineurin inhibitor + mycophenolate (MMF)	MMF for about 4–6 weeks	RIC/NMA transplants; less mucositis than methotrexate
ATG-based	Rabbit ATG before transplant + CNI + methotrexate/MMF	Unrelated donors (reduces chronic GVHD)
Post-transplant cyclophosphamide (PTCy)	Cyclophosphamide 50 mg/kg on days +3 and +4, then tacrolimus + MMF from day +5	Haploidentical transplants [23]; increasingly MUD and MMUD [24]
Alemtuzumab-based	In vivo T-cell depletion	Some UK centres; aplastic anaemia
Abatacept added to CNI + methotrexate	CTLA4-Ig blocks T-cell co-stimulation	MUD/MMUD in some countries
Sirolimus-based	mTOR inhibitor with tacrolimus	Some US centres
Ex vivo T-cell depletion	CD34 selection, $\alpha\beta$ depletion	Paediatric haplo, selected adults

How PTCy works: after the graft is infused, alloreactive donor and recipient T cells proliferate rapidly in response to mismatched antigens. A high dose of cyclophosphamide on days +3 and +4 kills these dividing alloreactive cells while sparing resting T cells (including some virus-specific memory cells) and stem cells, which have high levels of aldehyde dehydrogenase that inactivates cyclophosphamide. PTCy is associated with **more BK virus haemorrhagic cystitis, HHV-6 reactivation and early CMV infection**, and with delayed engraftment and cardiac toxicity.

26.2 The drugs in detail

Drug	Mechanism	Monitoring	Main toxicities	Interactions relevant to anti-infectives
Ciclosporin	Calcineurin inhibitor: blocks IL-2 transcription in T cells	Trough levels (e.g. about 100–300 μg/L, centre-specific)	Nephrotoxicity, hypertension, hypomagnesaemia, tremor, hirsutism, gum hyperplasia, **PRES**, **TA-TMA**	CYP3A4/P-gp substrate: levels raised by azoles (posaconazole, voriconazole), **letermovir** (letermovir dose reduced to 240 mg with ciclosporin), macrolides, ritonavir; lowered by rifampicin. Added nephrotoxicity with foscarnet, cidofovir, aminoglycosides, amphotericin
Tacrolimus	Calcineurin inhibitor	Trough levels (e.g. 5–15 μg/L)	As ciclosporin; also hyperglycaemia; less hirsutism	Same; voriconazole and posaconazole often require large tacrolimus dose reductions; letermovir increases tacrolimus levels

Drug	Mechanism	Monitoring	Main toxicities	Interactions relevant to anti-infectives
Methotrexate	Antiproliferative	Levels if renal impairment or effusions	Mucositis, delayed engraftment, liver toxicity	Cotrimoxazole and some antibiotics increase toxicity
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase → blocks lymphocyte purine synthesis	Sometimes levels	Myelosuppression, diarrhoea, **CMV and other viral infections**	Additive marrow toxicity with ganciclovir/valganciclovir
Sirolimus	mTOR inhibitor	Trough levels	TA-TMA (with CNI), SOS/VOD, hyperlipidaemia, poor wound healing	Strongly affected by azoles (voriconazole contraindicated or large dose reduction)
ATG	Polyclonal antibodies deplete T cells	Absolute lymphocyte count	Infusion reactions, serum sickness	Delays CMV- and EBV-specific T-cell recovery
PTCy	See above		Haemorrhagic cystitis, cardiotoxicity	BK and HHV-6 association

26.3 Tapering

- Without GVHD, calcineurin inhibitors are usually tapered from about day +90 to +180 (earlier after RIC for malignancy, to enhance GVL; slower for non-malignant disease).
- Each taper step is a moment when GVHD may flare — and when anti-viral immunity begins to recover.

Chapter 27 — Acute graft-versus-host disease

Acute GVHD is an inflammatory attack by donor T cells on recipient tissues, classically the **skin, gastrointestinal tract and liver**. It is a leading cause of non-relapse mortality and the main driver of the infections seen in the months after transplant, because its treatment — corticosteroids and other immunosuppressants — further impairs immunity [29].

27.1 Pathophysiology: the three-phase model

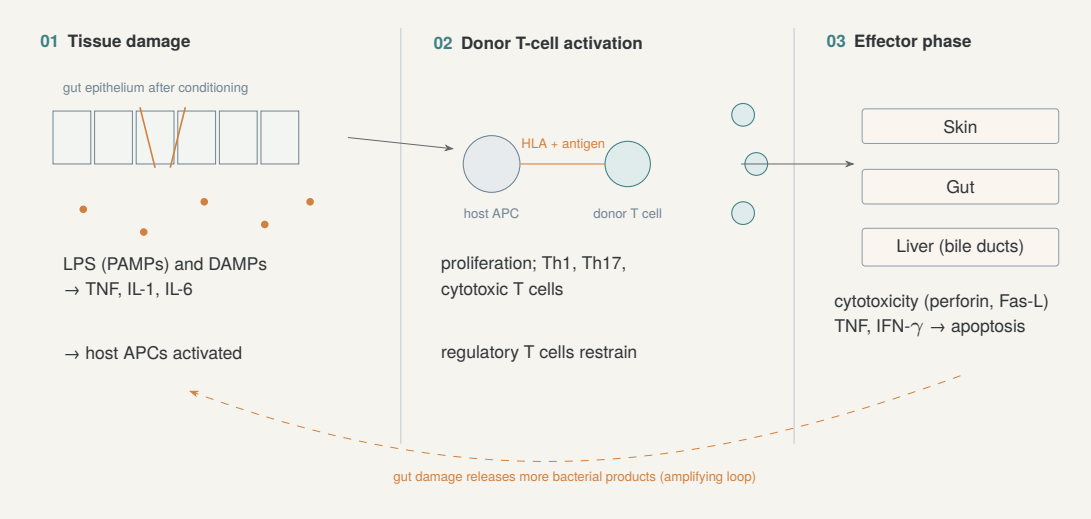


Figure 32: The three-phase model of acute GVHD [29].

1. **Tissue damage and priming.** Conditioning damages the gut lining, skin and other tissues. Bacterial products (lipopolysaccharide — PAMPs) and damaged-cell signals (DAMPs: ATP, uric acid, HMGB1) activate host antigen-presenting cells and release inflammatory cytokines (TNF, IL-1, IL-6). This is why more intensive conditioning and gut damage increase GVHD.
2. **Donor T-cell activation.** Donor T cells recognise host HLA and minor antigens on activated antigen-presenting cells, proliferate and differentiate into Th1, Th17 and cytotoxic effector cells. Regulatory T cells normally restrain this; their deficiency favours GVHD.
3. **Effector phase.** Cytotoxic T cells (perforin/granzyme, Fas ligand) and cytokines (TNF, IFN-γ) destroy target cells — intestinal stem cells in the crypts, keratinocytes, bile duct epithelium. Gut damage releases more bacterial products, creating a self-amplifying loop. Loss of intestinal microbiome diversity (from antibiotics and conditioning) is associated with more GVHD and higher mortality.

27.2 Clinical features and staging

- **Timing:** classically before day +100, but defined now by clinical features rather than timing; "late acute GVHD" occurs after day +100, often during immunosuppression taper or after DLI.
- **Incidence:** grade II–IV in about 30–50% of allogeneic recipients (lower with PTCy or ATG), grade III–IV in about 10–15%.

Organ	Clinical features	Staging (MAGIC) [30]
Skin	Maculopapular rash, often palms, soles, ears, face first; can progress to erythroderma and blistering	Stage 1: $<25\%$ body surface; 2: 25–50%; 3: $>50\%$; 4: generalised erythroderma with bullae or desquamation

Organ	Clinical features	Staging (MAGIC) [30]
Liver	Cholestatic jaundice (rising bilirubin, ALP)	By bilirubin: 1: 34–50 μmol/L (2.1–3 mg/dL); 2: 51–102; 3: 103–255; 4: $>$ 255 μmol/L
Lower GI tract	Watery (later bloody) diarrhoea, abdominal cramps, ileus	Adult stool volume per day: 1: 500–999 mL; 2: 1000–1500 mL; 3: $>$ 1500 mL; 4: severe pain $\pm$ ileus or grossly bloody stool
Upper GI tract	Anorexia, nausea, vomiting	Stage 1 only (persistent symptoms)

Overall grade (MAGIC): grade I = skin stage 1–2 only; grade II = skin stage 3, and/or liver stage 1, and/or upper GI, and/or lower GI stage 1; grade III = liver stage 2–3 and/or lower GI stage 2–3; grade IV = skin, liver or lower GI stage 4.

