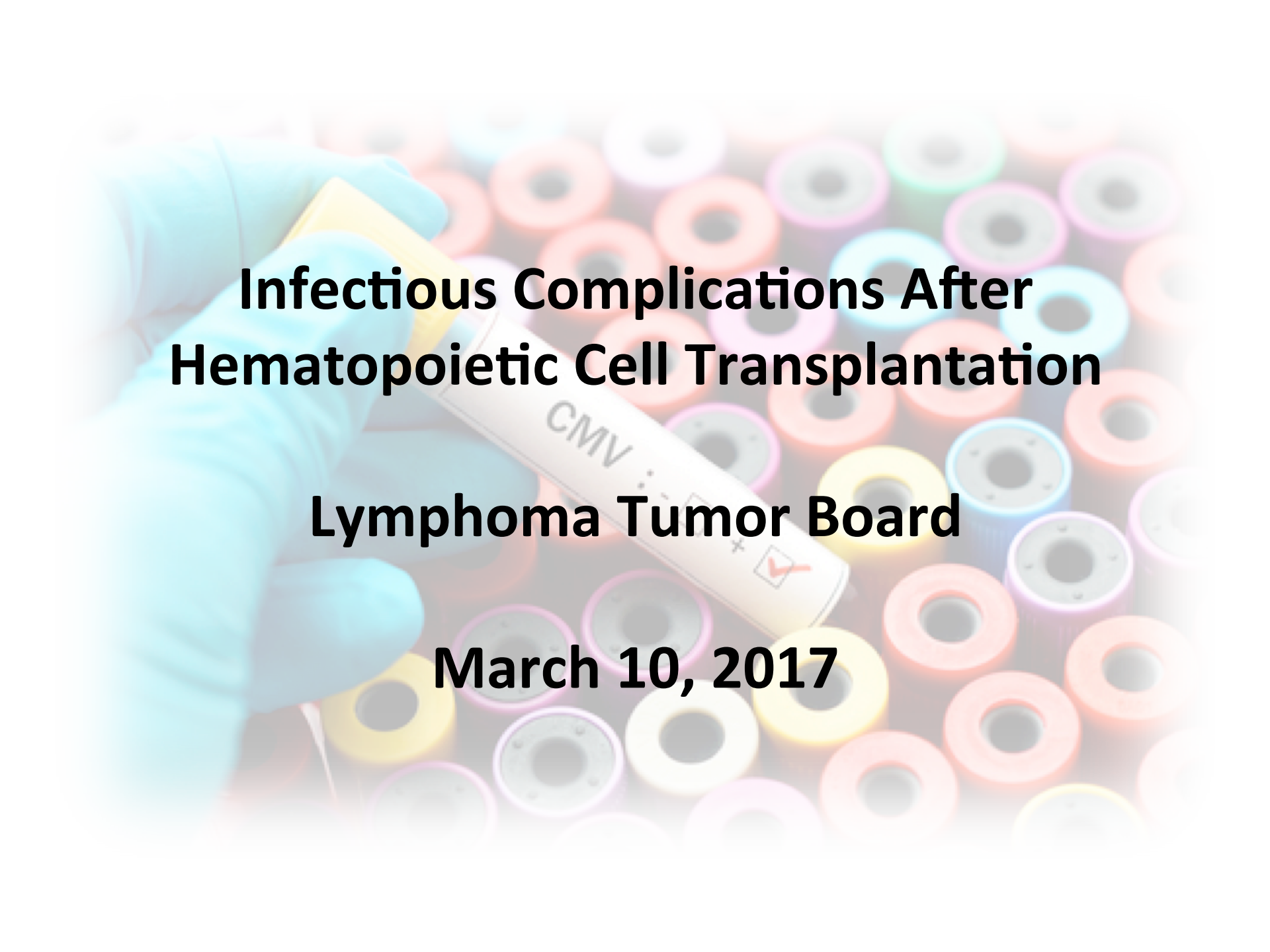
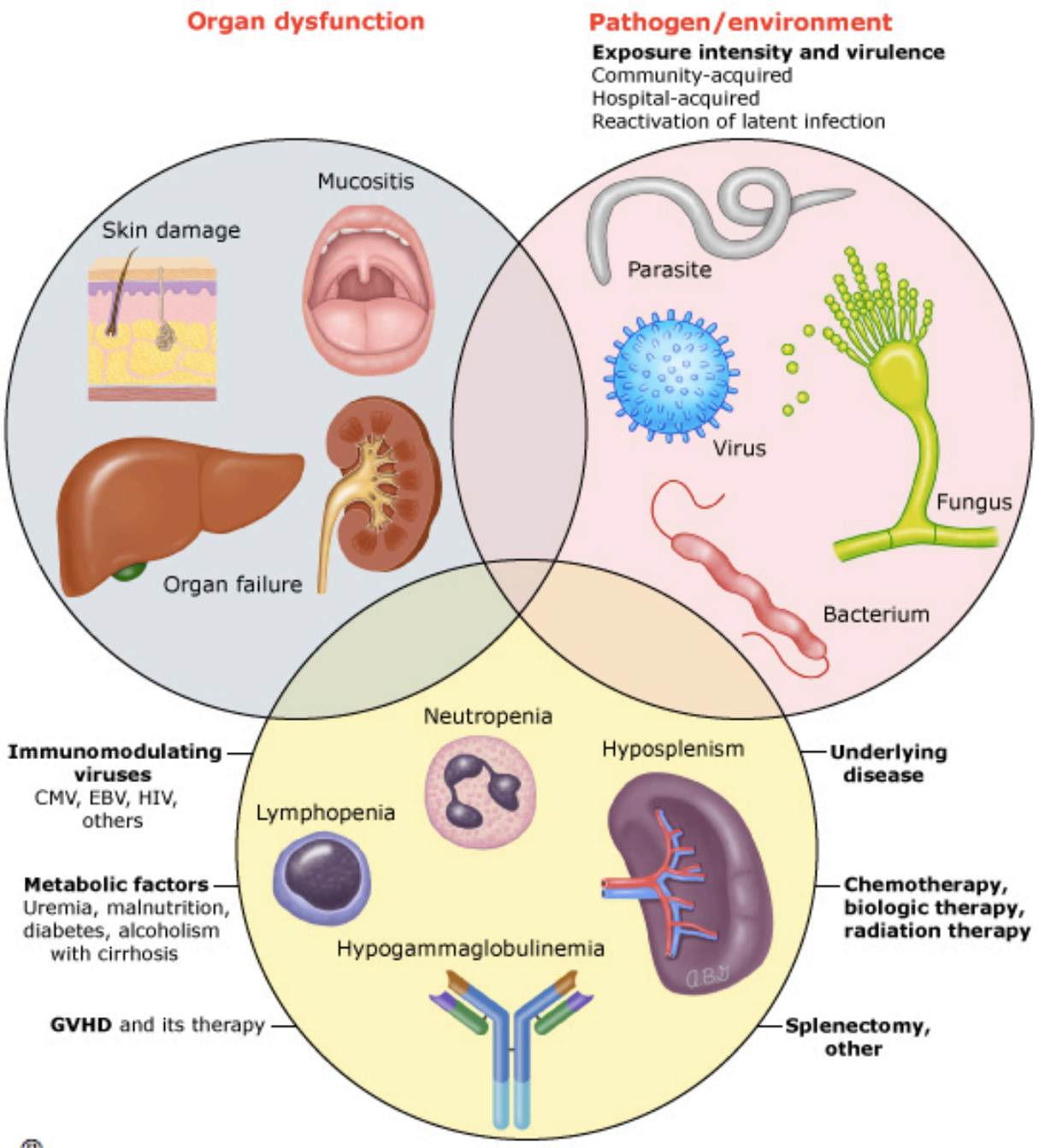


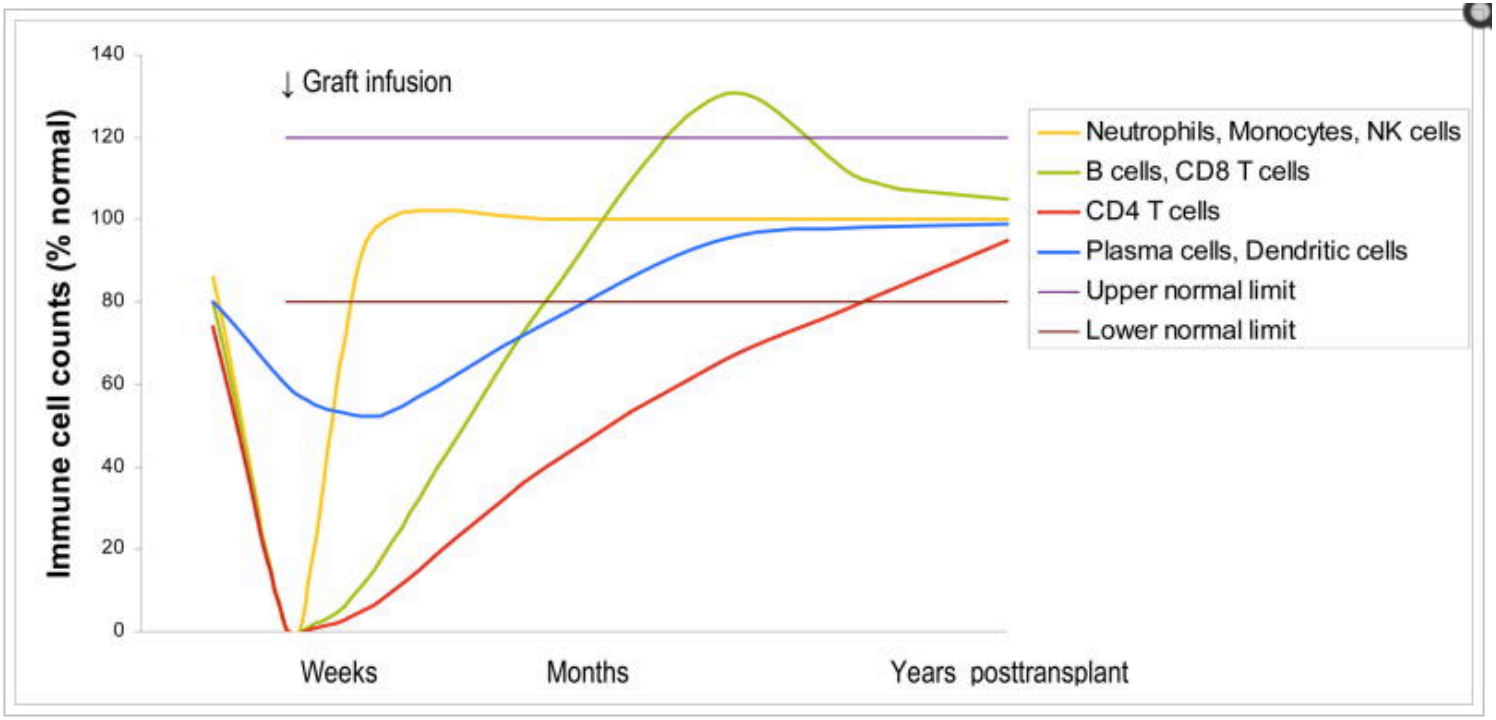
Infectious Complications After Hematopoietic Cell Transplantation

