Immununosuppression: An Overview

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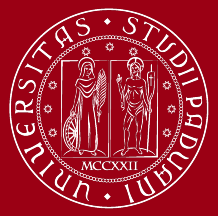


Introduction & Epidemiology

The growing population of immunocompromised hosts

- **Estimated 5-6% of the Italian population** is immunocompromised (Martinson and Lapham, 2024)
- **1%** of children fall into cohort of immunocompromised (VERDI project)
- **2.8%** meet criteria for drug-induced immunosuppression (Wallace et al., 2021)

What causes immunocompromise?

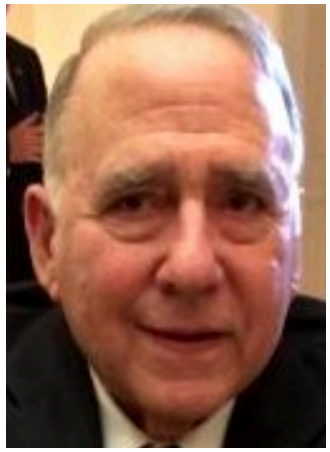
Major categories:

- Active treatment for malignancies
- Solid organ transplant (SOT)
- Hematopoietic cell transplant (HCT)
- CAR-T cell therapy
- Primary immunodeficiency
- Advanced HIV infection
- High-dose corticosteroids & biologics

The net state of immunosuppression

Defining net state of immunosuppression

A concept by Dr. Robert Rubin (MGH Boston):



“Composite of host factors, underlying disease, treatment, and other factors contributing to infection risk”

“Every organ in the human body is interesting….but becomes more interesting when infected”

This remains one of the most useful conceptual frameworks for thinking about infection risk in immunocompromised patients. It

Components of the “net immunosuppresed state”

Host Factors

- Advanced age
- Malnutrition
- Diabetes
- Organ dysfunction
- Hypogammaglobulinemia

Treatment Factors

- Immunosuppressive drugs
- Chemotherapy
- Radiation
- Surgery/hardware
- Duration of therapy

Components (continued)

Underlying Disease

- Autoimmune disease
- Malignancy type
- Organ failure stage

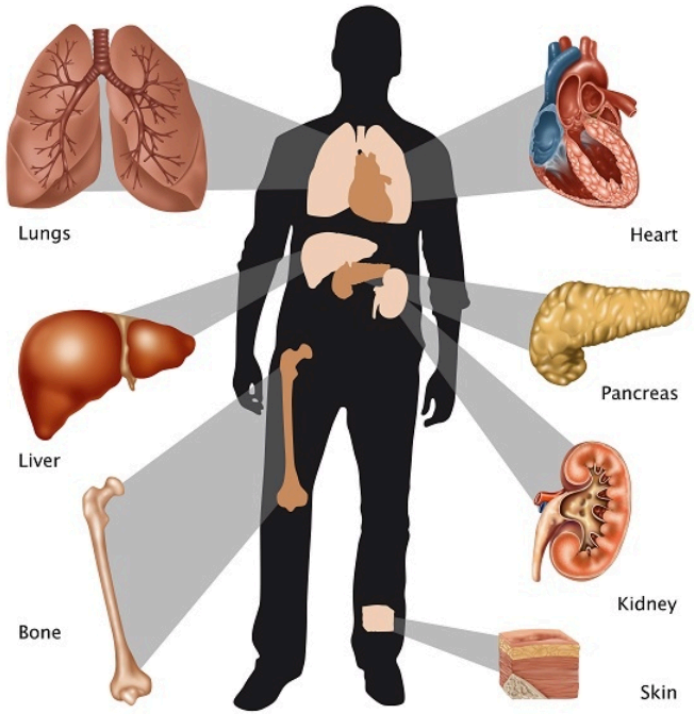
Infectious Factors

- HIV, CMV, EBV status
- Microbiome alterations
- Prior infections

Infectious Complications & Mortality

SOT Recipients

- **6%** died from infection within first year (Swiss cohort) (Delden et al., 2020)
- **55%** had infections in first year (German renal cohort) (Sommerer et al., 2022)
  - Half occurred in first 3 months
  - Bacteria: 66%, Viruses: 29%, Fungi: 5%