27.3 Diagnosis: the differential is often infection

Organ	GVHD mimics to exclude
Skin	Drug reactions (antibiotics, cotrimoxazole), engraftment syndrome, viral exanthems (HHV-6), conditioning toxicity
Gut	**CMV enterocolitis**, **adenovirus**, **norovirus**, rotavirus, *C. difficile*, mycophenolate toxicity, conditioning toxicity, neutropenic enterocolitis
Liver	**SOS/VOD**, drug toxicity (azoles, cotrimoxazole, TPN), viral hepatitis (**HBV reactivation, HEV, adenovirus, HSV, VZV, CMV**), fungal infection, iron overload, biliary obstruction

Biopsy helps: skin (basal vacuolar change, dyskeratotic keratinocytes with surrounding lymphocytes), gut (**crypt epithelial apoptosis**, crypt dropout in severe cases), liver (bile duct injury). Biopsies should be examined with **immunohistochemistry or PCR for CMV and adenovirus** — viral infection and GVHD frequently coexist, and GVHD treatment drives viral reactivation.

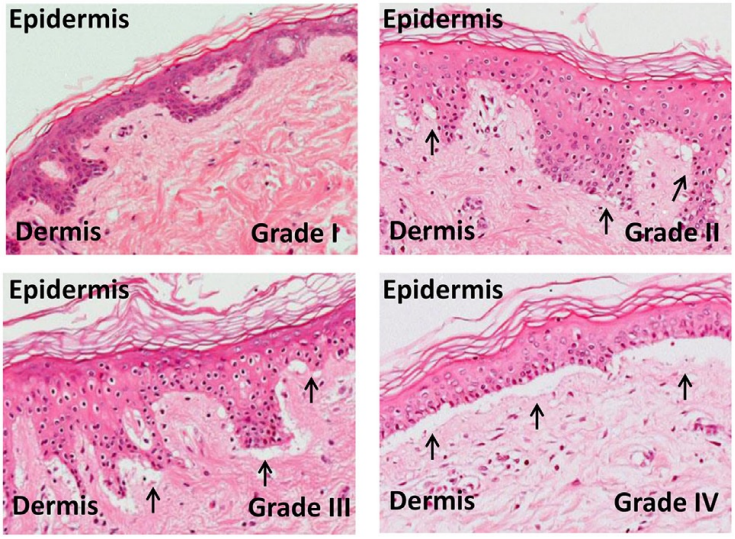


Figure 33: Histological grades of skin graft-versus-host disease (from an open-access research publication). Image: Sakhila Ghimire, Daniela Weber, Emily Mavin,Xiao nong Wang,Anne Mary Dickinson and Erns…, CC BY 4.0, via Wikimedia Commons.

Biomarkers. Blood levels of ST2 and REG3α (the MAGIC algorithm probability) predict non-response and mortality at diagnosis of GVHD and are used in some centres to guide treatment intensity.

27.4 Treatment

- **Grade I:** topical steroids; optimise calcineurin inhibitor levels.
- **Grade II–IV:** systemic **methylprednisolone or prednisolone 1–2 mg/kg/day** (1 mg/kg for isolated skin or upper GI grade II), with topical/non-absorbable steroids (budesonide, beclomethasone) for gut involvement.
- **Steroid-refractory acute GVHD** — progression after 3 days, no improvement after 7 days, or incomplete response after 28 days of steroids. Affects about a third to half of patients needing steroids. **Ruxolitinib** is the standard second-line drug, superior to best available therapy in the REACH2 trial [31]. Other options: extracorporeal photopheresis, vedolizumab, α1-antitrypsin, faecal microbiota transplantation, mesenchymal stromal cells (approved for children in some countries), anti-TNF or anti-IL-2 receptor antibodies.
- **Supportive care:** nutrition, pain control, fluid and electrolyte replacement for massive diarrhoea, octreotide, careful transfusion.
- **Outcome:** steroid-refractory gut or liver GVHD carries high mortality — often from **infection**.

27.5 Why acute GVHD drives viral infection

- **High-dose steroids** suppress T-cell function → CMV, adenovirus, EBV, HHV-6, VZV, respiratory viruses; also *Pneumocystis* and moulds.
- **Ruxolitinib** adds JAK-STAT blockade of antiviral cytokine signalling.
- **GVHD itself** damages the thymus and lymphoid tissue, slowing immune reconstitution.
- Gut GVHD breaks the mucosal barrier → bacteraemia and fungaemia.
- Practical consequences: **intensified CMV monitoring** (weekly or more), mould-active azole prophylaxis, continued or restarted letermovir in some centres, and a low threshold for testing.

Chapter 28 — Chronic graft-versus-host disease

Chronic GVHD is a multisystem disorder resembling autoimmune diseases (scleroderma, Sjögren syndrome, lichen planus, bronchiolitis obliterans). It is the main cause of late morbidity and non-relapse mortality after allogeneic transplant, but it is also associated with a lower risk of relapse [32].

28.1 Pathophysiology

- **Thymic damage** (from conditioning and acute GVHD) impairs negative selection, allowing autoreactive and alloreactive T cells to emerge.
- **Deficient regulatory T cells**.
- **B-cell dysregulation** — high BAFF levels, autoantibodies, alloantibodies.
- **Th17 and follicular helper T cells**.
- **Macrophage-driven fibrosis** (CSF-1 receptor-dependent), TGF-β, and tissue remodelling.
- Risk factors: prior acute GVHD, PBSC grafts, female donor to male recipient, older age, HLA mismatch, no ATG.

28.2 Diagnosis and scoring (NIH 2014 consensus [33])

- **Diagnostic features** (enough on their own): skin poikiloderma, lichen planus-like or sclerotic changes, fasciitis, joint contractures; oral lichen planus-like changes; oesophageal web or stricture; bronchiolitis obliterans proven by biopsy; vaginal scarring.
- **Distinctive features** (need confirmation): depigmentation, nail dystrophy, alopecia, xerostomia, mouth ulcers, dry eyes (keratoconjunctivitis sicca), myositis.
- **Organ scoring** 0–3 in eight organs: skin, mouth, eyes, gastrointestinal tract, liver, lungs, joints and fascia, genital tract.
- **Global severity: mild** (1–2 organs, maximum score 1, lung 0); **moderate** (3 or more organs with score 1, or any organ score 2, or lung score 1); **severe** (any organ score 3, or lung score 2–3).
- **Bronchiolitis obliterans syndrome (BOS)** — obstructive lung disease (FEV1/VC < 0.7, FEV1 $< 75\%$ predicted with decline) — has high mortality; respiratory viral infections can trigger or worsen it.

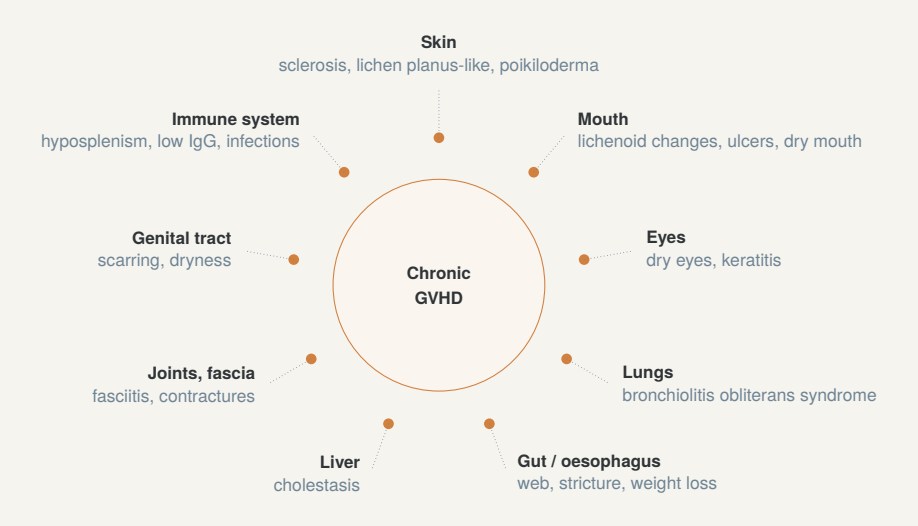


Figure 34: Organs affected by chronic GVHD and their typical features (NIH 2014 scores eight organs [33]; immune dysfunction added because it drives late infections).

28.3 Treatment

- **First line:** prednisolone about 1 mg/kg/day, often with a calcineurin inhibitor; topical and organ-specific treatment (topical steroids, dental care, eye drops and scleral lenses, inhaled steroids with azithromycin and montelukast for BOS).
- **Steroid-refractory or dependent disease:** ruxolitinib (REACH3), belumosudil (ROCK2 inhibitor), axatilimab (CSF-1R antibody), ibrutinib, extracorporeal photopheresis, rituximab, sirolimus, imatinib, low-dose IL-2.
- **Duration:** often years.