Lymphoma Tumor Board

March 10, 2017

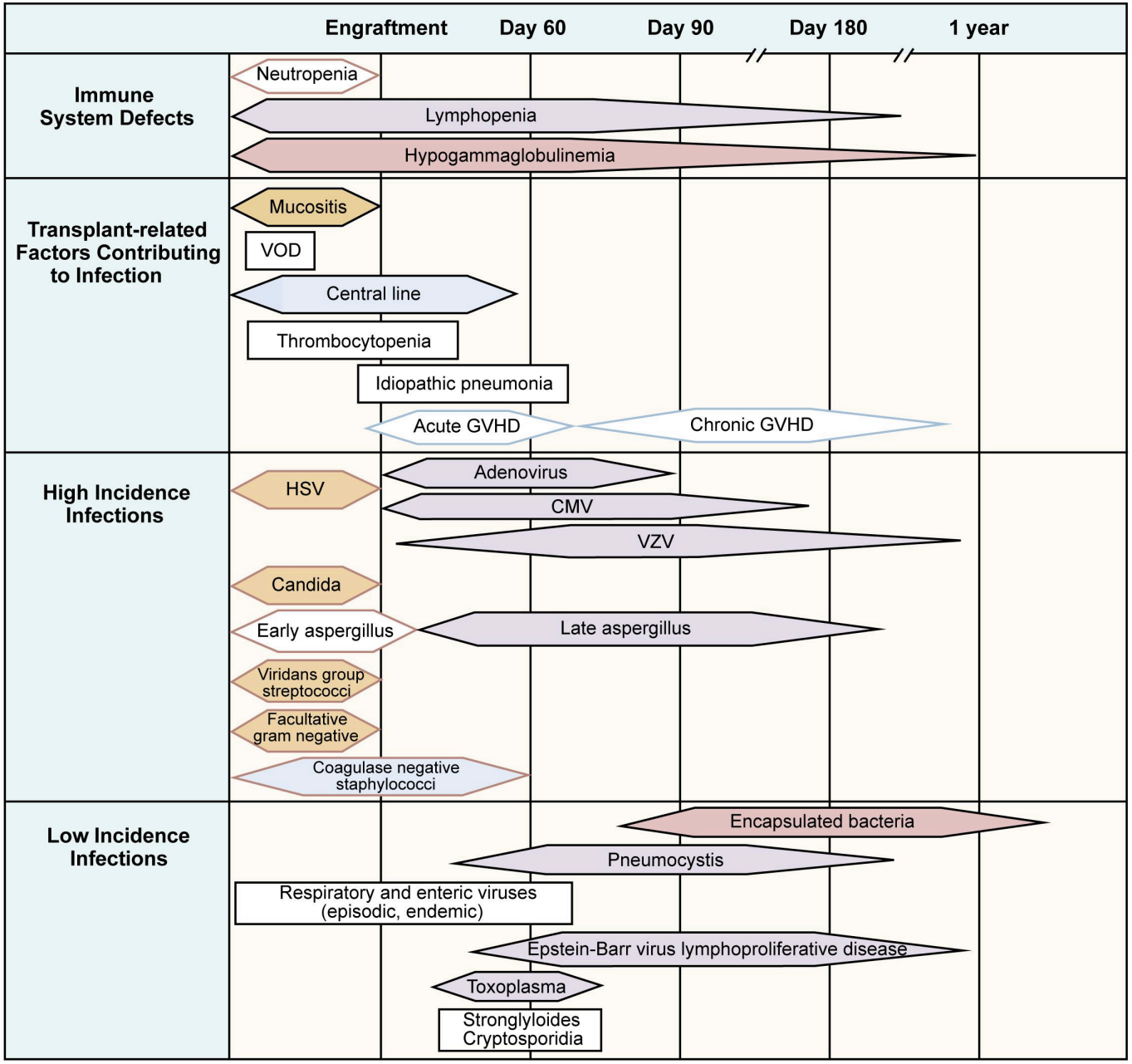


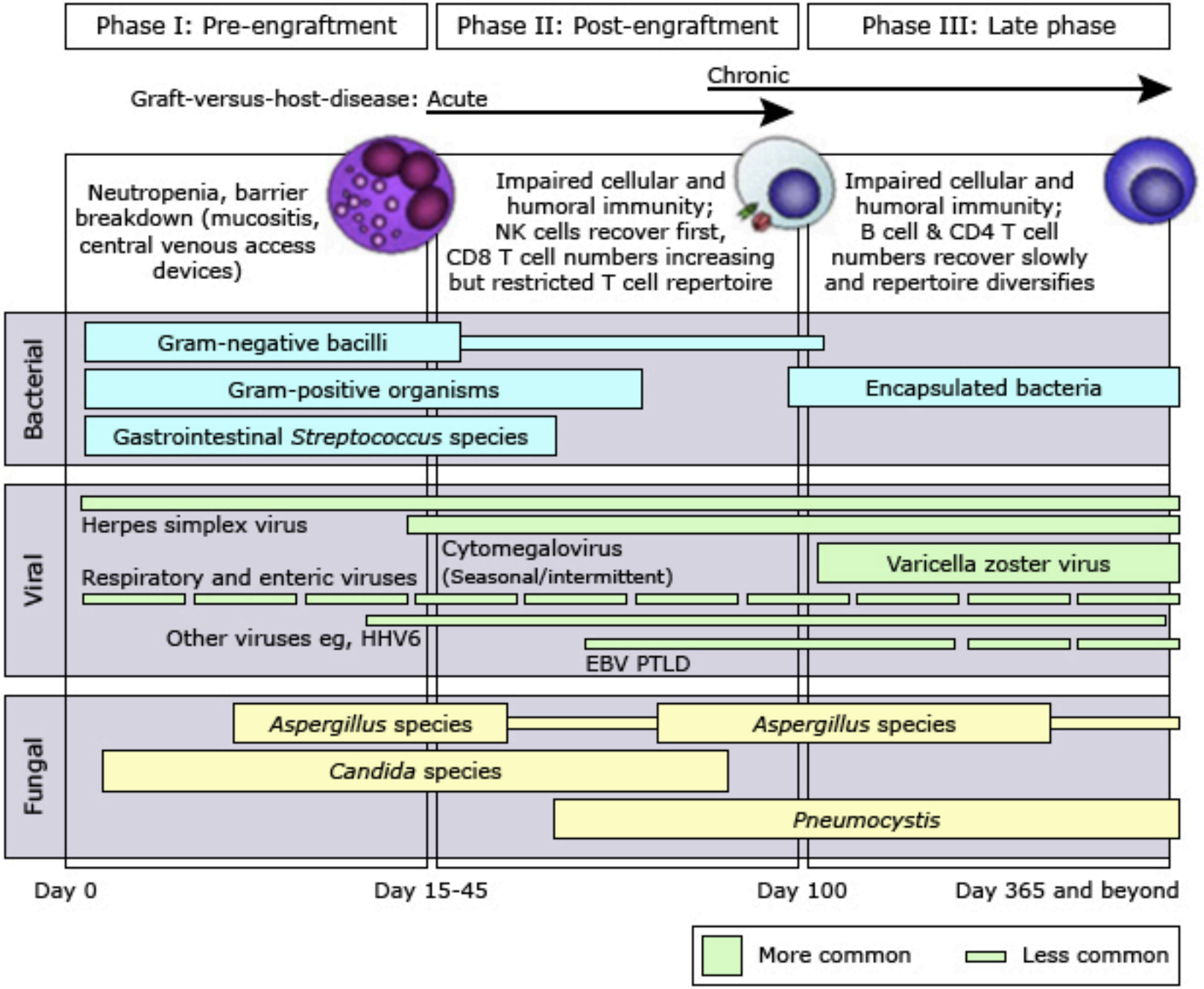
Recovery of immune cells after allogeneic HCT