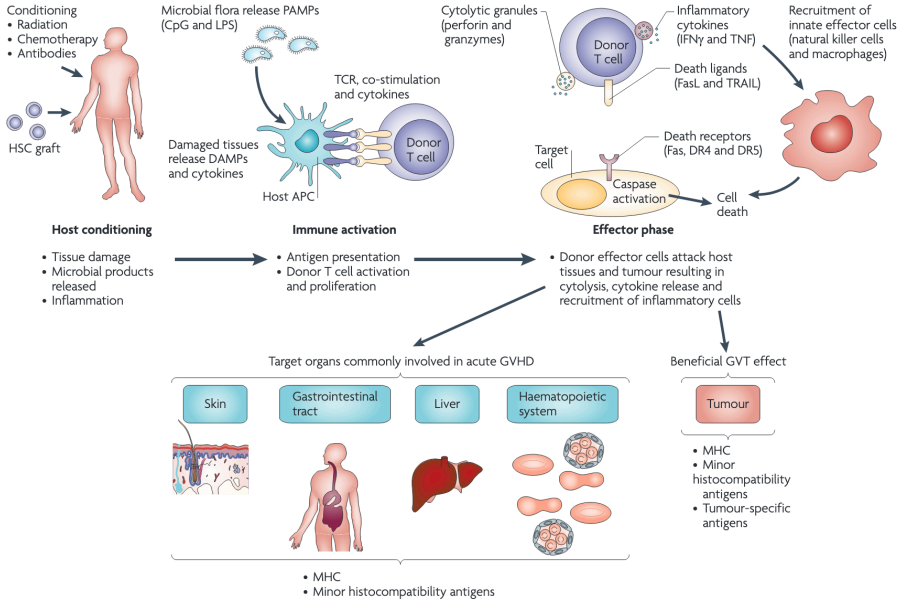


SOT recipients face particular risks from surgical complications, hardware-related infections, and the combination of surgical stress plus

Hematopoetic stem cell transplantation (HSCT) recipients

Type	Stem Cell Source	Donor	Immunosuppression
Autologous	Peripheral blood, Bone marrow	Self	Moderate; no GvHD prophylaxis required; recovery within weeks
Allogeneic — matched related	Peripheral blood, Bone marrow, Umbilical cord blood	HLA-matched sibling or family member	Severe; prolonged due to GvHD prophylaxis and risk of GvHD
Allogeneic — matched unrelated (MUD)	Peripheral blood, Bone marrow, Umbilical cord blood	HLA-matched unrelated donor (registry)	Very severe; higher GvHD risk than matched related; intensive prophylaxis
Allogeneic — haploidentical	Peripheral blood, Bone marrow	Half-matched family member (parent, child, sibling)	Very severe; requires intensive T-cell depletion or post-transplant cyclophosphamide
Allogeneic — umbilical cord blood	Umbilical cord blood	Unrelated cord blood unit	Very severe; delayed immune reconstitution due to low cell dose