28.4 Chronic GVHD and infection

- **Functional hyposplenism** → invasive pneumococcal disease — penicillin (or alternative) prophylaxis while on treatment for chronic GVHD [35].
- **Hypogammaglobulinaemia** → immunoglobulin replacement in selected patients.
- **Prolonged steroids and other immunosuppressants** → late CMV, VZV, *Pneumocystis*, moulds, nocardiosis, respiratory viruses with progression to lower tract disease.
- **Mucosal disease** → oral HSV and *Candida*; dry eyes → bacterial and HSV keratitis.
- **Vaccines** — inactivated vaccines can still be given during chronic GVHD (responses reduced); **live vaccines are contraindicated** [46].

Chapter 29 — Immune reconstitution

Transplant replaces the marrow in weeks, but rebuilding a working immune system takes months to years. The pattern of recovery explains the timing of viral infections after transplant [34].

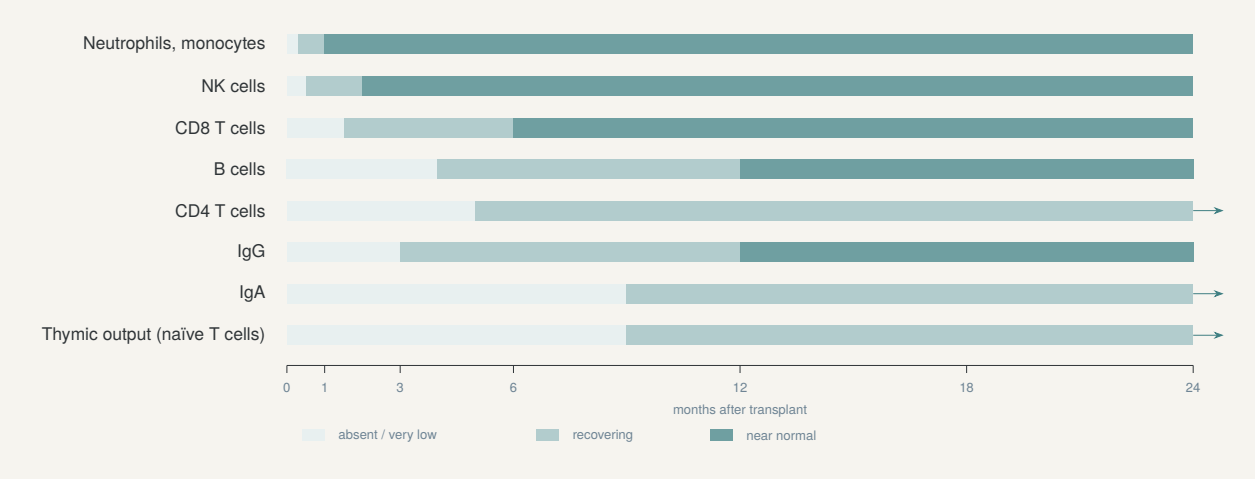


Figure 35: Approximate immune reconstitution after allogeneic transplant without major complications [34]. ATG, T-cell depletion, cord blood, GVHD and older age slow every bar.

29.1 The sequence

Component	Approximate recovery after allogeneic transplant	Notes
Neutrophils, monocytes	2–4 weeks	Monocytes first
NK cells	1–2 months	Early NK cells (CD56bright) are less cytotoxic; NK recovery helps control CMV early
CD8 T cells	2–6 months (numbers)	Mainly expansion of donor memory T cells (peripheral expansion); CMV reactivation drives large CMV-specific CD8 expansions
CD4 T cells	6–12 months to $> 200/\mu$L; years to normal	Needs thymic output for diversity; slowest in older patients, after ATG/alemtuzumab, T-depletion, cord blood, and with GVHD
B cells	6–12 months (longer after rituximab or with chronic GVHD)	Naïve, transitional B cells first; class-switched memory B cells late
IgG	Lowest about 3–4 months (as recipient plasma cells die)	Recovery months later
IgA	Last — often years	Mucosal infections
Thymic output (TRECs)	1–2 years or longer; may never fully recover in older adults	Determines T-cell repertoire diversity

29.2 Two pathways of T-cell recovery

1. **Thymus-independent:** mature donor T cells in the graft expand in the lymphopenic host (homeostatic and antigen-driven). This gives early protection — including donor memory T cells against viruses the donor has met — but a narrow repertoire. T-cell depletion and ATG remove many of these cells.
2. **Thymus-dependent:** new naïve T cells from donor stem cells pass through the recipient thymus. This restores diversity but is slow and age-dependent, and is impaired by conditioning and GVHD.

29.3 Factors that slow immune recovery

- ATG, alemtuzumab, ex vivo T-cell depletion
- Cord blood grafts (naïve cells, no donor viral memory)
- HLA-mismatched and haploidentical donors
- GVHD and its treatment
- Older recipient age (thymic involution)
- Viral infections (CMV, HHV-6) and some antivirals (ganciclovir marrow toxicity)
- Rituximab and other B-cell-depleting treatment after transplant

29.4 Monitoring

- Lymphocyte subsets (CD4, CD8, CD19, NK) at about 3, 6, 12 months guide *Pneumocystis* and antiviral prophylaxis duration and the timing of live vaccines.
- **CMV-specific T-cell assays** (interferon-γ release or intracellular cytokine staining) help predict who will control CMV after stopping prophylaxis, in centres that use them.
- Immunoglobulin levels guide replacement therapy.

Chapter 30 — Infections after transplantation: the framework

30.1 Timeline of infection risk

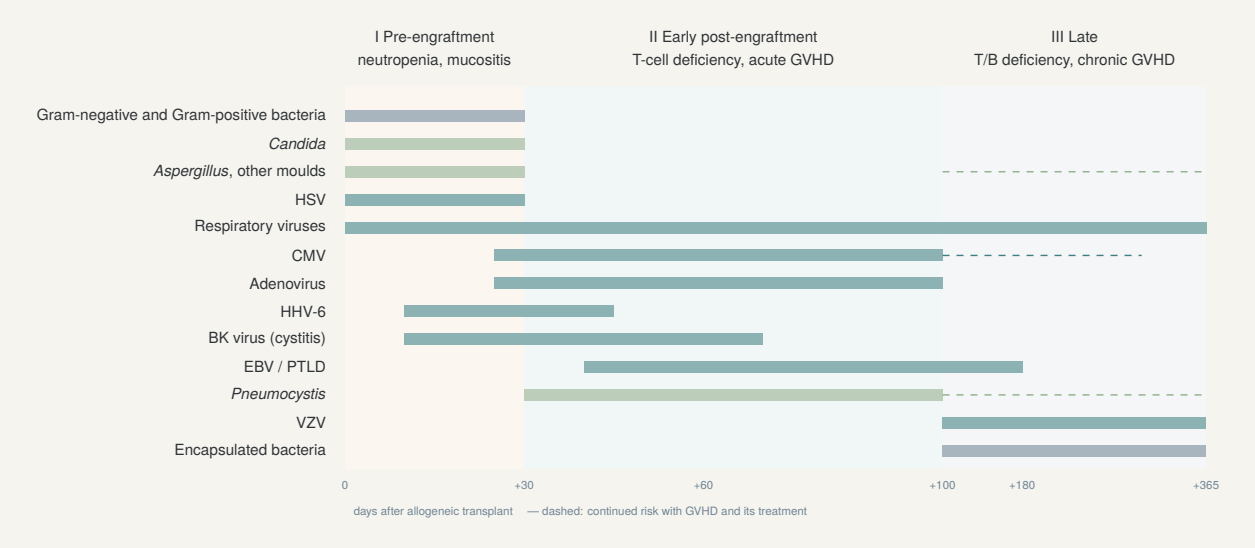


Figure 36: Phases of infection risk after allogeneic transplantation (after Tomblyn et al. [35]). Solid bars show peak periods; dashed lines show ongoing risk with GVHD.

Infections after allogeneic transplant follow a predictable sequence determined by the immune defects of each period [35]:

Phase	Main immune defects	Typical infections
I — Pre-engraftment (day 0 to about +30)	Neutropenia, mucositis, central lines	Bacteraemia (Gram-negative rods, viridans streptococci, CoNS), *Candida*, early *Aspergillus*, **HSV**, community respiratory viruses
II — Early post-engraftment (about +30 to +100)	Severe T-cell deficiency; acute GVHD and steroids	**CMV**, **adenovirus**, **HHV-6**, **EBV** (PTLD), **BK virus** (haemorrhagic cystitis), respiratory viruses, *Pneumocystis*, *Aspergillus*, *Toxoplasma*
III — Late (beyond +100)	Slow T- and B-cell recovery; chronic GVHD, hyposplenism, hypogammaglobulinaemia	**VZV**, late CMV, EBV PTLD, encapsulated bacteria (pneumococcus), moulds, respiratory viruses, *Pneumocystis* if prophylaxis stopped

After **autologous** transplant, phase I is similar but shorter, and later infections are mainly VZV, respiratory viruses, and (less often) CMV in heavily pretreated patients or after CD34-selected grafts.