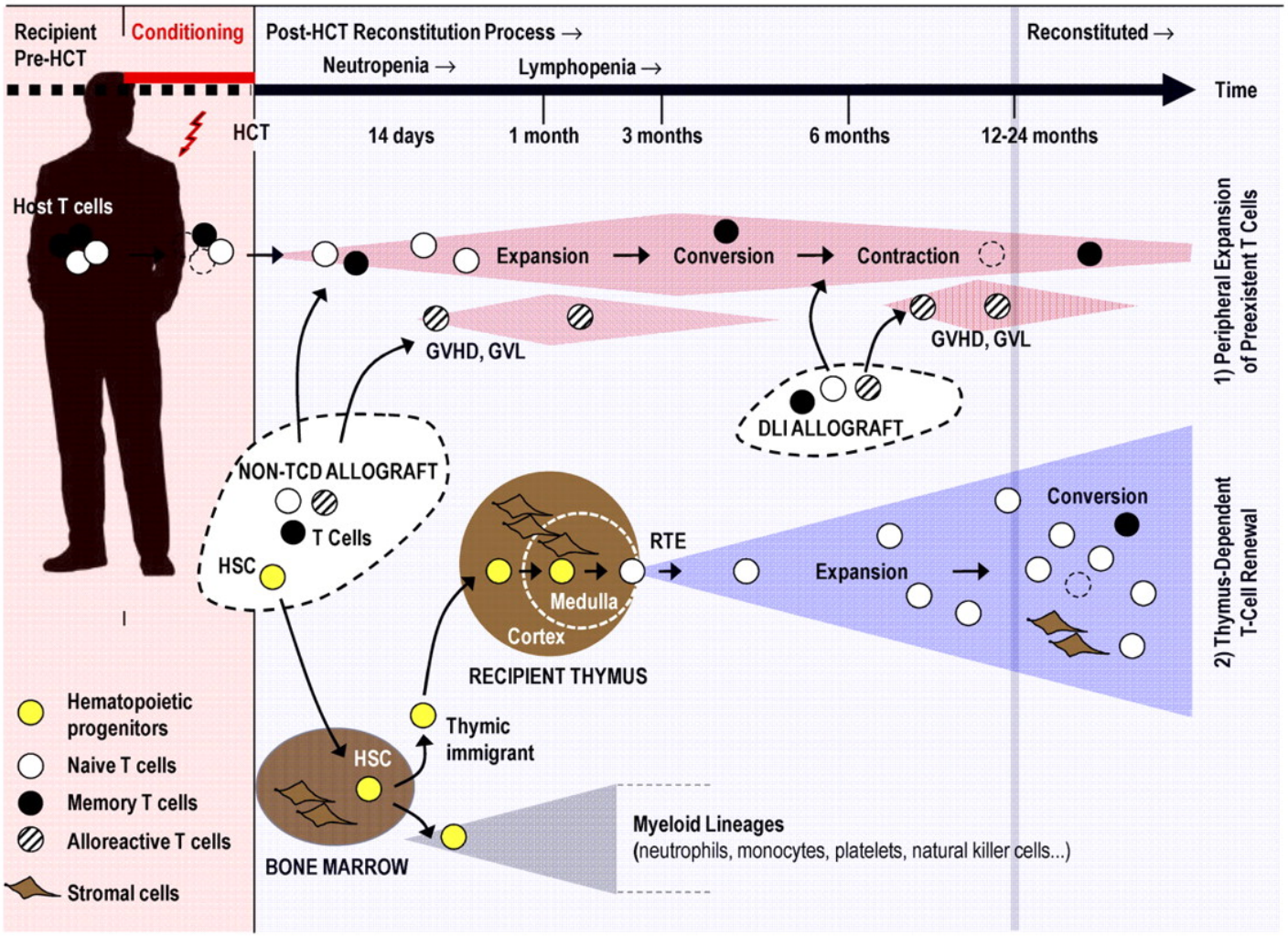
Approximate immune cell counts (expressed as percentage of normal counts) peri– and post–myeloablative hematopoietic cell transplantation. Nadirs are higher and occur later after nonmyeloablative than myeloablative transplantation, as recipient cells persist after nonmyeloablative transplant for several weeks to months (in the presence of GVHD) or longer (in the absence of GVHD). The orange line represents the innate immune cells (e.g., neutrophils, monocytes, and natural killer [NK] cells), the recovery of which is influenced by the graft type (fastest with filgrastim-mobilized blood stem cells, intermediate with marrow, and slowest with umbilical cord blood). The green line represents the recovery of CD8+ T-cells and B-cells, the counts of which may transiently become supranormal. B-cell recovery is influenced by graft type (fastest after cord blood transplant) and is delayed by GVHD and/or its treatment. The blue line represents the recovery of relatively radiotherapy/chemotherapy-resistant cells such as plasma cells, tissue dendritic cells (e.g., Langerhans cells) and, perhaps, tissue macrophages/microglia. The nadir of these cells may be lower in patients with acute GVHD due to graft-versus–host-plasma cell/Langerhans cell effect. The red line represents CD4+ T-cells, the recovery of which is influenced primarily by T-cell content of the graft and patient age (faster in children than adults). From Storek J: *Immunological reconstitution after hematopoietic cell transplantation – its relation to the contents of the graft*. Expert Opinion on Biological Therapy (Informa) 8(5):583–597, 2008.

Phases of Predictable Immune Suppression and Associated Opportunistic Infections



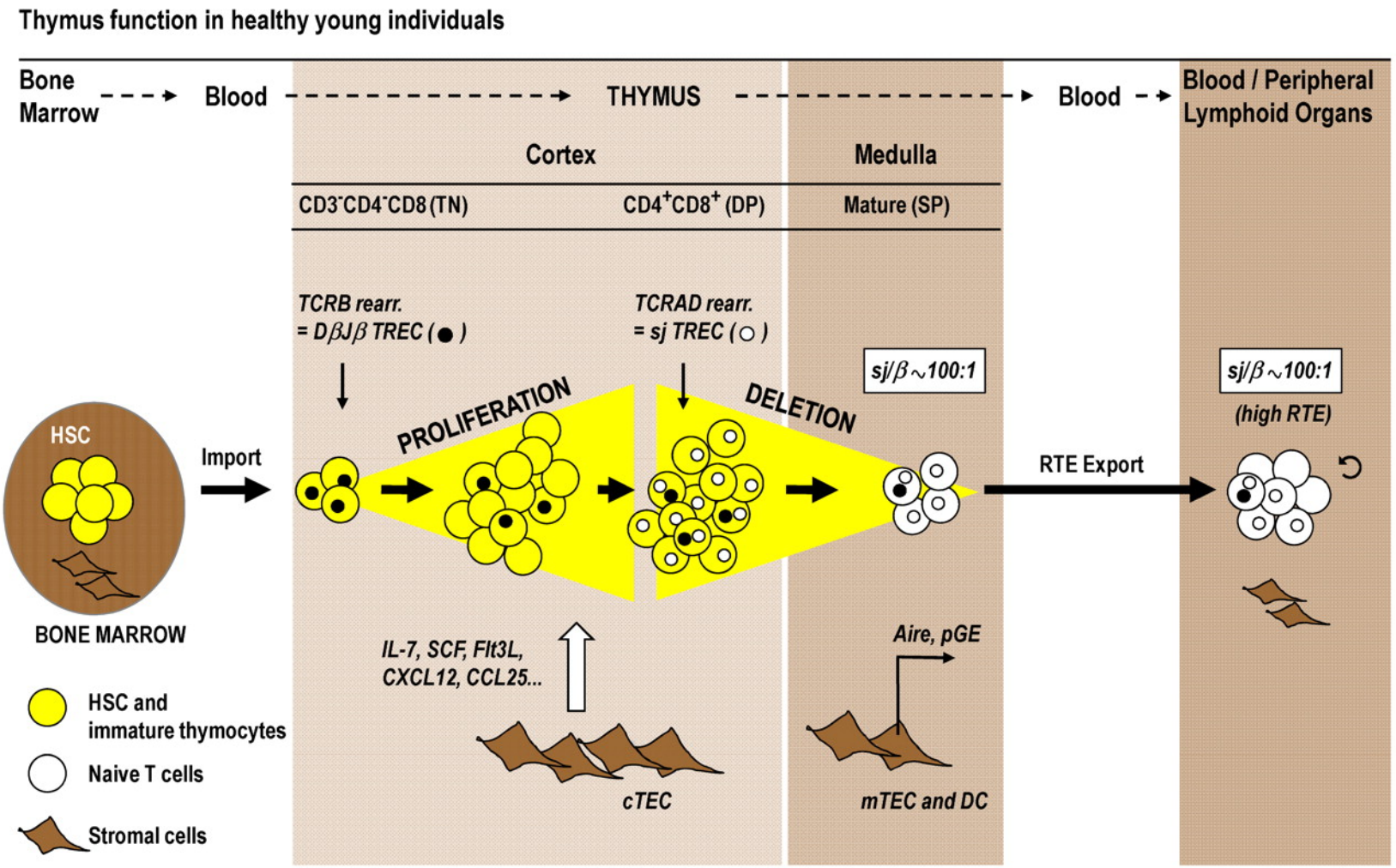

Phase I: Pre-engraftment
Phase II: Post-engraftment
Phase III: Late phase
Graft-versus-host-disease: Acute
Chronic
Neutropenia, barrier breakdown (mucositis, central venous access devices)
Impaired cellular and humoral immunity; NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire
Impaired cellular and humoral immunity; B cell & CD4 T cell numbers recover slowly and repertoire diversifies
Bacterial
Gram-negative bacilli
Gram-positive organisms
Gastrointestinal Streptococcus species
Encapsulated bacteria
Viral
Herpes simplex virus
Respiratory and enteric viruses
Cytomegalovirus (Seasonal/intermittent)
Varicella zoster virus
Other viruses eg, HHV6
EBV PTLD
Fungal
Aspergillus species
Aspergillus species
Candida species
Pneumocystis
Day 0
Day 15-45
Day 100
Day 365 and beyond
More common
Less common

T-cell regenerative pathways after allogeneic HCT. Pretransplantation conditioning reduces the patient's existing naive (○) and memory (●) T cells



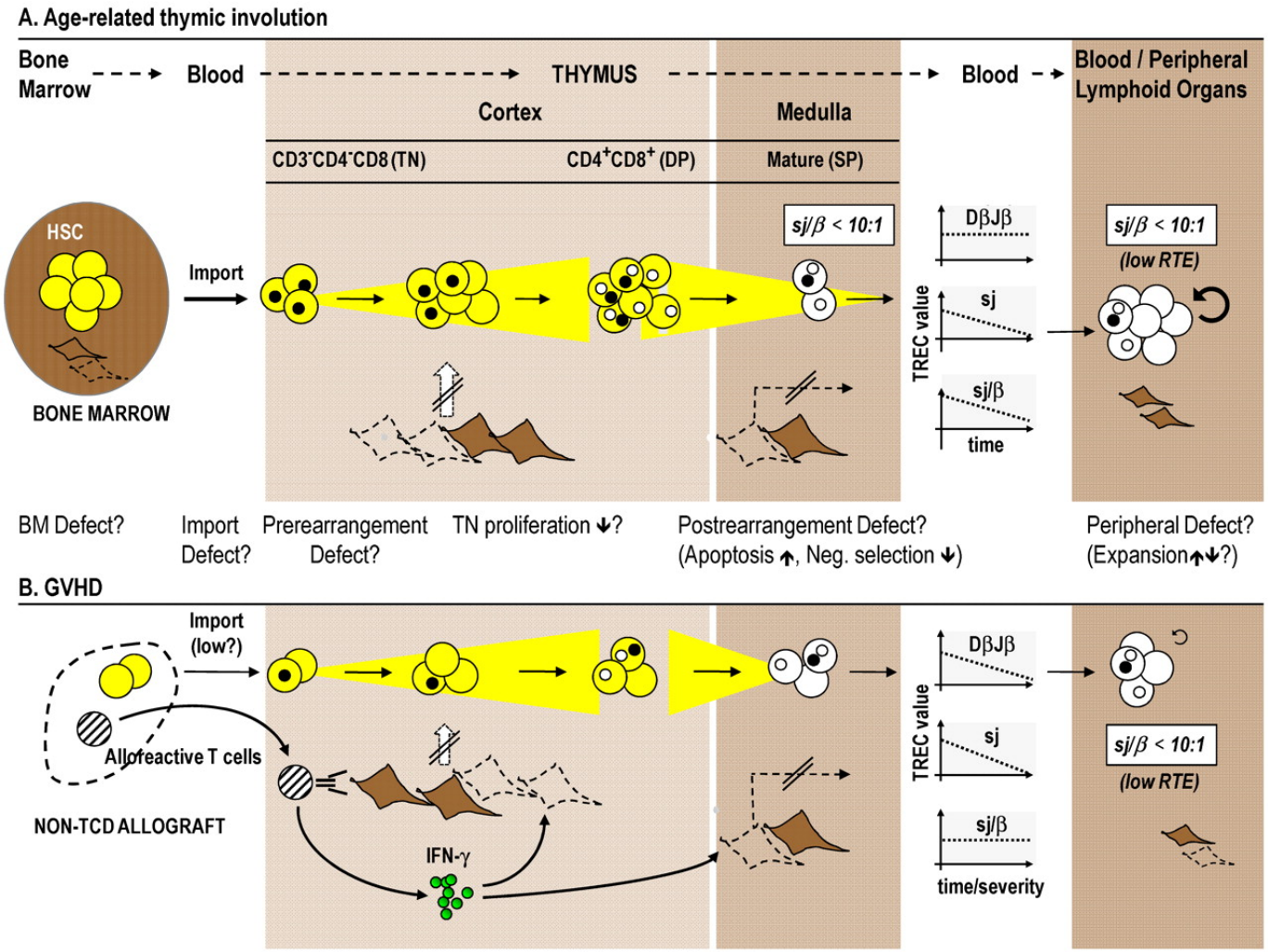
Werner Krenger et al. Blood 2011;117:6768-6776