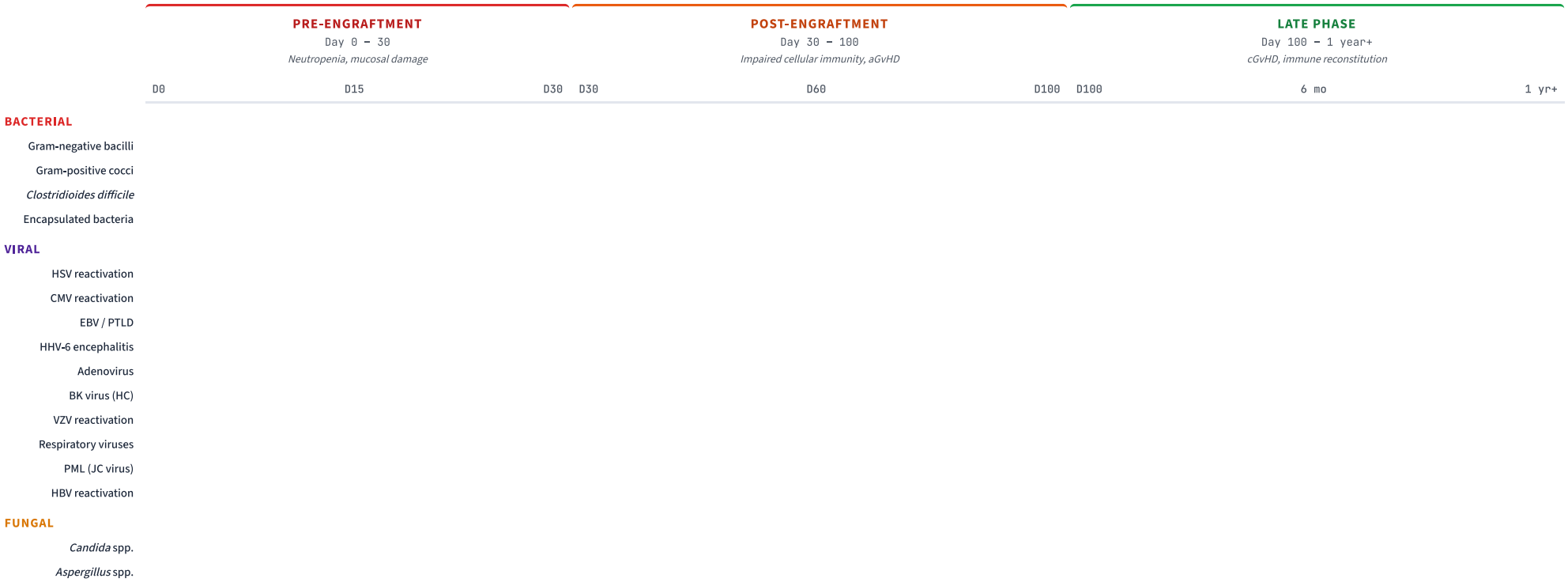
Allogeneic hematopoetic stem cell transplantation (HSCT) recipients