Modifiers: GVHD and steroids, cord blood, haplo with PTCy (BK, HHV-6, CMV), ATG/alemtuzumab (CMV, adenovirus, EBV), T-cell depletion, older age, CMV serostatus, prior infections, and geographic exposures (TB, *Strongyloides*, endemic fungi).

30.2 Standard prophylaxis after allogeneic transplant

Target	Agent (typical)	Duration (typical)
HSV and VZV	Aciclovir or valaciclovir	At least 1 year, and while on immunosuppression

Target	Agent (typical)	Duration (typical)
CMV (seropositive recipients)	**Letermovir** [38]	From day 0–28 to day +100; extended to day +200 in high-risk patients
Yeasts and moulds	Fluconazole pre-engraftment in low mould risk; **posaconazole** (or voriconazole) when mould risk high (AML/MDS, GVHD on steroids)	Until engraftment / during GVHD treatment
Pneumocystis	**Cotrimoxazole** (alternatives: atovaquone, dapsone, pentamidine) [45]	From engraftment for at least 6 months and while on immunosuppression
Toxoplasma (seropositive recipients)	Cotrimoxazole (if tolerated) or PCR monitoring	As for *Pneumocystis*
Encapsulated bacteria	Penicillin V (or alternative)	During chronic GVHD treatment
HBV	Entecavir/tenofovir for HBsAg+ or anti-HBc+ recipients	Usually $\geq$ 12 months after stopping immunosuppression
Hypogammaglobulinaemia	Immunoglobulin replacement	Selected patients with low IgG and infections
Strongyloides	Ivermectin before transplant if seropositive or exposed	Pre-transplant

30.3 Monitoring strategies

- **Viral load monitoring** (usually weekly to day +100, then less often while immunosuppressed): CMV (all R+ or D+/R−, even on letermovir in many centres), EBV (high-risk: ATG, T-depletion, haplo, cord, mismatch), adenovirus (paediatric and high-risk adults: blood and stool).
- **Fungal biomarkers:** serum galactomannan in patients not on mould-active prophylaxis.
- **Symptom-driven testing:** respiratory multiplex PCR, BAL with comprehensive viral, fungal and bacterial testing, stool viral panels, CSF PCR (HHV-6, HSV, VZV, JC, *Toxoplasma*, CMV, EBV), blood PCR for HHV-6, parvovirus B19 or HEV in unexplained cytopenias or hepatitis.

Chapter 31 — Cytomegalovirus after transplantation

CMV is the most important viral infection after allogeneic transplant. It causes disease directly and has "indirect" effects — marrow suppression, bacterial and fungal superinfection, GVHD interactions and increased non-relapse mortality [36,37].

31.1 Risk

Donor/recipient serostatus	Risk after allogeneic transplant
D−/R−	Very low (primary infection only via blood products — prevented by leucodepleted or CMV-negative products)
D+/R−	Low to moderate (primary infection from graft)
D+/R+	High (reactivation of recipient virus; donor immunity may help)
D−/R+	**Highest** — recipient virus reactivates with no donor CMV-specific immunity

Additional risk factors: haplo, MMUD and cord blood donors; ATG and alemtuzumab; T-cell depletion; GVHD and steroids; PTCy (early reactivation).

31.2 Definitions [36]

- **CMV infection:** detection of CMV (DNA in blood, antigen, culture).
- **Clinically significant CMV infection (csCMVi):** CMV disease, or viraemia leading to pre-emptive treatment.
- **CMV disease:** end-organ disease with symptoms plus CMV in tissue (histology/IHC, culture, or, for pneumonia, BAL PCR with thresholds and clinical context): pneumonia, gastrointestinal disease, hepatitis, retinitis, encephalitis, nephritis, cystitis, myocarditis.
- **Refractory CMV infection:** CMV DNA increases more than 1 $\log_{10}$ after at least 2 weeks of appropriately dosed antiviral therapy (probable refractory: persistent viral load at the same level).
- **Resistant CMV:** refractory infection with a genetic mutation conferring resistance (UL97, UL54, UL56/UL89).

31.3 Prevention

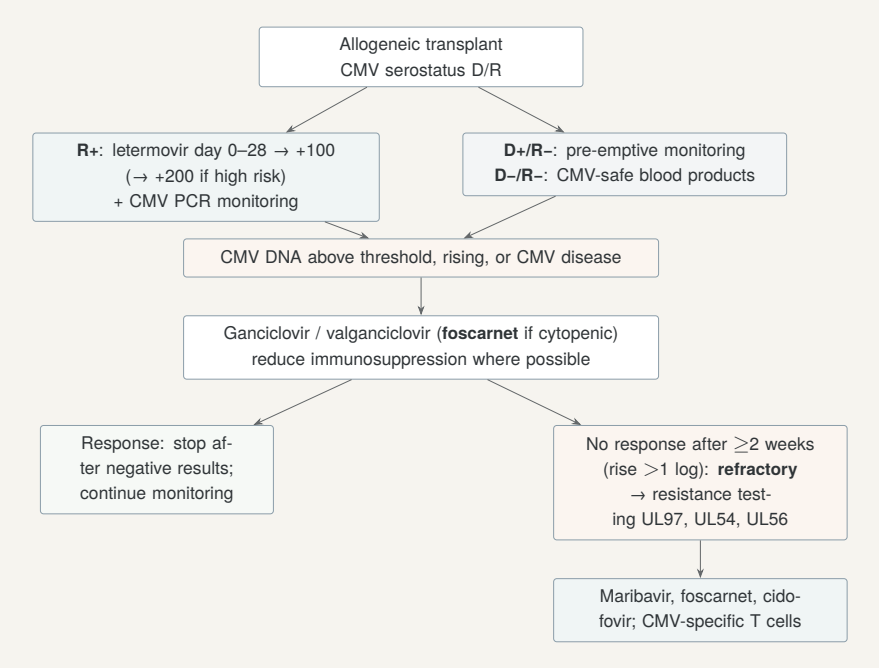


Figure 37: A simplified CMV pathway after allogeneic transplant (after ECIL-7 [37] and the letermovir and maribavir trials [38,39]). Thresholds and choices are centre-specific.

- **Letermovir prophylaxis** (terminase complex inhibitor, oral or IV) for CMV-seropositive recipients from day 0 to +28 until day +100: in the pivotal trial it reduced clinically significant CMV infection at week 24 (about 38% vs 61%) and all-cause mortality at week 24 [38]. Extension to day +200 reduces late CMV in high-risk patients. Letermovir does **not** cause marrow suppression and does **not** cover HSV/VZV (aciclovir continues).
- **Low-level DNAemia on letermovir** ("blips") is common and often reflects abortive infection or non-infectious DNA; many centres do not treat low, stable levels without symptoms. Interpret with the same assay over time.
- **Late CMV** after stopping letermovir (between day +100 and +200) occurs in a minority, particularly with GVHD or steroids — monitoring continues after prophylaxis ends.
- **Pre-emptive therapy** (the older standard, still used where letermovir is not given or for D+/R−): weekly CMV PCR, treatment when the viral load crosses a centre-specific threshold or rises rapidly.
- **CMV-specific cell-mediated immunity assays** can help decide when to stop prophylaxis or monitoring.

31.4 Treatment

Drug	Mechanism	Main toxicity	Notes
Ganciclovir (IV) / valganciclovir (oral)	UL97 phosphorylation → polymerase (UL54) inhibition	**Myelosuppression** (neutropenia)	First-line; avoid or use with care before engraftment and in poor graft function
Foscarnet	Direct polymerase inhibitor	**Nephrotoxicity**, electrolyte loss (Mg, K, Ca, PO_4), genital ulcers, seizures	Preferred when marrow is fragile; ganciclovir resistance

Drug	Mechanism	Main toxicity	Notes
Cidofovir	Nucleotide polymerase inhibitor	**Nephrotoxicity** (with probenecid and hydration), neutropenia	Third line; also used for adenovirus and BK
Maribavir	UL97 kinase inhibitor	Taste disturbance; antagonises ganciclovir	For refractory/resistant CMV: higher viraemia clearance at week 8 than investigator-assigned therapy (about 56% vs 24%) in the SOLSTICE trial [39]; not for CNS disease
Letermovir (treatment)	Terminase inhibitor		Not established as treatment; low barrier to resistance (UL56)
CMV-specific T cells	Adoptive immunotherapy		Refractory cases; donor-derived or third-party banked cells
Immunoglobulin (CMV-specific or standard)	Antibody		Sometimes added for CMV pneumonia; evidence limited

Practical points

- Typical pre-emptive course: induction-dose therapy for at least 2 weeks and until the viral load is below threshold (often two consecutive results), then stop or maintenance.
- **Reduce immunosuppression** where possible — the most effective "antiviral".
- **Resistance testing** (UL97, UL54, UL56) when viral load rises after $\geq$ 2 weeks of adequate therapy.
- **CMV pneumonia** carries high mortality; diagnosis requires BAL with CMV testing and exclusion of other causes; HRCT shows ground-glass and nodular changes.
- **CMV gastrointestinal disease** can occur **without viraemia** — biopsy is essential when GVHD and CMV are both possible.