Normal thymic T-cell maturation and export



Werner Krenger et al. Blood 2011;117:6768-6776

The effects of age and GVHD on T-cell maturation and export



Werner Krenger et al. Blood 2011;117:6768-6776

Risk of infectious complications after allogeneic HCT

- HCT is associated with high risk of mortality due to several factors: Regimen-related toxicity, infection, & graft vs. host disease (GVHD)
- Infection is reported as the primary cause of death in 8% of autologous HCT patients and 17-20% of allogeneic HCT recipients
- Risk assessments for posttransplant infection should be performed before transplant, taking into consideration:
  - Underlying disease, donor stem cell source, histoincompatibility, previous therapies, co-morbidities
- Myeloablative HCT recipients usually experience severe pancytopenia that can last days to weeks post HCT
- Time of neutrophil recovery depends on the type of donor stem cell graft
- Myeloablative regimens damage mucosal surfaces, which provide an environment in which pathogens can thrive
- Result is infectious complications in immediate posttransplant period that present with febrile neutropenia

Factors affecting risk of infection after allogeneic HCT

Factors affecting the risk of infection

Factor	Risk of infection
Type of transplant	Higher risk with allogeneic, lower risk with autologous or syngeneic, depending on graft manipulation and clinical setting, including previous therapies
Time from transplant	Lower risk with more time elapsed from transplant
Pre-transplant factors	Higher risk with extensive pre-transplant immunosuppressive therapy (e.g. fludarabine, clofaribine), prolonged pre-transplant neutropenia, or pre-transplant infection
GVHD	Higher risk with grade III–IV acute GVHD or extensive chronic GVHD
HLA match	Higher risk with HLA-mismatched donors, particularly with haploidentical donors
Disease (e.g., leukemia) status	Higher risk with more advanced disease at the time of transplant
Donor type	Higher risk with marrow unrelated donor than with a fully matching sibling donor
Graft type	Highest risk with cord blood, intermediate risk with bone marrow and lowest risk with colony stimulating factor-mobilized blood stem cells. Higher risk with T-cell–depleted grafts (depending upon method used)
Immunosuppression after transplant	Higher with immunosuppressive drugs, in particular with corticosteroids, anti-thymocyte globulin, alemtuzumab
Conditioning intensity	Lower risk in the first 1–3 months posttransplant with low dose chemo/radiotherapy
Neutrophil engraftment	Higher risk with delayed engraftment/non-engraftment

Common bacterial infections after allogeneic HCT

- Central Line-Associated Bloodstream Infections (CLABSI)
  - Catheter-associated infections are a leading cause of bloodstream infections
  - Prevention: antimicrobial/antiseptic ointments and antimicrobial lock prophylaxis
- *Streptococcus pneumoniae*
  - Can be life-threatening
  - Prevention: prophylactic antibiotics in patients with chronic GVHD
- Viridans streptococci
  - Prevention: Chemotherapy-induced oral mucositis can lead to of viridans streptococcal bacteremia and sepsis. Dental consults are <u>mandatory</u> for HCT candidates to access their oral health.
  - Antibiotics given for a minimum of 21 days after transplant
- Enteric gram-negative organisms
  - Compromise of intestinal mucosal integrity due to conditioning regimen-associated damage and GVHD are important risk factors
  - Prevention: prophylactic fluoroquinolones when neutropenia develops
- *Haemophilus influenzae* type b
  - HCT recipients who are exposed to persons with Hib disease should receive prophylaxis with 4 days of rifampin or alternative antimicrobial. Droplet precautions.

Common viral infections after allogeneic HCT (1)

- Cytomegalovirus (CMV)
  - Shed from the oropharynx and the genitourinary track of both immuncompetent and immunosuppressed subjects.
  - Prevention: Prophylaxis to patients at risk post HCT. Ganciclovir, high-dose acyclovir, and valacyclovir have shown efficacy in preventing CMV reactivation
  - Use of CMV-seronegative donors and filtering blood products
- Epstein-Barr Virus (EBV)
  - EBV results from reactivation of endogenous infection or transmission of EBV from the graft
  - Monitor blood for EBV DNA load
- Herpes simplex virus (HSV)
  - Prevention: Acyclovir prophylaxis is mandatory for all HSV-seropositive allogeneic recipients to prevent HSV reactivation during the early posttransplant period.
- Varicella-zoster virus (VZV)
  - Prevention: Antiviral drugs such as long-term (~1 year) acyclovir prophylaxis to prevent reactivation of latent VZV
  - If reactivation, intravenous acyclovir until 2 days after all lesions have crusted over

Common viral infections after allogeneic HCT (2)

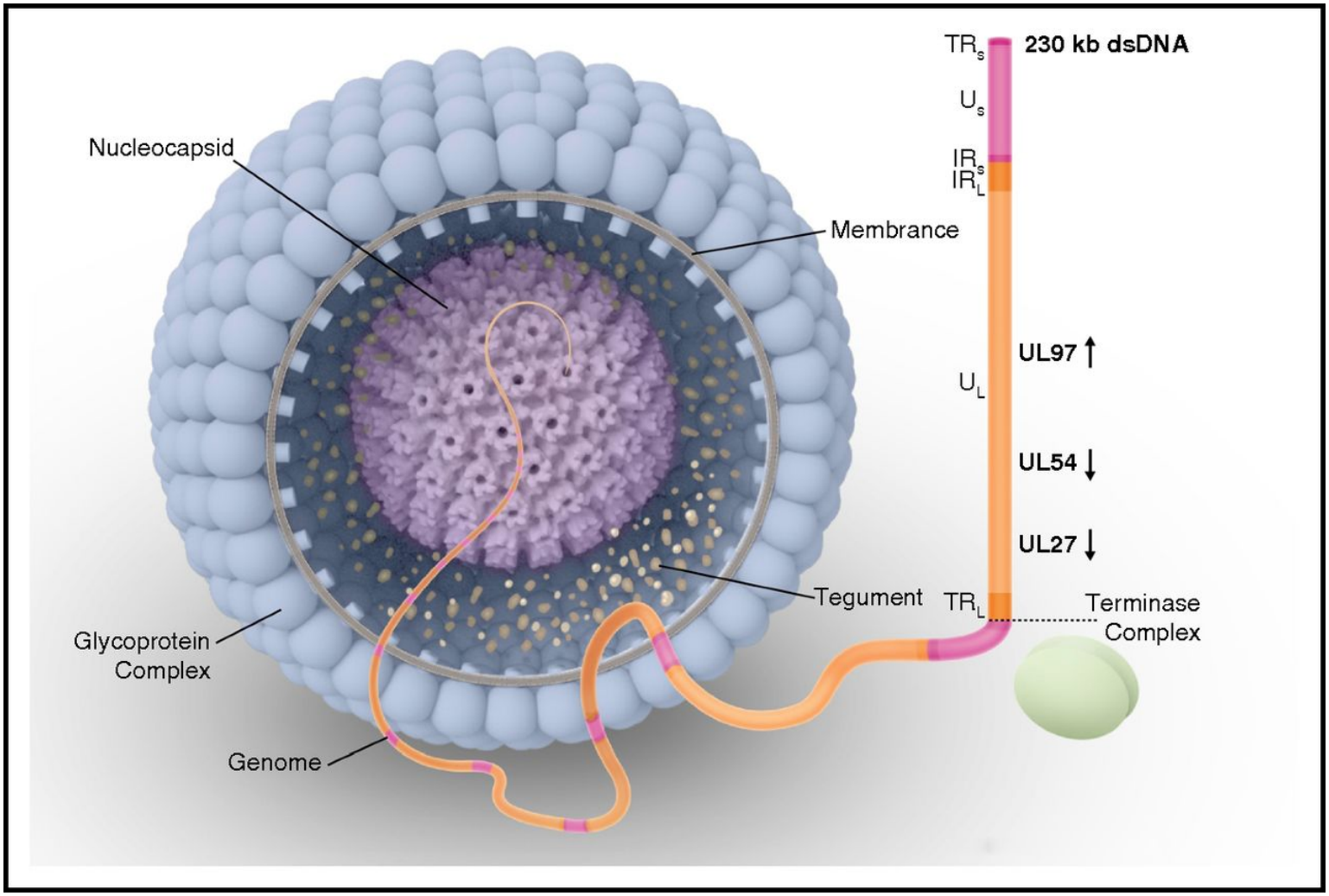
Hepatitis viruses

Severe hepatitis B has been observed in HCT recipeints in the following situations:

- "HBV-naïve HCT recipients exposed to HBV via an infected donor, infected blood products, or through sexual contact;
- HCT recipients with chronic hepatitis B experiencing prolonged immune suppression;
- HCT recipients with serological evidence of resolved HBV infection who have reverse seroconversion following prolonged immune suppression;
- HCT patients—generally in countries with endemic HBV—with latent occult hepatitis B (all serologic markers negative) that activates following prolonged immune suppression."