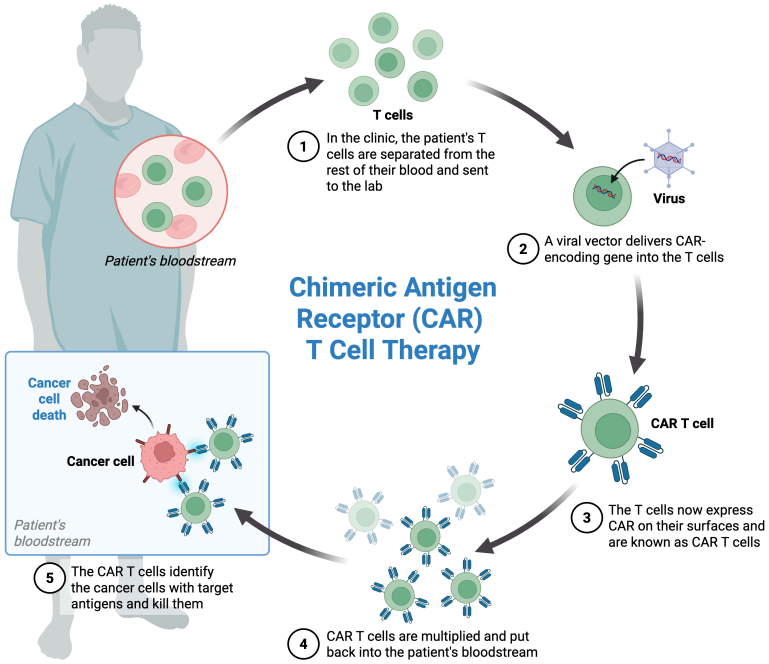
Timeline of Infection Risk

Infections After Allogeneic Hematopoietic Stem Cell Transplantation

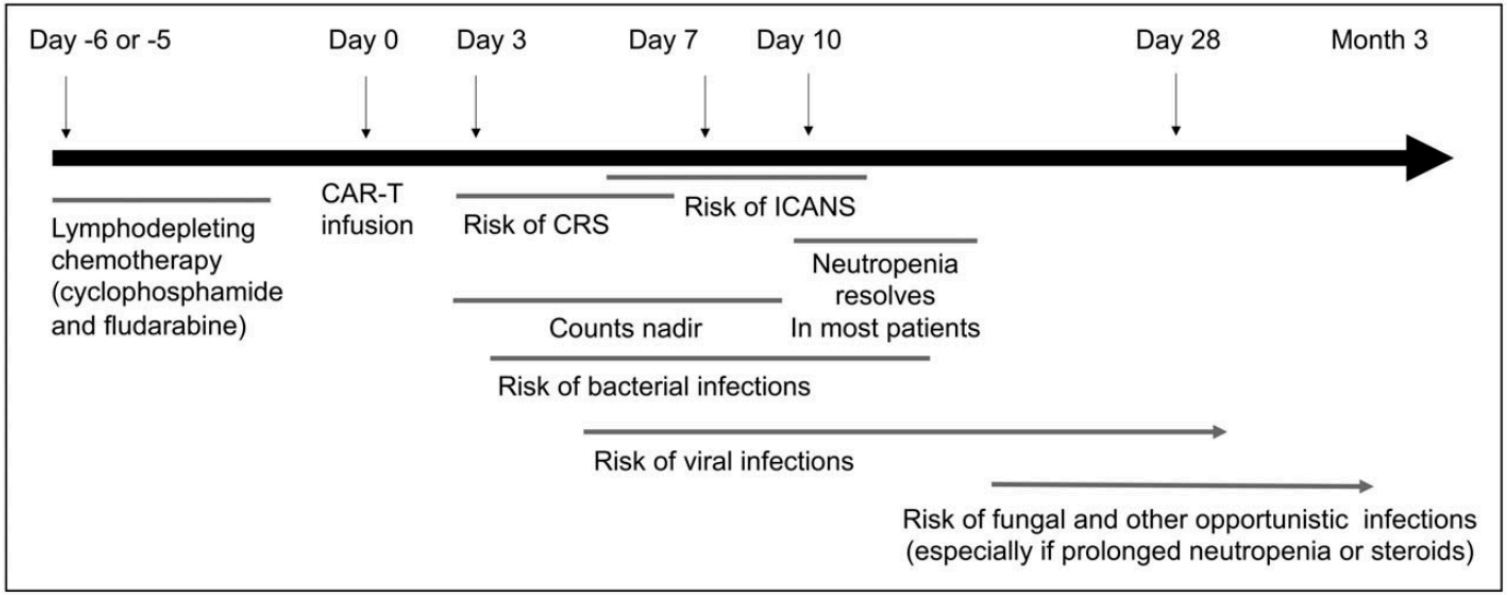
Temporal distribution of infectious complications by pathogen type and transplant phase



What is CAR-T therapy?



Immunosuppression timeline with CAR-T



CAR-T cell therapy

- Patients are **profoundly immunosuppressed**
- Up to 1/3 suffer serious bacterial infection in first 30 days (Stewart and Henden, 2021)
- Cytokine release syndrome complicates assessment
- Prolonged B-cell aplasia → hypogammaglobulinemia

Measuring Immunosuppression

Available Markers

Useful in HIV:

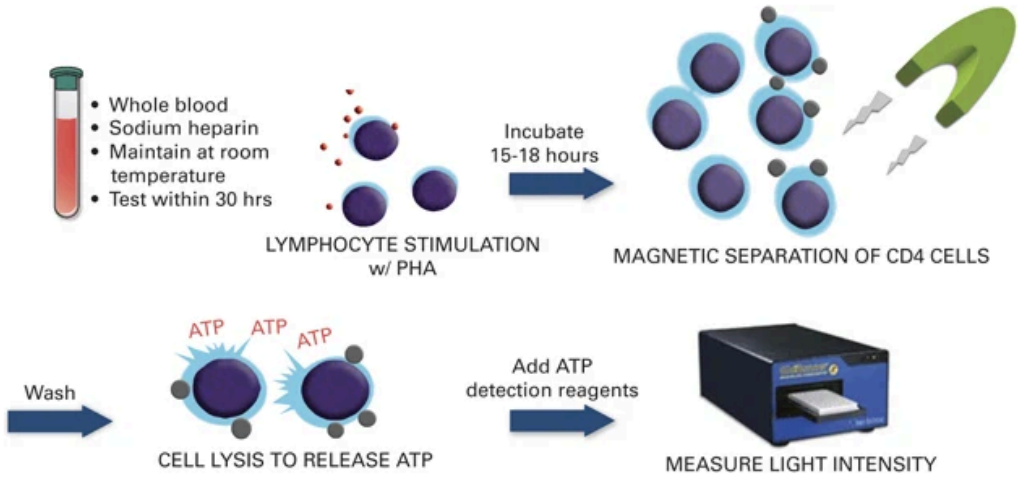
- CD4 count
- CD4 percentage
- CD4/CD8 ratio

General markers:

- Neutrophil count
- Lymphocyte count
- Immunoglobulin levels

Unfortunately, we lack reliable composite markers or algorithms to predict infection risk in most immunocompromised populations outside

Emerging biomarkers



- **Viral reactivation** (EBV, CMV, TTV, BK) → correlates with immunosuppression
- **QuantiFERON Monitor** → may identify over-immunosuppression
- **ImmuKnow assay** → correlates with infection/rejection risk
- Traditional markers (ESR, CRP, procalcitonin) → **NOT predictive**

Sources of Infection

Community-acquired pathogens

- Most common infections **mimic community pathogens**
- Immunocompromised patients are often “sentinel cases” in outbreaks
- Respiratory viruses, GI pathogens
- *Norovirus*, *C. difficile*

Healthcare-associated pathogens

- **Increased risk of MDR organisms** due to frequent healthcare contact
- Catheter-related infections
- Pneumonia
- UTI

Reactivation of latent infections

Key pathogens to screen for and monitor:

- *Mycobacterium tuberculosis*
- *Strongyloides*
- Hepatitis B
- *Coccidioides*, *Histoplasma*
- *Trypanosoma cruzi* (Chagas)

Donor-derived infections

- Organ transplant
- Stem cell transplant
- Blood products
- Usually within **first 6 months**
- Most common infections:
  - Cytomegalovirus
  - Epstein-Barr virus (post-transplant lymphoproliferative disease)
  - Herpes simplex and varicella zoster
  - Hepatitis B,C
  - HIV
  - Bacterial infections
  - Fungal infections (*Candida, Aspergillus*)

Components of Host Defense

Overview of immune system

Innate Immunity

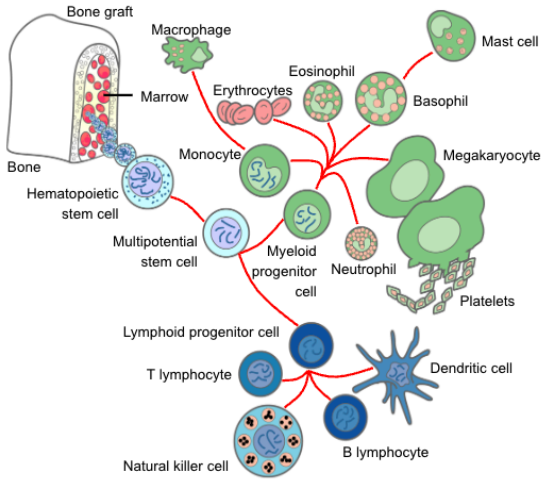
- Granulocytes
- Monocytes/Macrophages
- NK cells
- Complement
- Physical barriers

Acquired Immunity

- Cellular (T cells)
- Humoral (B cells)
- Antibody production

Granulocytes (neutrophils)