Chapter 32 — EBV and post-transplant lymphoproliferative disorder

32.1 What happens

- EBV persists latently in B cells, controlled by EBV-specific cytotoxic T cells. When T-cell immunity is profoundly suppressed early after transplant, EBV-infected B cells proliferate, producing **EBV DNAemia** and sometimes **PTLD** — a spectrum from polyclonal lymphoid hyperplasia to monoclonal lymphoma (mostly DLBCL-like) [40].
- After allogeneic transplant, PTLD is usually of **donor** B-cell origin and occurs mostly within the first 6 months.
- **Risk factors:** ATG or alemtuzumab, ex vivo T-cell depletion (especially selective T-cell depletion leaving B cells), HLA mismatch, haplo or cord blood donors, EBV-seronegative recipient with seropositive donor, splenectomy, second transplant.

32.2 Monitoring and pre-emptive treatment

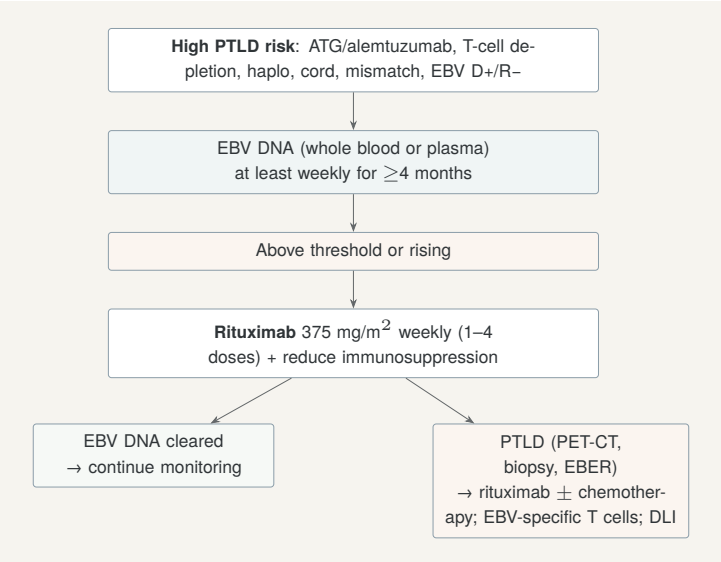


Figure 38: EBV monitoring and pre-emptive treatment after allogeneic transplant (after ECIL-6 [40]).

- **High-risk patients:** EBV DNA monitoring (whole blood or plasma — be consistent) at least weekly for at least 4 months [40].
- **Pre-emptive therapy:** at a centre-specific threshold or rising load, give **rituximab** (375 mg/m^2 weekly, usually 1–4 doses until EBV DNA is undetectable), with reduction of immunosuppression where possible. This has markedly reduced PTLD mortality.
- **Rituximab consequences:** B-cell depletion for months, hypogammaglobulinaemia, impaired vaccine responses, risk of HBV reactivation and enteroviral or norovirus persistence.

32.3 Diagnosis and treatment of established PTLD

- **Symptoms:** fever, lymphadenopathy, tonsillar enlargement, organ infiltration (liver, gut, CNS), rapidly rising EBV load; may mimic infection or GVHD.
- **Diagnosis:** PET-CT, tissue biopsy with histology, immunophenotype, clonality and **EBER in situ hybridisation**.
- **Treatment:** rituximab ± reduction of immunosuppression; chemotherapy (e.g. R-CHOP) if refractory; **EBV-specific cytotoxic T cells** (donor-derived, or third-party banked cells such as tabelecleucel, approved in Europe for relapsed/refractory EBV-positive PTLD); DLI (risk of GVHD).

Chapter 33 — Other viral infections after transplantation

33.1 Adenovirus

- **Who:** mostly children (endogenous reactivation from lymphoid tissue, plus community infection), and adults with T-cell depletion, haplo or cord transplants, or GVHD [44].
- **Spectrum:** asymptomatic shedding (stool), haemorrhagic cystitis, nephritis, enteritis/colitis, hepatitis, pneumonitis, encephalitis, and **disseminated disease** with high mortality.
- **Monitoring** in high-risk paediatric patients: weekly blood PCR (and stool PCR — high stool loads precede DNAemia).
- **Treatment:** reduction of immunosuppression; **cidofovir** (standard or weekly low-dose with probenecid), with renal monitoring; brincidofovir where available; **adenovirus-specific T cells**. Lymphocyte recovery is the strongest predictor of clearance.

33.2 HHV-6

- **Reactivation** (mostly HHV-6B) is detected in about 30–50% of allogeneic recipients in the first weeks, more often after cord blood transplant [41].
- **Disease: post-transplant acute limbic encephalitis** (confusion, short-term memory loss, seizures, SIADH; MRI changes in the medial temporal lobes), mainly 2–6 weeks after transplant and especially after cord blood; also delayed engraftment, marrow suppression, and possibly pneumonitis.
- **Diagnosis:** HHV-6 DNA in CSF with compatible clinical findings; plasma HHV-6 DNA supports. Exclude **inherited chromosomally integrated HHV-6** (about 1% of people; very high DNA levels in whole blood and tissues reflect integrated genomes, not infection — check donor and recipient).
- **Treatment:** foscarnet or ganciclovir; routine monitoring and pre-emptive therapy of asymptomatic DNAemia are not recommended [41].

33.3 BK polyomavirus and haemorrhagic cystitis

- BK virus is latent in the urothelium in most adults. After allogeneic transplant, viruria is very common; **BK virus-associated haemorrhagic cystitis (BKV-HC)** occurs in roughly 10–25%, typically weeks 2–8, more often after **haplo transplants with PTCy**, myeloablative conditioning, and with GVHD [43].
- **Diagnosis:** haematuria with painful voiding (cystitis) plus high-level BK viruria (usually > 7 $\log_{10}$ copies/mL); plasma BK DNAemia correlates with severity. **Early** haemorrhagic cystitis within 72 hours of cyclophosphamide is chemical (acrolein), not viral.
- **Grading:** I microscopic haematuria; II macroscopic; III macroscopic with clots; IV clots with urinary retention or renal impairment needing intervention.
- **Treatment:** supportive — hyperhydration, forced diuresis, analgesia, platelet support, continuous bladder irrigation for clots, urological procedures. **Cidofovir** (IV low dose or intravesical) has limited evidence; BK-specific T cells in trials. Reducing immunosuppression helps where possible.
- **BK nephropathy** (common after kidney transplant) is rare after HSCT but contributes to renal impairment.

33.4 Respiratory viruses

- RSV, influenza, parainfluenza (especially type 3), hMPV, rhinovirus, seasonal coronaviruses, adenovirus and SARS-CoV-2 cause upper respiratory infection that can progress to **lower respiratory tract disease** with high mortality, particularly early after transplant, with lymphopenia ($< 0.2 \times 10^9$/L), neutropenia, steroids, older age, or myeloablative conditioning [42].

- **Management:** testing by multiplex PCR; isolation; for RSV LRTI — ribavirin (oral or aerosolised) in selected patients; influenza — oseltamivir (prolonged courses and resistance monitoring in immunocompromised); SARS-CoV-2 — antivirals per current guidance, with interaction checks (nirmatrelvir–ritonavir with calcineurin inhibitors needs specialist pharmacy advice); immunoglobulin in selected cases.
- **Pre-transplant respiratory virus infection:** defer conditioning when possible.
- **Late effect:** respiratory virus LRTI is associated with later airflow obstruction and BOS.

33.5 Herpes simplex and varicella-zoster virus

- **HSV:** reactivation in most seropositive patients without prophylaxis, causing severe mucositis or oesophagitis; prevented by aciclovir.
- **VZV:** without prophylaxis, zoster occurs in about a quarter to a third of allogeneic recipients in the first years; **visceral disseminated VZV** can present with severe abdominal or back pain, hepatitis or SIADH **before** any rash — test blood for VZV DNA. Prophylaxis for at least 1 year (longer during immunosuppression); recombinant zoster vaccine after transplant.

33.6 Hepatitis viruses

- **HBV:** recipients with HBsAg or anti-HBc receive antiviral prophylaxis; reactivation after transplant can occur years later, especially when immunosuppression stops or with chronic GVHD treatment. Donors with HBV markers can transmit infection; HBV-immune donors can transfer protective immunity ("adoptive immunity transfer").
- **HCV:** treated with direct-acting antivirals before or after transplant; donor HCV infection is treated in the recipient.
- **HEV:** chronic hepatitis E is an under-recognised cause of unexplained hepatitis — test HEV RNA.