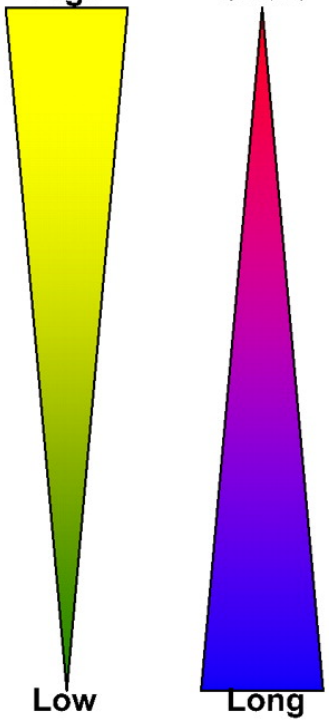
Pretransplant assessment for serologic evidence of infection with Hepatitis A, B, and C viruses is <u>mandatory</u>.

Human CMV virion structure and structural components



Firas El Chaer et al. Blood 2016;128:2624-2636

CMV viral load to start preemptive therapy (PET) used at the FHCRC in Seattle, WA, and the Karolinska Institute, Stockholm, Sweden.

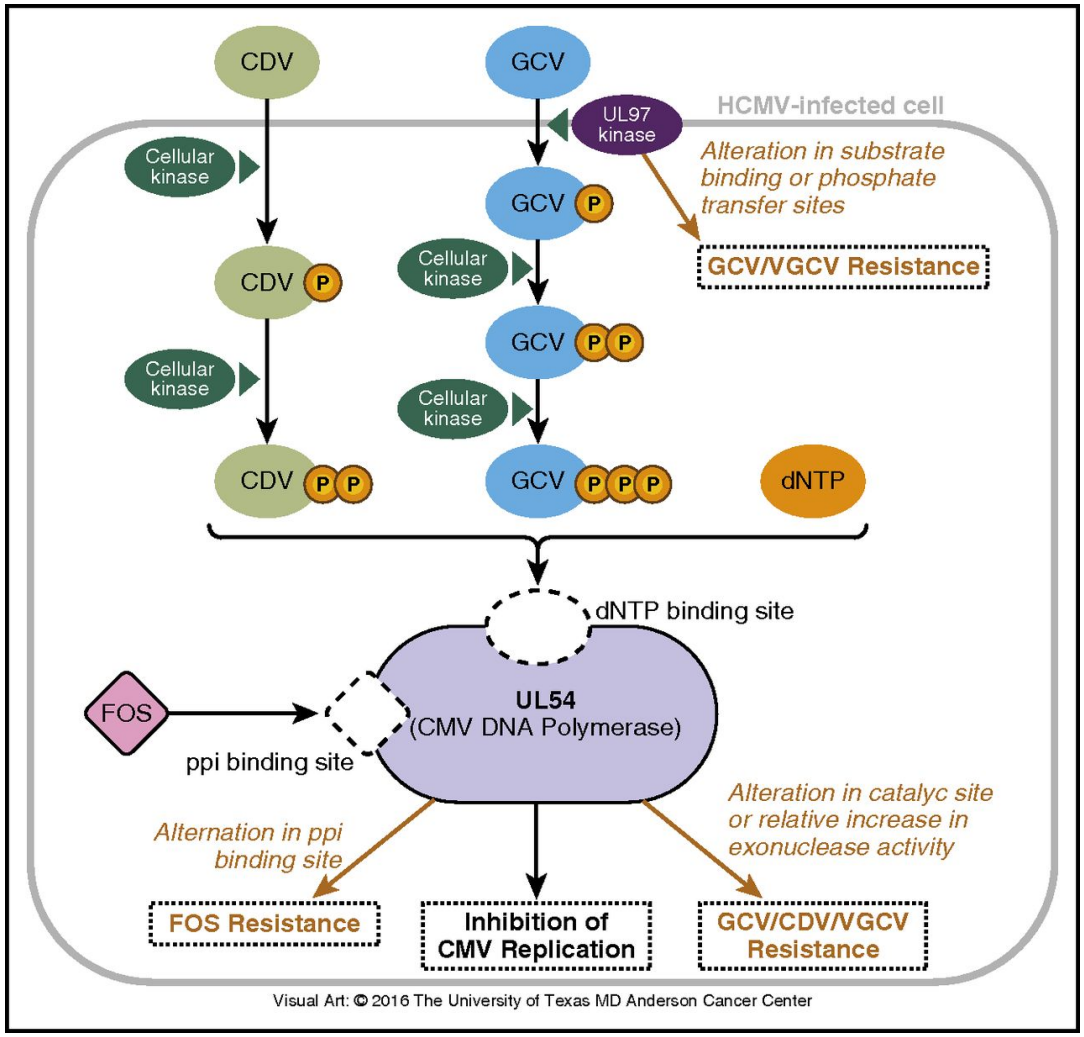


Immuno-suppression	CMV doubling time	Risk Groups	CMV Plasma DNA Level to Start PET at FHCRC*	CMV Whole Blood DNA Level to Start PET at Karolinska Institute**
		Cord blood	Any level	1000 copies
		Allograft - High-dose steroids⁺ - T cell depletion - Anti-T cell antibodies - CD34 selection	> 100 copies/mL	1000 copies
		Allograft - Low dose steroids - No T cell depletion or anti T cell antibodies	> 500 copies/mL > or 5-fold ⇑ †	1000 copies
		Allograft - after day 100	> 1000 copies/mL > or 5-fold ⇑ †	1000 copies if GVHD Other individual assessment based on ⇑

* Assays performed weekly or twice weekly (highest risk); limit of detection 25 copies/mL
⁺ 1 mg per kg of prednisone or higher
† If initial level is less than threshold
** Assays performed weekly, limit of detection 50 copies/mL

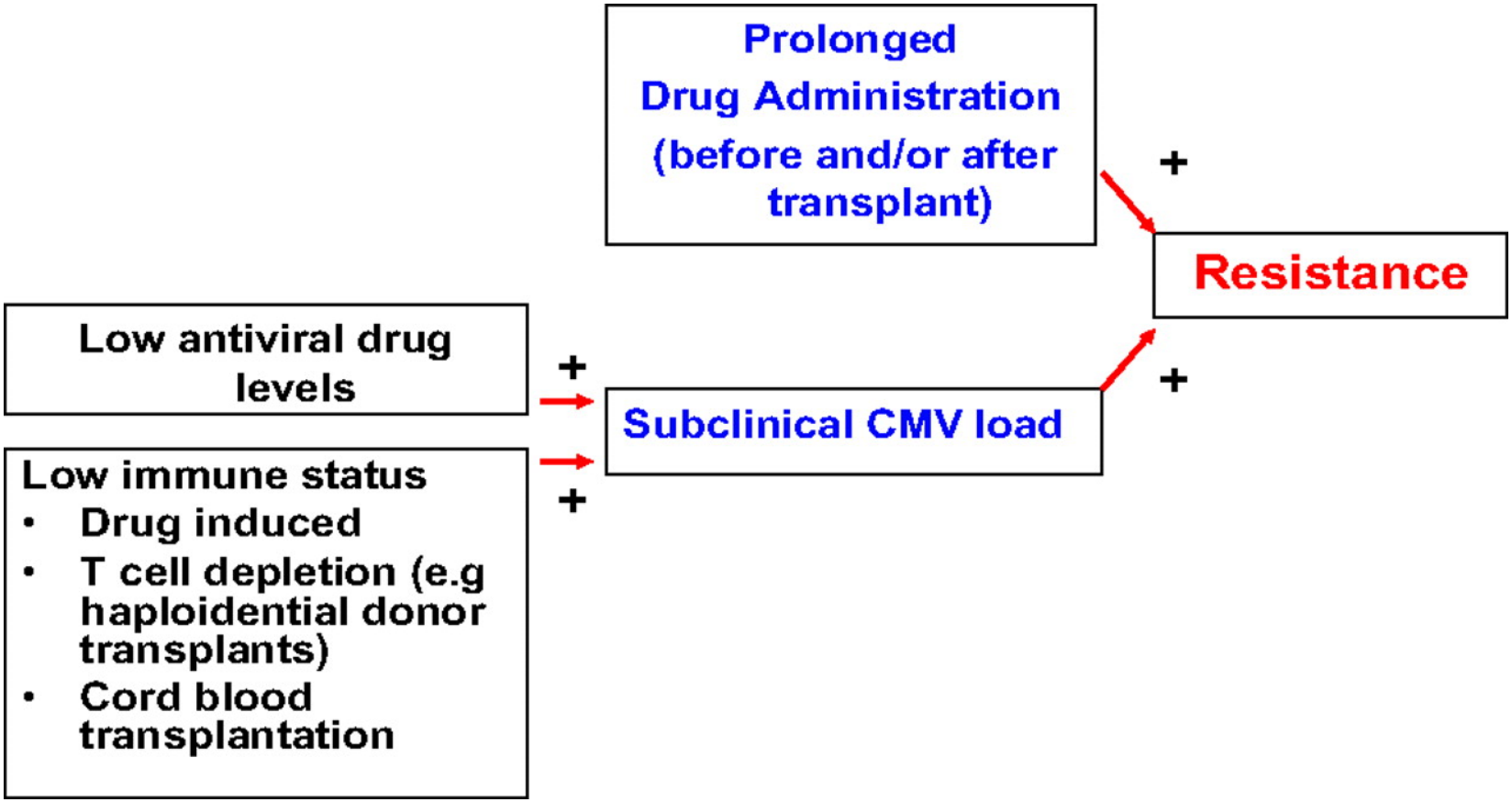
Michael Boeckh, and Per Ljungman Blood 2009;113:5711-5719