- Chemotherapy & radiation → **neutropenia**
- Duration: 3-4 weeks or longer
- **Primary risk factor** for infection
- Risk increases with:
  - Depth of neutropenia
  - Duration of neutropenia
- Concurrent organ dysfunction



Corticosteroid effects on neutrophils

Paradoxical effects:

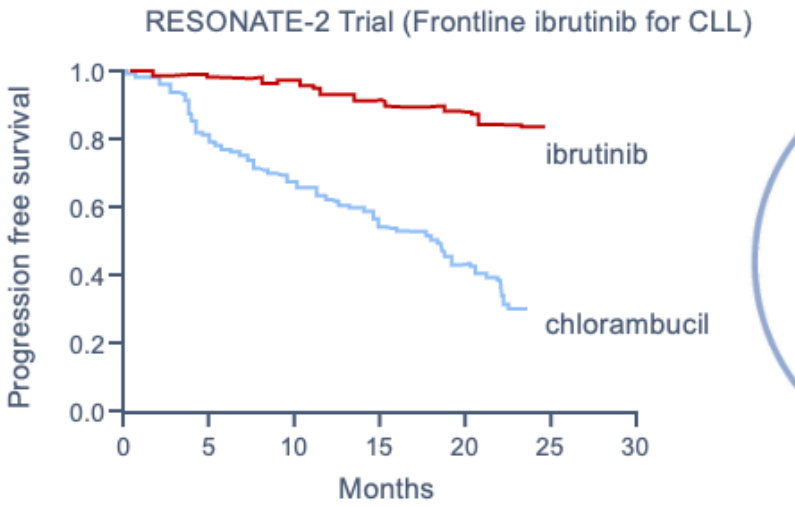
- ↑ Granulocytopoiesis (apparent benefit)
  - BUT: ↓ Accumulation at infection site
- ↓ Adherent capacity
- ↓ Chemotaxis
- ↓ Phagocytosis
- ↓ Intracellular killing

Monocytes & macrophages

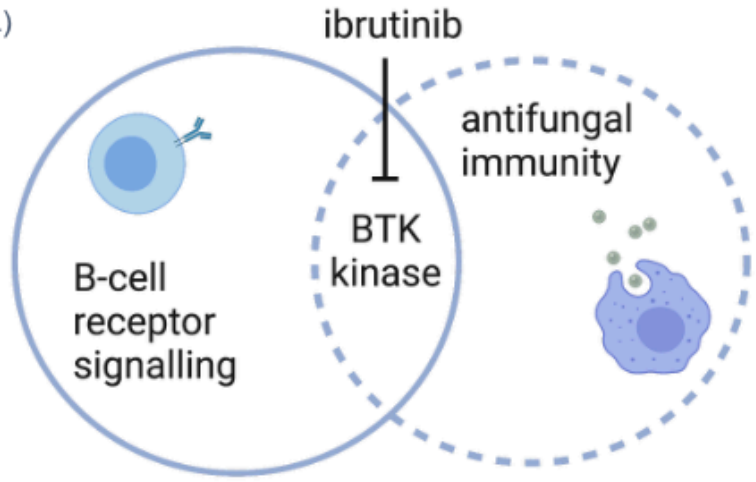
- **Monocytopenia** parallels neutropenia
- Macrophage activation requires **T-cell cytokines** (IFN-γ)
- Explains cellular immunodeficiency susceptibility
- Targeted therapies can have **unexpected effects**

Ibrutinib is a good example—designed as a BTK inhibitor for B cells, but has broader effects on macrophage function contributing to