33.7 Other viruses

- **Parvovirus B19:** pure red cell aplasia or graft dysfunction; immunoglobulin treatment.
- **JC virus (PML):** rare; associated with prolonged immunosuppression and rituximab.
- **Norovirus, rotavirus, sapovirus, astrovirus:** chronic diarrhoea that mimics gut GVHD.
- **Enteroviruses:** respiratory disease; rare chronic meningoencephalitis in B-cell-depleted patients.
- **Measles, mumps:** risk in unvaccinated contacts; post-exposure immunoglobulin.

33.8 Virus-specific T cells

- **Concept:** transfer of T cells specific for CMV, EBV, adenovirus, BK, HHV-6 or others, either from the donor or from **banked third-party donors** partially HLA-matched to the patient.
- **Production:** expansion with viral antigens, or direct selection of virus-specific cells (e.g. by interferon-γ capture or multimers).
- **Use:** refractory CMV, EBV PTLD (tabelecleucel), adenovirus, BK haemorrhagic cystitis — mostly in specialist centres and trials. GVHD risk is low.

Chapter 34 — Bacterial, fungal and parasitic infections after transplantation

34.1 Bacteria

- **Pre-engraftment bacteraemia:** Gram-negative rods (*E. coli*, *Klebsiella*, *Pseudomonas*), viridans streptococci (mucositis), coagulase-negative staphylococci (lines), enterococci (including VRE). Rising antimicrobial resistance (ESBL, carbapenemase producers) shapes empirical therapy.
- ***C. difficile*** infection is common with antibiotics; diarrhoea differential includes GVHD and viruses.
- **Late:** pneumococcal sepsis (chronic GVHD, hyposplenism), *Nocardia*, *Listeria*, mycobacteria (tuberculosis reactivation in endemic settings; non-tuberculous mycobacteria in lines).

34.2 Fungi

Infection	Setting	Diagnosis	Notes
Candida bloodstream infection	Neutropenia, mucositis, lines	Blood cultures, β-D-glucan	Azole prophylaxis reduces incidence; *C. auris* emerging
Invasive aspergillosis	Neutropenia, GVHD on steroids	CT (nodules, halo sign), serum/BAL galactomannan, PCR	Mould-active prophylaxis in high risk; voriconazole or isavuconazole treatment
Mucormycosis	Prolonged neutropenia, steroids, diabetes, iron overload, voriconazole exposure	Tissue, PCR, CT (reversed halo)	Surgery + liposomal amphotericin B
Pneumocystis	Lymphopenia, steroids, no prophylaxis	BAL PCR, β-D-glucan	Cotrimoxazole prophylaxis prevents most cases
Fusarium, *Scedosporium*	Prolonged neutropenia	Blood cultures (*Fusarium*), skin lesions	Often azole-resistant

34.3 Parasites

- ***Toxoplasma gondii*** reactivation in seropositive allogeneic recipients (encephalitis, pneumonitis, myocarditis, disseminated) — cotrimoxazole prophylaxis or blood PCR monitoring.
- ***Strongyloides stercoralis*** hyperinfection with steroids — screen and treat with ivermectin before transplant in exposed patients.
- Malaria, *Leishmania*, *T. cruzi*: transmissible by donors; relevant to donor screening and to recipients from endemic areas.

Chapter 35 — Non-infectious complications

Many transplant complications look like infection. A virologist asked about a febrile patient with hepatitis, pneumonitis, cystitis, encephalopathy or diarrhoea must keep these in the differential diagnosis.

35.1 Sinusoidal obstruction syndrome / veno-occlusive disease (SOS/VOD)

- **What happens:** conditioning (busulfan, melphalan, TBI), and drugs such as inotuzumab and gemtuzumab, damage hepatic sinusoidal endothelium; cells and debris obstruct sinusoids, causing post-sinusoidal portal hypertension and liver failure.
- **Timing:** classically within 21 days of transplant; late-onset forms occur [27].
- **EBMT criteria for adults (classical):** within 21 days, bilirubin ≥ 2 mg/dL (≥ 34 μmol/L) plus two of: painful hepatomegaly, weight gain $> 5\%$, ascites [27]. Ultrasound may show hepatomegaly, ascites, gallbladder wall thickening and reversed portal flow.
- **Severity** graded mild to very severe by bilirubin trajectory, renal function, weight gain and organ failure.
- **Prevention:** ursodeoxycholic acid; busulfan level targeting; avoidance of hepatotoxic drugs; defibrotide prophylaxis in high-risk children.
- **Treatment: defibrotide**; fluid and sodium restriction, diuretics, paracentesis; organ support.
- **Infection relevance:** distinguish from viral hepatitis (HBV, HEV, adenovirus, HSV, VZV), drug toxicity (azoles, cotrimoxazole) and GVHD of the liver.

35.2 Transplant-associated thrombotic microangiopathy (TA-TMA)

- Endothelial injury with complement activation $\rightarrow$ microangiopathic haemolysis, thrombocytopenia and organ damage (kidney, gut, lungs, brain, serosa) [28].
- **Triggers:** calcineurin inhibitors and sirolimus, conditioning (TBI, busulfan), GVHD, and **infections — CMV, adenovirus, HHV-6, BK, and bacterial or fungal sepsis**.
- **Features:** rising LDH, schistocytes, falling haptoglobin, transfusion-refractory thrombocytopenia, hypertension, **proteinuria** (an early marker), raised serum terminal complement (sC5b-9).
- **Treatment:** remove triggers (switch calcineurin inhibitor), treat infections and GVHD, control hypertension; complement blockade (eculizumab, ravulizumab) for high-risk disease.

35.3 Engraftment syndrome

- **Spitzer criteria [26]:** within 96 hours of neutrophil engraftment — major: fever ≥ 38.3 °C without identifiable infection, erythrodermatous rash $> 25\%$ body surface, non-cardiogenic pulmonary oedema (hypoxia, infiltrates); minor: hepatic dysfunction, renal insufficiency, weight gain $> 2.5\%$, transient encephalopathy. Diagnosis needs 3 major or 2 major + 1 minor.
- Commoner after autologous transplant and with G-CSF; responds quickly to steroids.
- **Pre-engraftment syndrome** (cord blood) is similar.
- Infection must be excluded first — fever and pulmonary infiltrates at engraftment overlap with bacterial, fungal and viral pneumonia.

35.4 Pulmonary complications

Complication	Timing	Features	Notes
Idiopathic pneumonia syndrome (IPS)	Days to weeks	Diffuse infiltrates, hypoxia, no infection found	**Diagnosis of exclusion — BAL with comprehensive testing**: bacterial, fungal, *Pneumocystis*, CMV, HHV-6, adenovirus, respiratory virus multiplex PCR; treated with steroids ± etanercept
Diffuse alveolar haemorrhage	Early	Progressively bloodier BAL returns, hypoxia	High-dose steroids; high mortality
Peri-engraftment respiratory distress	Around engraftment	Capillary leak	Overlaps with engraftment syndrome
Fluid overload, cardiac failure	Any		Echocardiogram, diuretics
Bronchiolitis obliterans syndrome	Months to years	Fixed airflow obstruction	Chronic GVHD of the lung; respiratory viruses can precipitate
Organising pneumonia	Months	Patchy consolidation	Responds to steroids

35.5 Haemorrhagic cystitis

- **Early (within 72 hours of conditioning):** chemical — acrolein from cyclophosphamide/ifosfamide; prevented by mesna and hyperhydration.
- **Late (weeks 2–8 and beyond):** viral — **BK virus** mostly; also adenovirus, occasionally CMV (Chapter 33.3).

35.6 Neurological complications

- **Posterior reversible encephalopathy syndrome (PRES):** headache, confusion, seizures, visual disturbance; hypertension; MRI shows posterior white matter oedema; associated with calcineurin inhibitors.
- **Infections:** HHV-6 encephalitis, *Toxoplasma*, fungal abscesses, PML, VZV vasculopathy, CMV (rare).
- **Drug toxicity:** busulfan seizures, high-dose cytarabine cerebellar syndrome, ifosfamide encephalopathy, foscarnet-related electrolyte disturbance and seizures, CAR-T ICANS.
- **Metabolic:** hyponatraemia (SIADH — HHV-6, VZV), hypomagnesaemia, uraemia, liver failure, Wernicke encephalopathy.

35.7 Kidney and metabolic complications

- Acute kidney injury from nephrotoxic drugs (calcineurin inhibitors, aminoglycosides, vancomycin, amphotericin, **foscarnet, cidofovir**), sepsis, SOS/VOD (hepatorenal), TA-TMA, BK nephropathy.
- Hypomagnesaemia and hypokalaemia (calcineurin inhibitors, foscarnet, amphotericin, diarrhoea).
- Hyperglycaemia (steroids, tacrolimus).

Chapter 36 — Relapse, measurable residual disease and its management

Relapse is the most common cause of death after allogeneic transplant for malignancy.