Mechanism of action of antiviral drugs for CMV



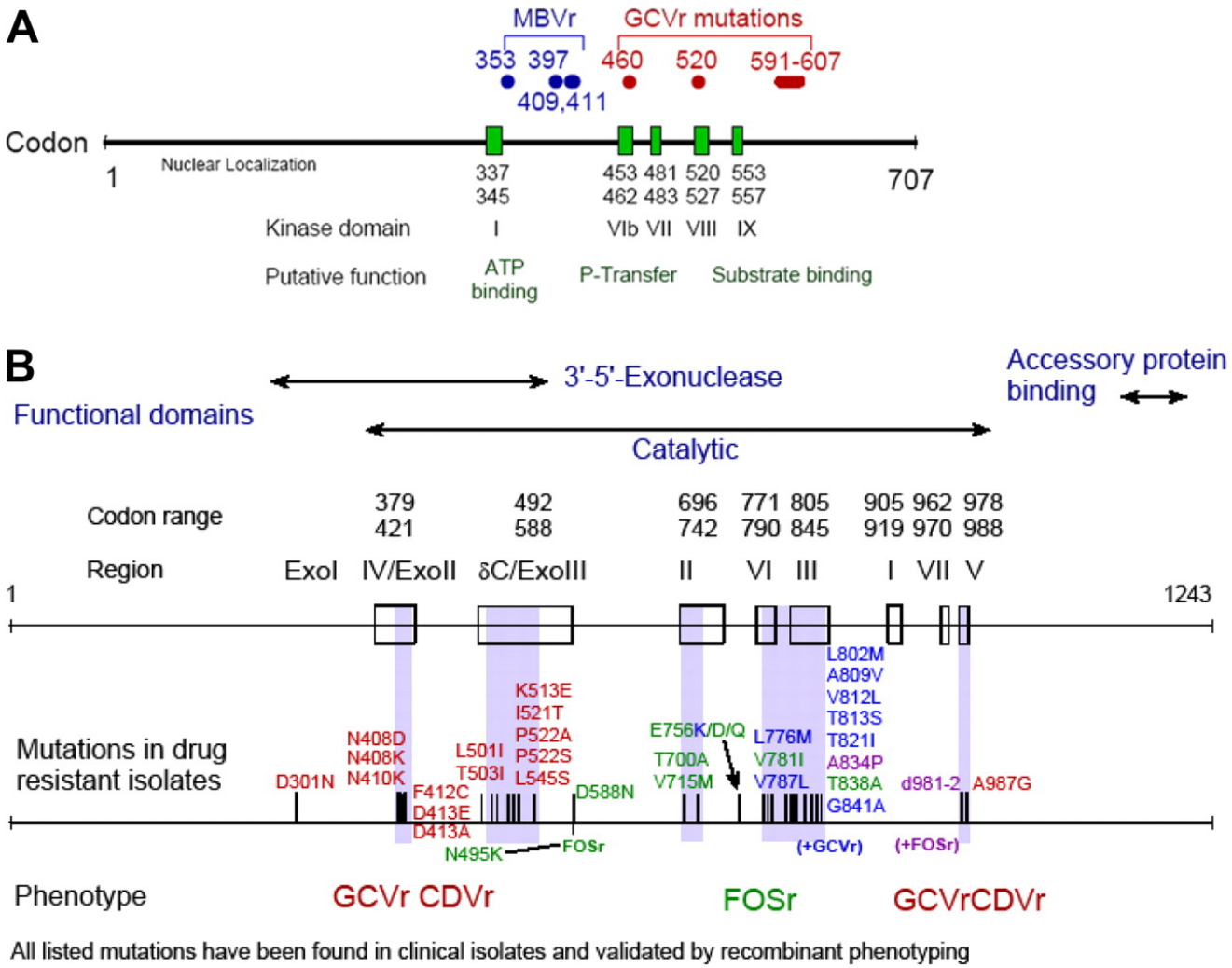
Firas El Chaer et al. Blood 2016;128:2624-2636

Pathogenesis of CMV drug resistance



Michael Boeckh, and Per Ljungman Blood
2009;113:5711-5719

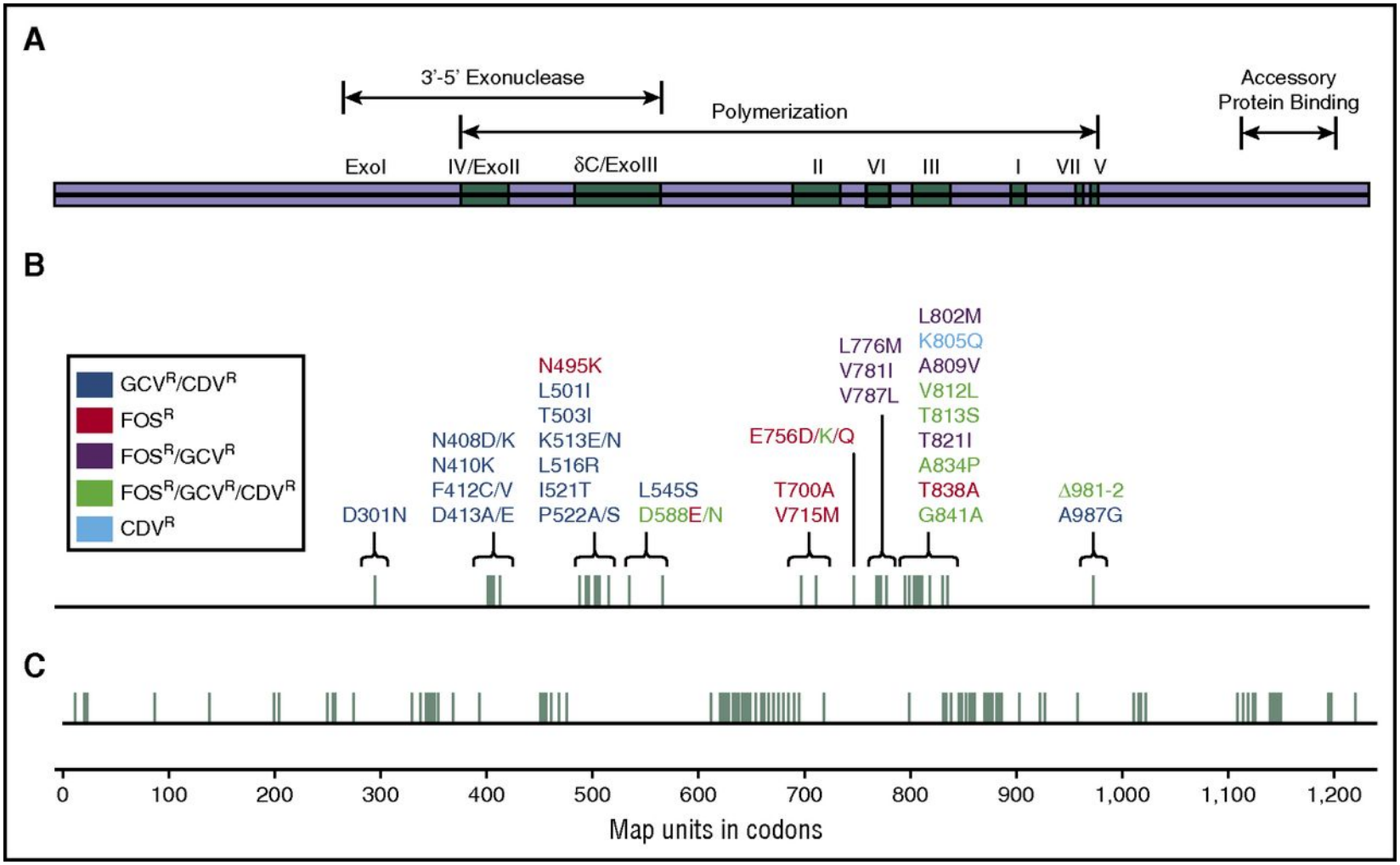
CMV drug resistance mutation maps



All listed mutations have been found in clinical isolates and validated by recombinant phenotyping

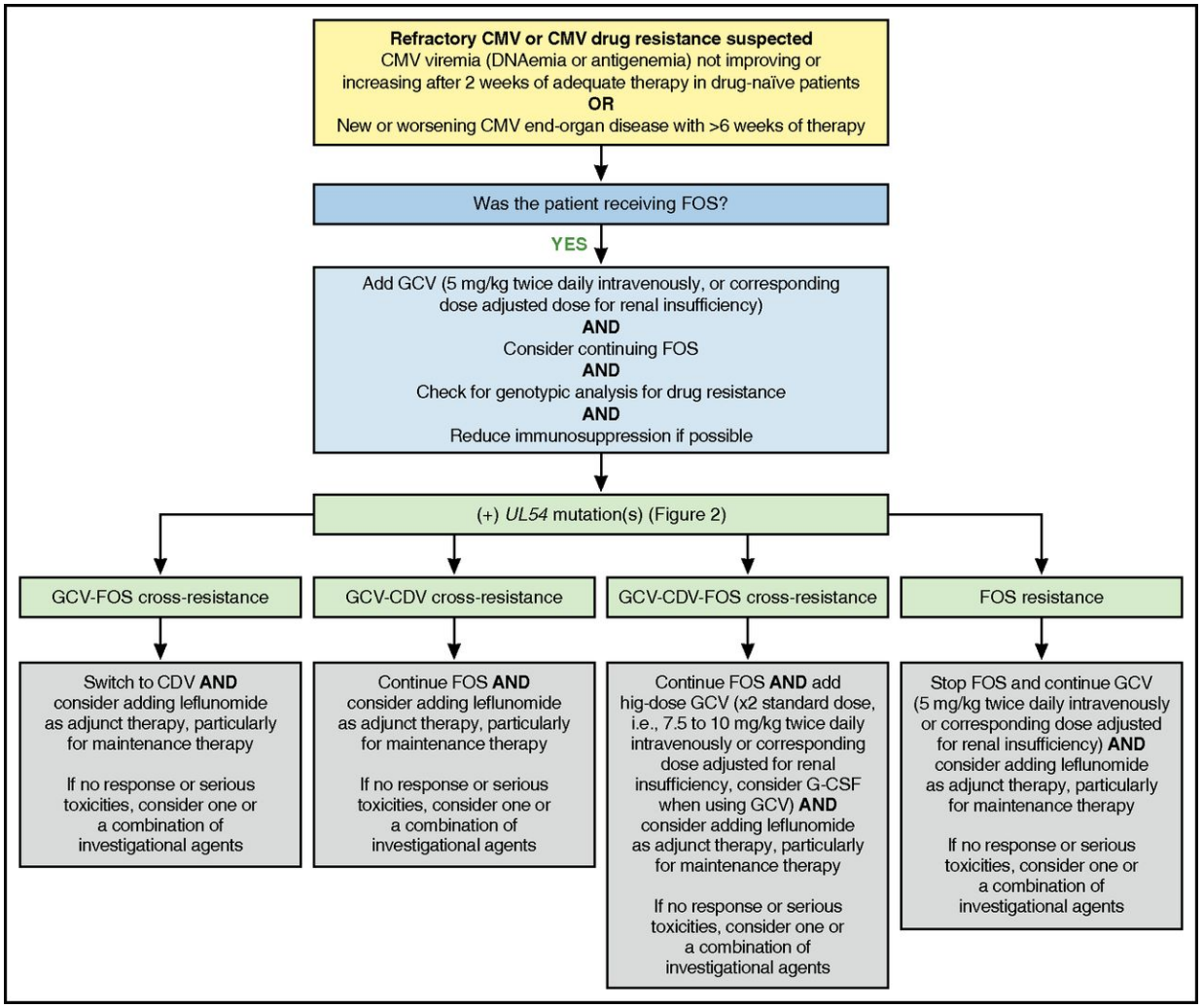
Michael Boeckh, and Per Ljungman Blood
2009;113:5711-5719