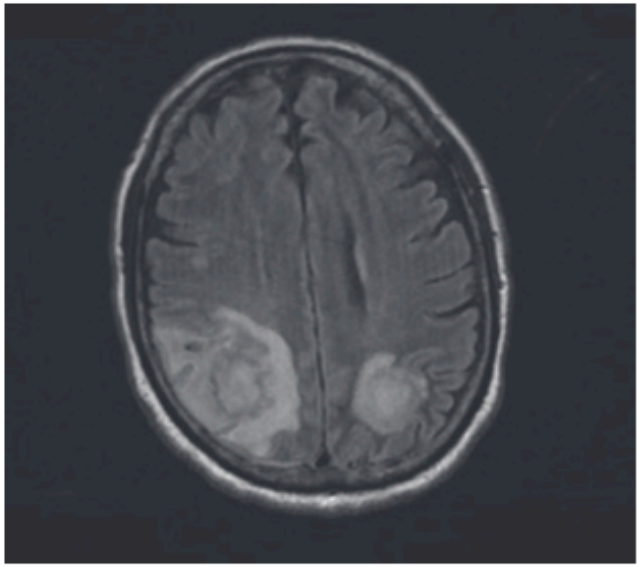
Ibrutinib



	Chlorambucil	Ibrutinib
Median survival	18.9	NR
HR	0.16 (0.09-0.28);	P<0.001



Unexpected fungal infections



T2-weighted FLAIR magnetic resonance imaging revealing multiple cerebral abscesses.

- Retrospective French surveillance (FILO) identified 33 cases of aspergillosis in ibrutinib-treated patients with chronic lymphocytic leukemia
- **CNS aspergillosis in 11/27 (40%),** most cases within 3 months of starting ibrutinib therapy
- All patients had refractory/ relapsed disease and additional predisposing factors in most of patients (e.g., steroids in 7, neutropenia in 5)

NK cells and platelets

NK Cells:

- Respond to viruses and malignancy
- CD56 receptor → *Aspergillus* recognition
- Dysfunction contributes to fungal susceptibility

Platelets:

- Increasingly recognized immune role
- Thrombocytopenia → independent bacteremia risk
- Protection against yeast and molds

Cellular immunity

Drugs that impair T-cell function:

- Corticosteroids
- Azathioprine, cyclosporine, tacrolimus
- mTOR inhibitors (sirolimus, everolimus)
- Purine analogues (fludarabine, cladribine)
- Alemtuzumab

Diseases: Hodgkin lymphoma, CLL

Targeted therapy risks

Drug	Mechanism	Infection Risk
Ruxolitinib	JAK-STAT inhibitor	TB, HBV reactivation
Ibrutinib	BTK inhibitor	Aspergillosis, PJP
Idelalisib	PI3K inhibitor	*P. jirovecii*

If you see a drug ending in “mab” or “nib” or “sib” ….consider unique infection risk

mab- monoclonal antibody-large protein biologic usually IV that binds extracellular targets (receptors, cytokines, cells); nib-small molecule

Humoral immunity

- **B cells** → antibody-secreting plasma cells
- Impaired in CLL, multiple myeloma
- Rituximab, CAR-T → **B-cell depletion**
- Profound, long-lasting hypogammaglobulinemia

Splenectomy: Loss of encapsulated bacteria defense-big 3

- *Streptococcus pneumoniae*
- *Haemophilus influenzae* type B
- *Neisseria meningitidis*

Less common: *Capnocytophaga canimorsus, Salmonella spp. E. coli*

PSV and PPSV23 vaccine, MENACWY and MenB vaccine, HIB, Influenzae- Vaccinate 2 weeks before elective splenectomy or 2 weeks after emergency splenetocmy

Physical Barriers

The Integument

Skin:

- Chemotherapy → hair loss, dryness
- Catheters → direct microbial access
- Broken skin → *S. aureus*, gram-negatives

Oropharynx:

- Xerostomia + antibiotics → thrush, bacterial overgrowth

Alimentary Tract

- **Microbiome disruption** with antibiotics→ *C. difficile*
- Mucosal barrier injury from chemotherapy
- Facilitates bacterial translocation
- With concomitant neutropenia allows progression to sepsis

Immunodeficiency-Pathogen Associations

Neutropenia: Gram-positive pathogens

- Coagulase-negative staphylococci more common than *Staphylococcus aureus* (most are from central venous catheter)
- Viridans streptococci
- Enterococci

Neutropenia: Gram-negative pathogens

- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*
- *Enterobacter* spp.