36.1 Monitoring

- **MRD** by flow cytometry or molecular methods (*NPM1*, *BCR::ABL1*, fusion transcripts, NGS for patient-specific mutations), commonly at day +30, +100, and periodically.
- **Chimerism** (Chapter 25.3), especially lineage-specific.
- Marrow examinations at standard time points.

36.2 Strategies

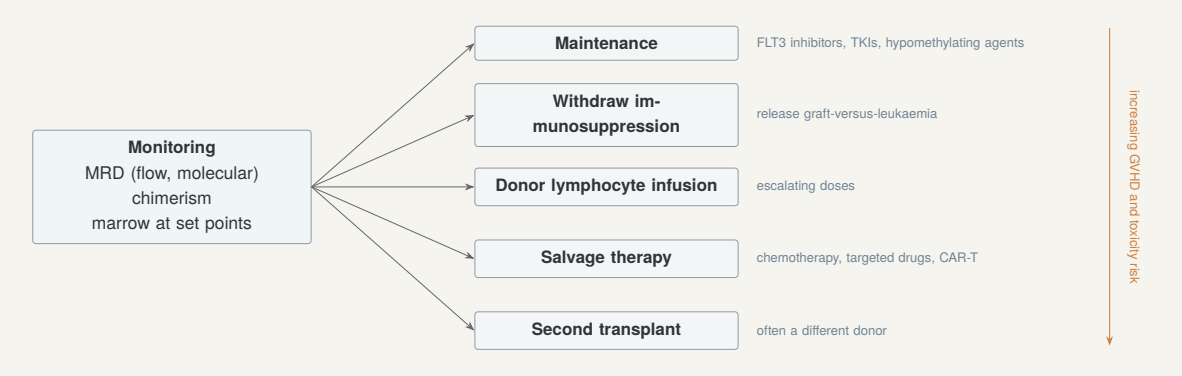


Figure 39: Strategies against relapse after allogeneic transplant.

- **Maintenance therapy** after transplant: FLT3 inhibitors (sorafenib, gilteritinib) for *FLT3*-mutated AML; TKIs for Ph-positive ALL and CML; hypomethylating agents; lenalidomide (myeloma, after autologous transplant).
- **Withdrawal of immunosuppression** to release GVL.
- **Donor lymphocyte infusion (DLI):** donor T cells given in escalating doses (e.g. starting around 10^5–10^6 CD3+ cells/kg, depending on donor type and timing) for mixed chimerism, MRD or relapse; most effective in CML and slower-growing disease; **risk of GVHD and marrow aplasia**.
- **Salvage therapy and second transplant** — sometimes with a different donor.
- **Immune escape:** after haploidentical or mismatched transplant, leukaemia can relapse by **losing the mismatched HLA haplotype** (genomic HLA loss), making it invisible to donor T cells — a different donor is then needed. Down-regulation of HLA class II is another escape mechanism.

Chapter 37 — Long-term follow-up, late effects and revaccination

37.1 Late effects

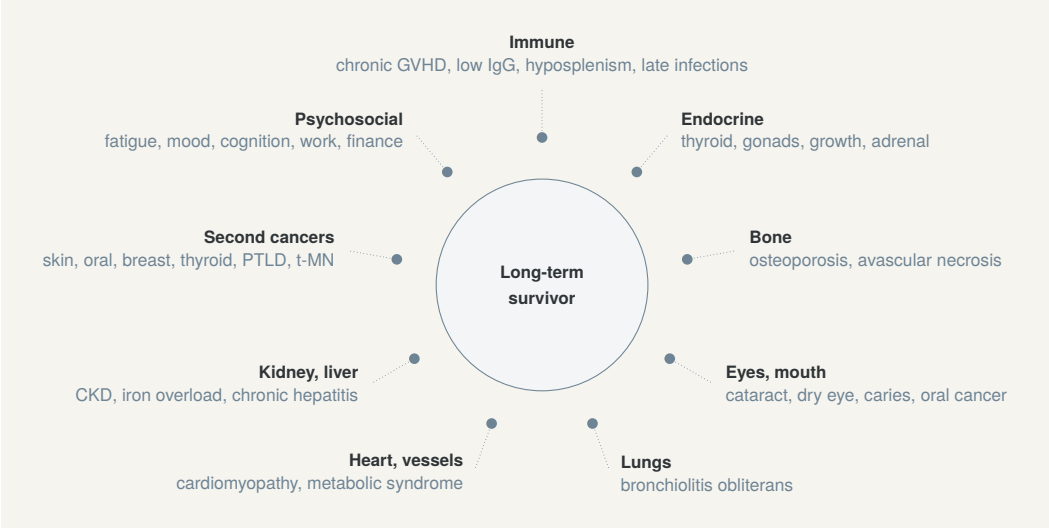


Figure 40: Late effects after transplantation that long-term follow-up screens for [47].

System	Late effects	Typical screening [47]
Immune	Chronic GVHD, hypogammaglobulinaemia, hyposplenism, late infections	Clinical review, immunoglobulins, vaccination status
Endocrine	Hypothyroidism, hypogonadism, infertility, growth failure in children, adrenal insufficiency after steroids, diabetes	Thyroid and gonadal function; growth monitoring
Bone	Osteoporosis, avascular necrosis (steroids)	Bone density, vitamin D
Eyes	Cataracts (TBI, steroids), dry eyes (chronic GVHD)	Annual eye review
Mouth	Xerostomia, dental caries, oral cancer risk	Dental review
Lungs	Bronchiolitis obliterans, restrictive disease	Pulmonary function tests
Heart and vessels	Cardiomyopathy (anthracyclines), hypertension, dyslipidaemia, metabolic syndrome, premature vascular disease	Blood pressure, lipids, glucose; echocardiogram when indicated
Kidney	Chronic kidney disease	Creatinine, urine protein
Liver	Iron overload, chronic hepatitis (HBV, HCV, HEV), GVHD	Liver tests, ferritin
Second cancers	Skin, oral and oesophageal squamous cancers (chronic GVHD), breast and thyroid (TBI), therapy-related myeloid neoplasms (after autologous transplant), PTLD	Skin checks, cancer screening programmes
Psychosocial	Fatigue, depression, anxiety, cognitive change, return to work, financial burden	Regular assessment and support

37.2 Revaccination after transplant

Transplant recipients lose protective immunity from previous vaccines and infections and must be revaccinated as if never immunised [46,18]. A typical schedule after allogeneic (and autologous) transplant:

Vaccine	When to start (typical)	Notes
Pneumococcal conjugate (PCV13/15/20)	3 months	3 doses 1 month apart, then a fourth dose (conjugate or polysaccharide, by product and guideline)
Influenza (inactivated)	3–6 months; annually	A second dose if given very early; vaccinate household contacts
COVID-19	3 months	Primary series and boosters per current guidance
Tetanus, diphtheria, pertussis, *Haemophilus influenzae* type b, inactivated polio	6 months	3 doses
Hepatitis B	6 months	Check response; higher-dose or repeat series if needed
Meningococcal (conjugate, B)	6–12 months	Per local guidance; especially with hyposplenism
HPV	6–12 months	Per age guidance
Recombinant zoster vaccine (non-live)	From about 2–12 months depending on transplant type and guidance	Two doses
Live vaccines (MMR; varicella)	$\geq$ **24 months**, only if no active GVHD, off immunosuppression for ≥ 1 year, and ≥ 8 months after last immunoglobulin dose (the "2–1–8 rule")	Contraindicated otherwise; live zoster, yellow fever and BCG generally avoided or need specialist advice

After CAR-T and bispecific antibodies: inactivated vaccines from about 3–6 months (responses often poor while B cells are absent); live vaccines only after immune recovery and specialist review.

37.3 Survivorship care

- Long-term follow-up clinics coordinate late-effect screening, vaccination, mental health, fertility and return-to-work support.
- Patients carry treatment summaries ("transplant passports") with their transplant type, donor, conditioning, GVHD history and vaccination record — useful information for any infection consultation.