Map of the CMV DNA polymerase gene (UL54 or pol)



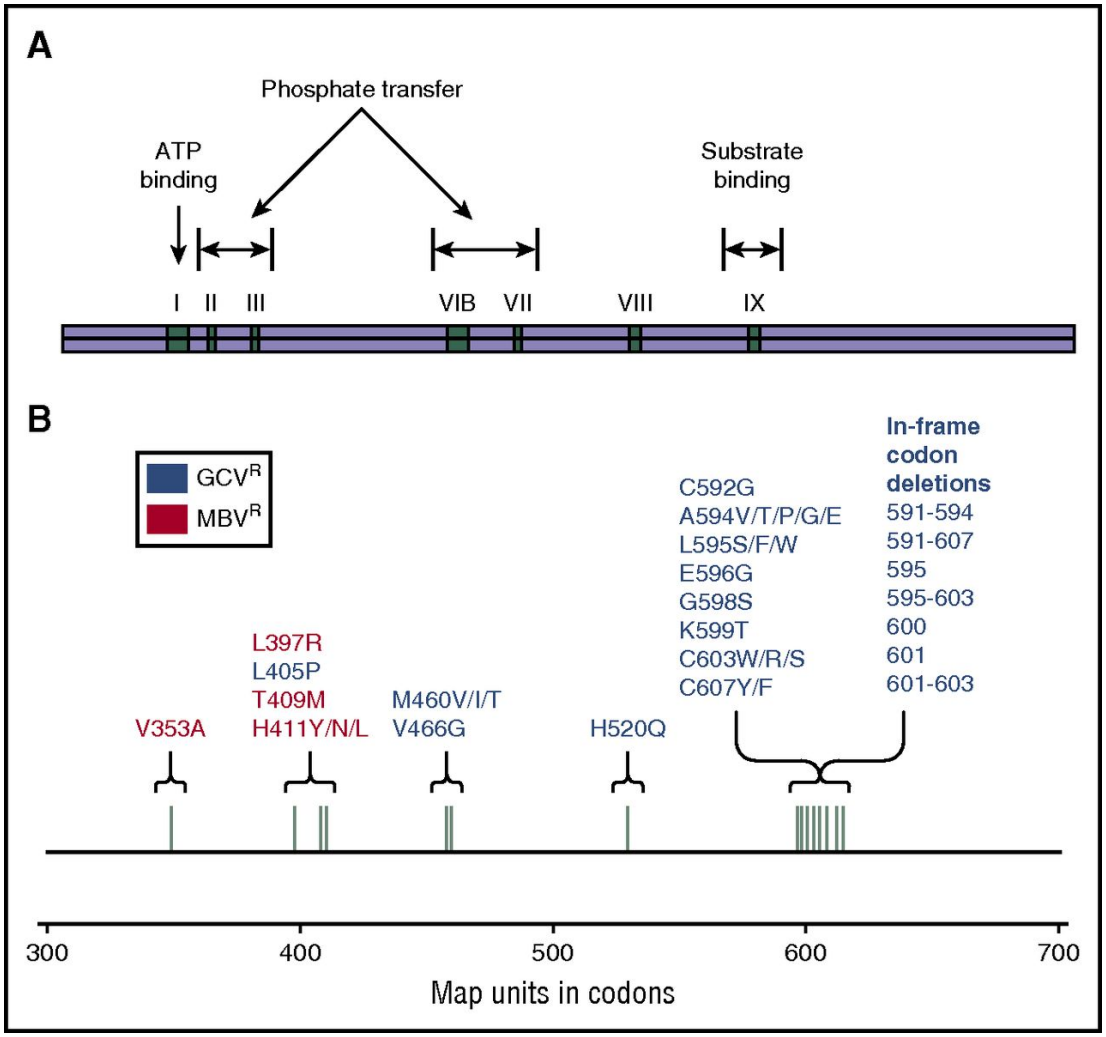
Firas El Chaer et al. Blood 2016;128:2624-2636

MD Anderson Cancer Center proposed algorithm for management of refractory or resistant CMV infection with UL54 mutation(s)



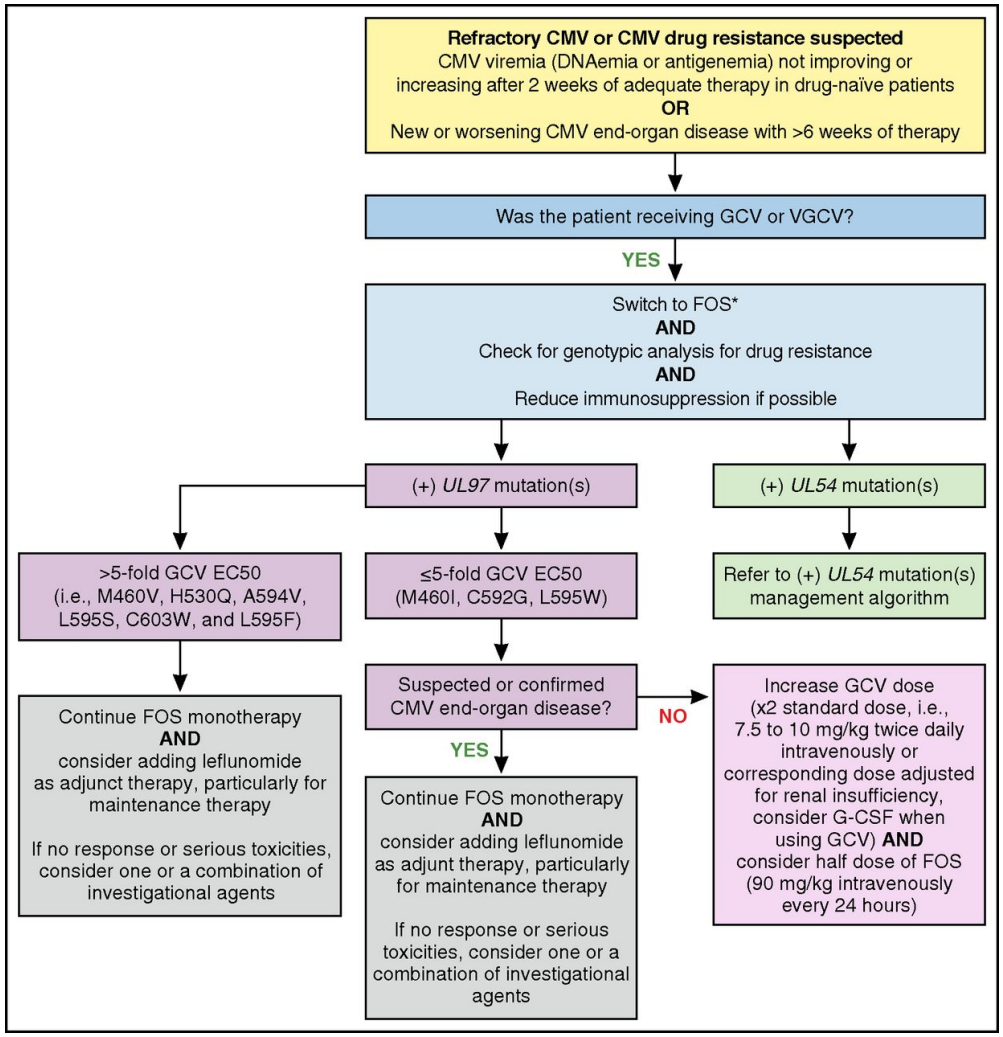
Firas El Chaer et al. Blood 2016;128:2624-2636

Map of the cytomegalovirus UL97 gene



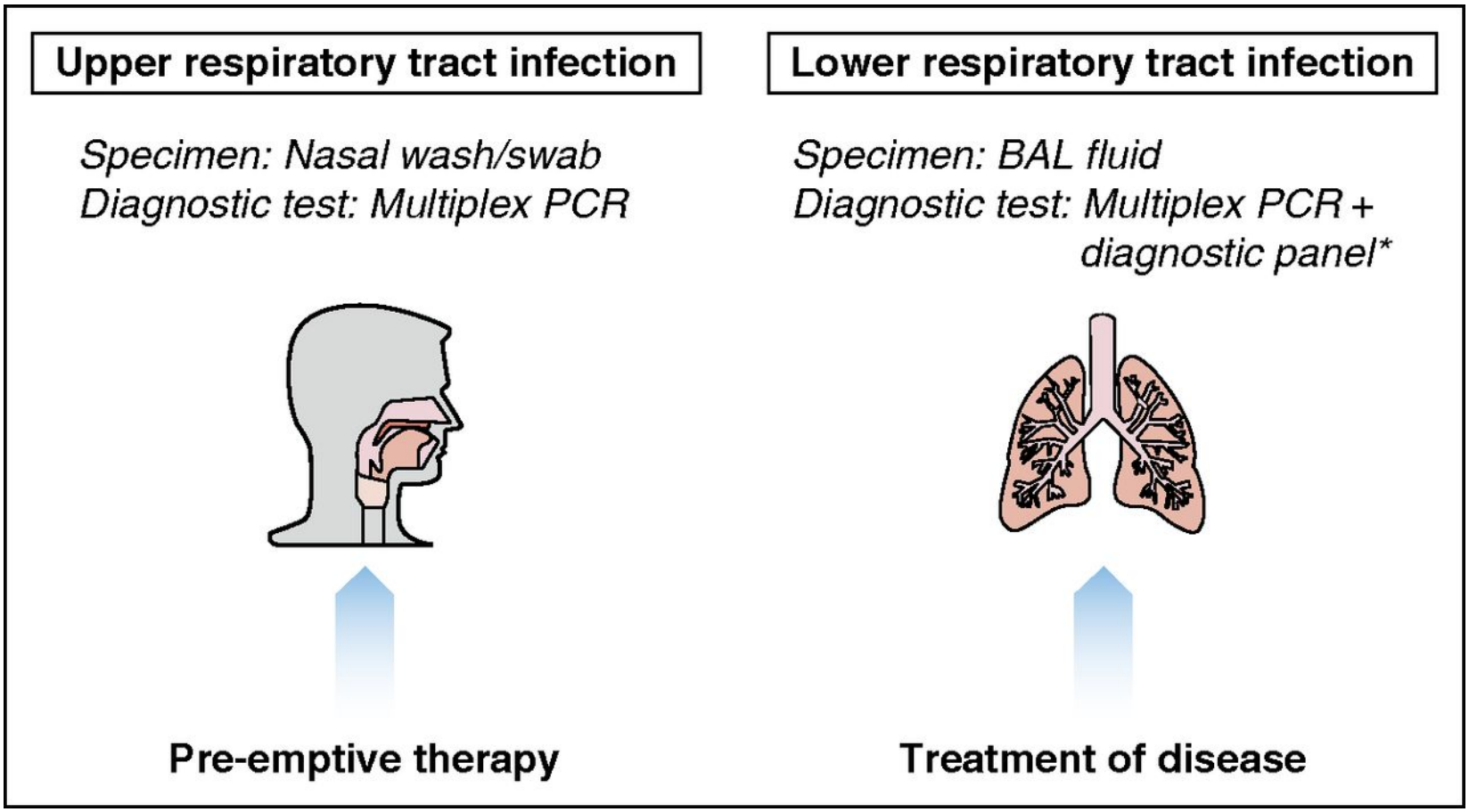
Firas El Chaer et al. Blood 2016;128:2624-2636