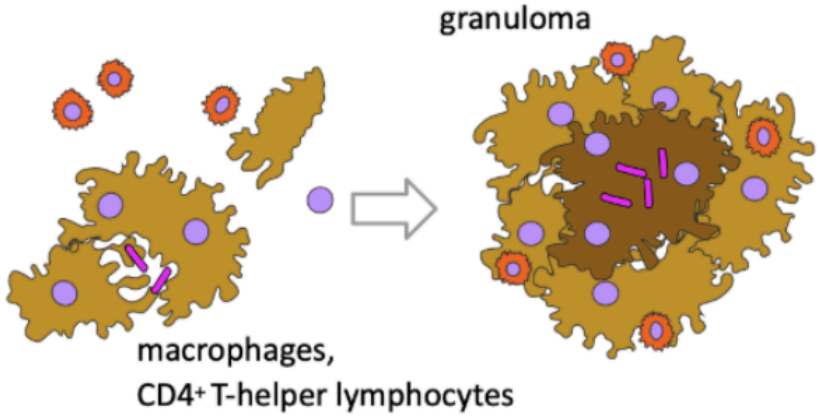
Impaired cellular immunity

Bacteria/Mycobacteria:

- *Listeria monocytogenes*
- *Nocardia* spp.
- *M. tuberculosis*
- Nontuberculous mycobacteria

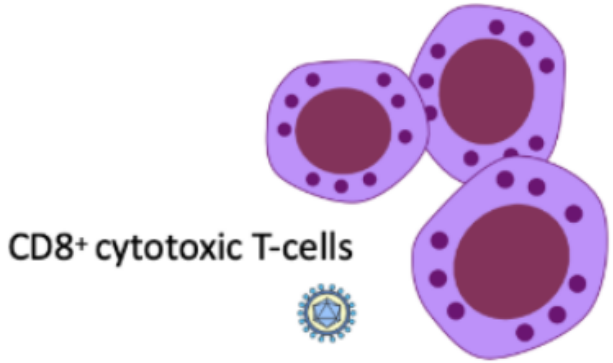
Fungi/Parasites:

- *P. jirovecii*
- *Aspergillus* spp.
- *Cryptococcus* spp.
- *Toxoplasma gondii*



Impaired cellular immunity (viruses)

- Herpesviruses (HSV, VZV, CMV, EBV)
- Respiratory viruses
- Polyomaviruses (BK, JC)
- Human papillomavirus



Impaired humoral immunity

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- Norovirus
- Hepatitis B virus

Prevention Strategies

Prophylaxis principles

TMP-SMX for PJP :typically 1 DS tablet daily also covers:

- *Toxoplasma*
- *S. aureus*
- *Nocardia*
- Many gram-positives/negatives

Antiviral prophylaxis: Val(acyclovir) for CMV (weak activity), HSV, VZV prevention. Valganciclovir or letermovir for higher risk CMV patients

Problem with TMP/SMX- rash, GI upset, and cytopenias—often limits adherence. Can use - 1 DS tablet 3×/week (e.g., Mon–Wed–Fri) or even single-strength daily. Add folic acid if patient has anemia or leukopenia. Valganciclovir is assocaited with dose-limiting myelosuppression.

Patient education

High-risk exposures to avoid:

- Gardening without protection (molds, *Nocardia*)
- Poor dental hygiene (*Actinomyces*, bacteremia)
- Marijuana smoking (*Aspergillus*)
- Raw seafood (*Vibrio*)
- Warm ocean swimming

Key Takeaways

Summary points

1. **6% of population** is immunocompromised
2. **Net state of immunosuppression** = composite assessment
3. **First 100 days after transplant** = highest risk period
4. **No single marker** predicts infection risk
5. **Know pathogen associations** with specific defects
6. **Prophylaxis** significantly alters risk profile

Clinical Pearls

Remember

- TMP-SMX provides broader coverage than just PJP prophylaxis
- Timing matters—early vs late infections differ
- Targeted therapies have unexpected infection risks
- Consider the whole patient, not just the lab values

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