Chapter 38 — The transplant unit: a practical guide

38.1 A day-by-day map of an allogeneic transplant

Day	What happens to the patient	What the team watches	Virology relevance
−14 to −8	Admission, line insertion, baseline tests	Fitness, infection screen	Baseline serology, respiratory virus PCR if symptomatic, CMV/EBV/HHV-6 baseline in some centres
−7 to −1	Conditioning (± TBI, ± ATG); start CNI; start prophylaxis	Nausea, seizures (busulfan), fluid balance, drug levels	Aciclovir starts; ATG fever and rigors
0	Stem cell infusion	Infusion reactions	Graft microbiology results
+1 to +6	Methotrexate or PTCy (days +3, +4); mucositis begins	Mouth, gut, electrolytes, renal function	HSV mucositis prevention; early BK viruria after PTCy
+5 to +14	Deepest aplasia; febrile neutropenia; transfusions; TPN	Cultures, sepsis, SOS/VOD signs	Respiratory virus testing; CMV PCR weekly from engraftment (or earlier per protocol)
+14 to +28	Engraftment; possible engraftment syndrome, early acute GVHD	Counts, rash, diarrhoea, liver tests	HHV-6 (encephalitis), early CMV, BK haemorrhagic cystitis
+21 to +35	Discharge when eating, counts stable, no fever, oral drugs tolerated	Outpatient review 2–3 times a week	
+30	Marrow and chimerism (often)	Disease and graft assessment	
+30 to +100	Outpatient; CNI levels; GVHD watch; CMV/EBV/adenovirus monitoring	Acute GVHD, infections, TA-TMA, renal function	The peak period for CMV, adenovirus, EBV, BK, *Pneumocystis*
+100	Restaging, chimerism, immune assessment; letermovir usually stops	Decisions on immunosuppression taper	Late CMV risk; continue monitoring if GVHD
+100 to +365	Taper immunosuppression; chronic GVHD may appear; revaccination starts	Chronic GVHD, relapse	VZV, late CMV, EBV PTLD, respiratory viruses
> 1 year	Long-term follow-up	Late effects	Live vaccines when criteria met

38.2 Reading a transplant patient's notes

A typical summary line looks like: *"Day +45 post 10/10 MUD alloHSCT (PBSC) for AML CR1, FluBu2 RIC with ATG, GVHD prophylaxis ciclosporin/MMF; CMV D−/R+ on letermovir; skin aGVHD stage 2 (grade I) on topical steroids; ciclosporin level 180."*

Decoding it:

- **Day +45** — 45 days after stem cell infusion (early post-engraftment phase).
- **10/10 MUD** — matched unrelated donor at HLA-A, -B, -C, -DRB1, -DQB1.
- **PBSC** — peripheral blood stem cells.
- **AML CR1** — first complete remission of AML.
- **FluBu2 RIC with ATG** — reduced-intensity fludarabine + 2 days busulfan; ATG for in vivo T-cell depletion (→ slower viral immunity, EBV risk).
- **CMV D−/R+** — highest CMV risk group; letermovir prophylaxis.

- **Skin aGVHD stage 2, grade I** — limited skin GVHD, no systemic steroids yet.
- **Ciclosporin level 180** — therapeutic drug monitoring (μg/L).

38.3 Questions transplant physicians commonly ask the virologist

- Is this CMV DNAemia significant, and should we treat or watch (on letermovir, after letermovir, or during GVHD)?
- Is the CMV rising because of resistance or because of immunosuppression? Which antiviral is safest for the marrow and kidney?
- Is this rash, diarrhoea, hepatitis or pneumonitis viral, GVHD, drug-related — or more than one?
- Is this HHV-6 result infection or chromosomal integration?
- Can we start conditioning with a respiratory virus detected?
- When can we stop aciclovir, letermovir or HBV prophylaxis?
- Does this donor's serology (CMV, HBV, HTLV, region-specific infections) affect donor choice?
- What is the safest timing for vaccines after transplant, CAR-T or rituximab?

38.4 Principles to keep in mind

- **Immunosuppression is the dominant variable.** Every result means something different at day +20 on steroids than at day +300 off treatment.
- **More than one process is common.** GVHD and CMV, drug toxicity and infection, relapse and infection often coexist.
- **Trends matter more than single values** for viral loads, drug levels, and chimerism.
- **The patient's donor, graft and conditioning predict their infections** — read the summary line first.

Appendix A — Abbreviations

Abbreviation	Meaning
aGVHD / cGVHD	Acute / chronic graft-versus-host disease
ALC / ANC	Absolute lymphocyte / neutrophil count
ATG	Anti-thymocyte globulin
BOS	Bronchiolitis obliterans syndrome
CAR-T	Chimeric antigen receptor T cells
CNI	Calcineurin inhibitor (ciclosporin, tacrolimus)
CR1, CR2	First, second complete remission
CRS	Cytokine release syndrome
csCMVi	Clinically significant CMV infection
D/R	Donor/recipient (serostatus)
DLI	Donor lymphocyte infusion
DSA	Donor-specific (anti-HLA) antibodies
ECP	Extracorporeal photopheresis
GVL / GVT	Graft-versus-leukaemia / graft-versus-tumour effect
HCT-CI	Haematopoietic cell transplantation comorbidity index
HSCT / HCT	Haematopoietic stem cell / cell transplantation
ICANS	Immune effector cell-associated neurotoxicity syndrome
IPS	Idiopathic pneumonia syndrome
MAC / RIC / NMA	Myeloablative / reduced-intensity / non-myeloablative conditioning
MMF	Mycophenolate mofetil
MRD	Measurable (minimal) residual disease
MSD / MUD / MMUD	Matched sibling / matched unrelated / mismatched unrelated donor
NRM	Non-relapse mortality
PBSC	Peripheral blood stem cells
PTCy	Post-transplant cyclophosphamide
PTLD	Post-transplant lymphoproliferative disorder
SOS/VOD	Sinusoidal obstruction syndrome / veno-occlusive disease
TA-TMA	Transplant-associated thrombotic microangiopathy
TBI	Total body irradiation
TKI	Tyrosine kinase inhibitor
TRM	Transplant-related mortality
VST	Virus-specific T cells

Appendix B — Key laboratory values in oncology and transplant care

Measure	Typical threshold or range	Meaning in practice
Neutrophils	$< 0.5 \times 10^9$/L	Severe neutropenia — febrile neutropenia pathway
Neutrophil engraftment	$\geq 0.5 \times 10^9$/L for 3 days	Engrafted
Platelets	$< 10 \times 10^9$/L	Prophylactic transfusion
CD4 count	$< 200/\mu$L	*Pneumocystis* risk; continue prophylaxis
IgG	< 4 g/L with infections	Consider immunoglobulin replacement
Bilirubin	≥ 34 μmol/L (2 mg/dL) early after transplant	SOS/VOD or liver GVHD work-up
Tacrolimus trough	About 5–15 μg/L (centre-specific)	Therapeutic range for GVHD prophylaxis
Ciclosporin trough	About 100–300 μg/L (centre-specific)	Therapeutic range
Ferritin	Very high (e.g. $>$ 10,000 μg/L)	HLH, IEC-HS, iron overload
LDH, haptoglobin, schistocytes, urine protein	Rising LDH, low haptoglobin, schistocytes, proteinuria	TA-TMA screen

Appendix C — Drug glossary for the virologist

Drug	Class	Relevance
Aciclovir / valaciclovir	Antiviral	HSV/VZV prophylaxis
Letermovir	CMV terminase inhibitor	CMV prophylaxis; raises CNI levels
Ganciclovir / valganciclovir	CMV polymerase inhibitor	Myelosuppression
Foscarnet	Pyrophosphate analogue	Nephrotoxicity, electrolytes
Cidofovir	Nucleotide analogue	Nephrotoxicity; CMV, adenovirus, BK
Maribavir	UL97 inhibitor	Refractory/resistant CMV
Entecavir / tenofovir	HBV antivirals	Prophylaxis of HBV reactivation
Posaconazole / voriconazole / isavuconazole	Triazole antifungals	CYP3A inhibition raises CNI, sirolimus, venetoclax, vincristine levels
Cotrimoxazole	Antibacterial	*Pneumocystis* and *Toxoplasma* prophylaxis; marrow suppression, hyperkalaemia
Ciclosporin / tacrolimus	Calcineurin inhibitors	GVHD prophylaxis; nephrotoxicity; interactions
Mycophenolate	Antiproliferative	Viral infections; marrow suppression
Sirolimus	mTOR inhibitor	GVHD prophylaxis; interactions
Ruxolitinib	JAK1/2 inhibitor	Steroid-refractory GVHD, myelofibrosis; viral reactivation
Rituximab	Anti-CD20	PTLD, lymphoma; HBV reactivation, PML
ATG / alemtuzumab	Lymphocyte-depleting antibodies	Delay antiviral immunity
Cyclophosphamide (PTCy)	Alkylating agent	Haemorrhagic cystitis; BK and HHV-6 association
Defibrotide	Endothelial protectant	SOS/VOD treatment
Tocilizumab	Anti-IL-6 receptor	CRS after CAR-T

Appendix D — Grading systems at a glance

System	What it grades	Reference
MAGIC criteria	Acute GVHD (organ stage and overall grade)	[30]
NIH 2014 consensus	Chronic GVHD (organ scores, global severity)	[33]
ASTCT consensus	CRS and ICANS after CAR-T	[13]
EBMT criteria	SOS/VOD diagnosis and severity	[27]
Jodele criteria	TA-TMA	[28]
Spitzer criteria	Engraftment syndrome	[26]
CMV definitions (Ljungman)	CMV infection and disease	[36]
HCT-CI	Comorbidity before transplant	[21]
ELN 2022	AML genetic risk	[6]
ECOG / Karnofsky	Performance status	Chapter 4

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