MD Anderson Cancer Center proposed algorithm for management of refractory or resistant CMV infection with UL97 mutation(s)



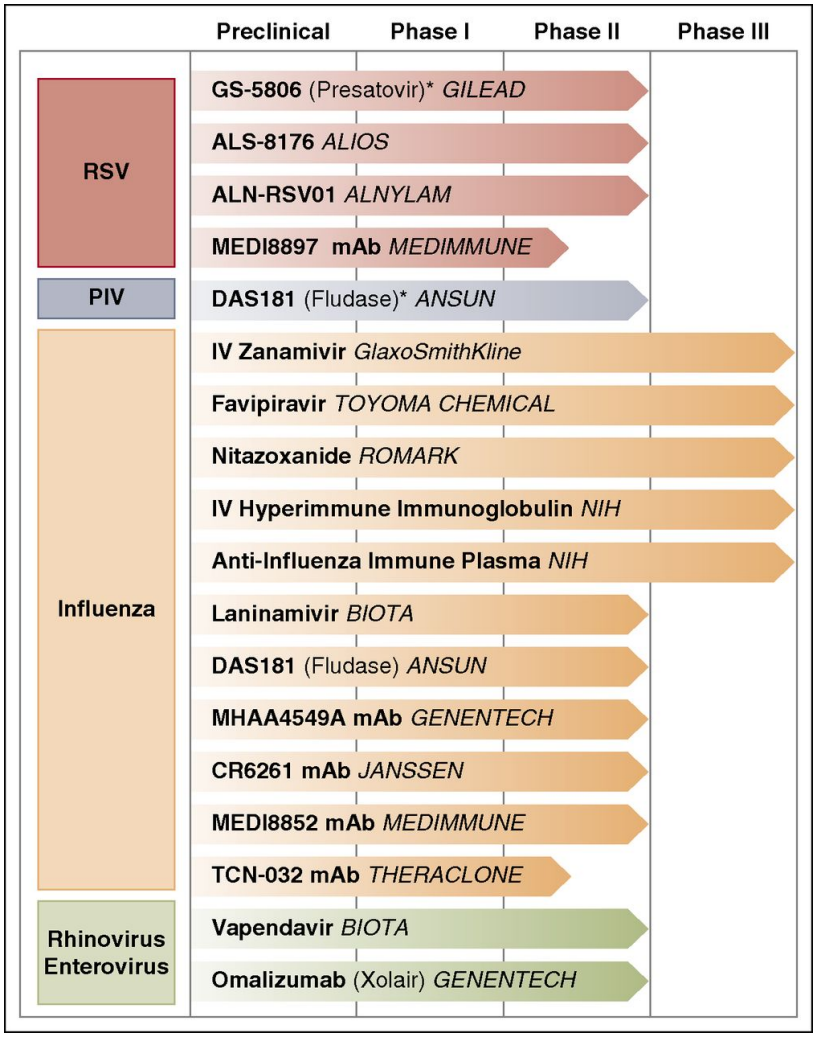
Firas El Chaer et al. Blood 2016;128:2624-2636

Therapeutic strategies for respiratory viral infections posttransplant



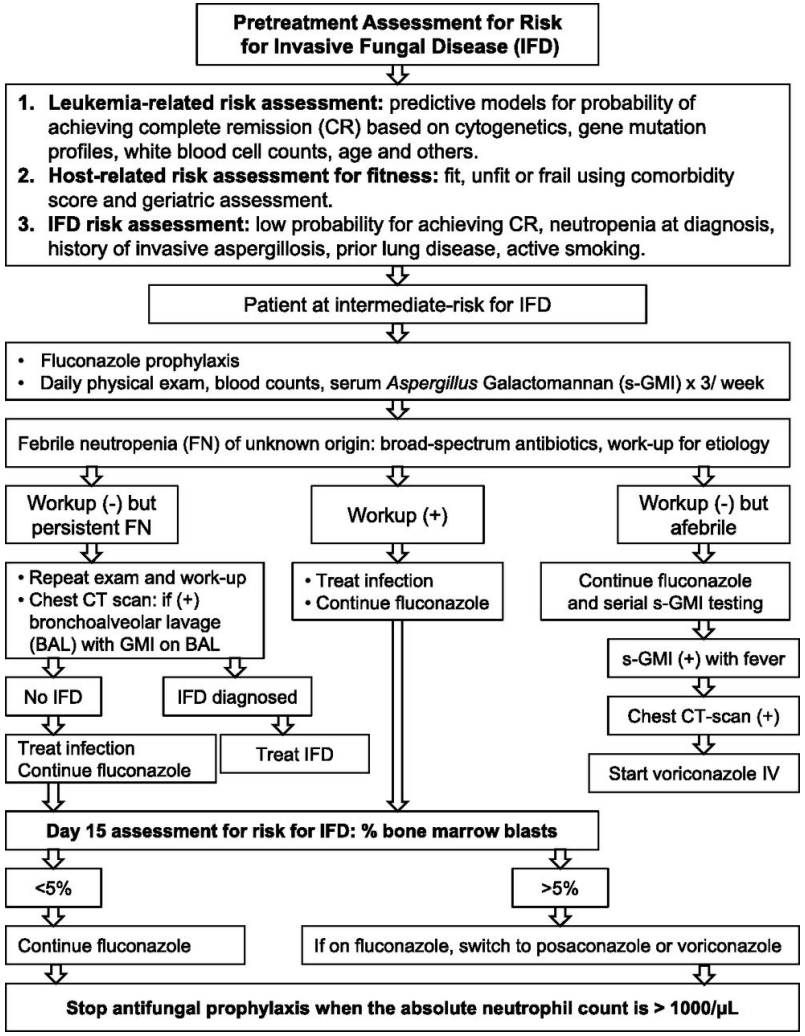
Alpana Waghmare et al. Blood 2016;127:2682-2692

Ongoing clinical trials for treatment of respiratory viral infections in patients with hematologic malignancy or HCT recipients



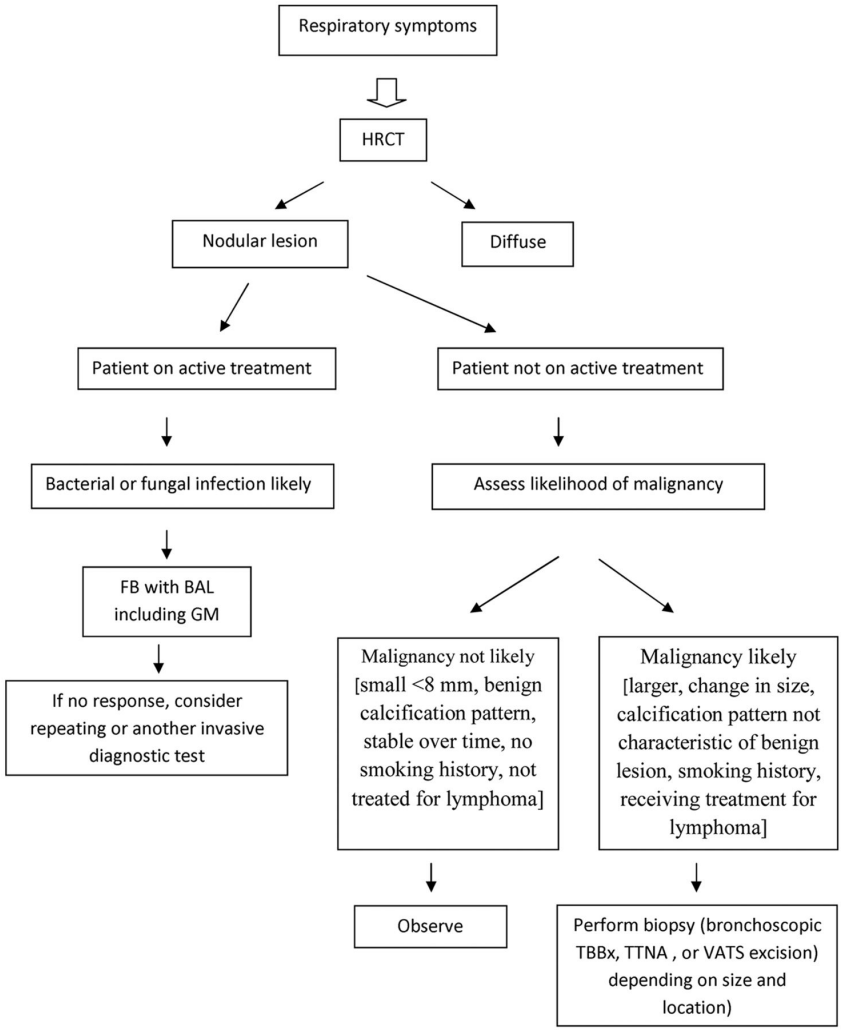
Alpana Waghmare et al. Blood 2016;127:2682-2692

Risk-adapted strategy for antifungal prophylaxis



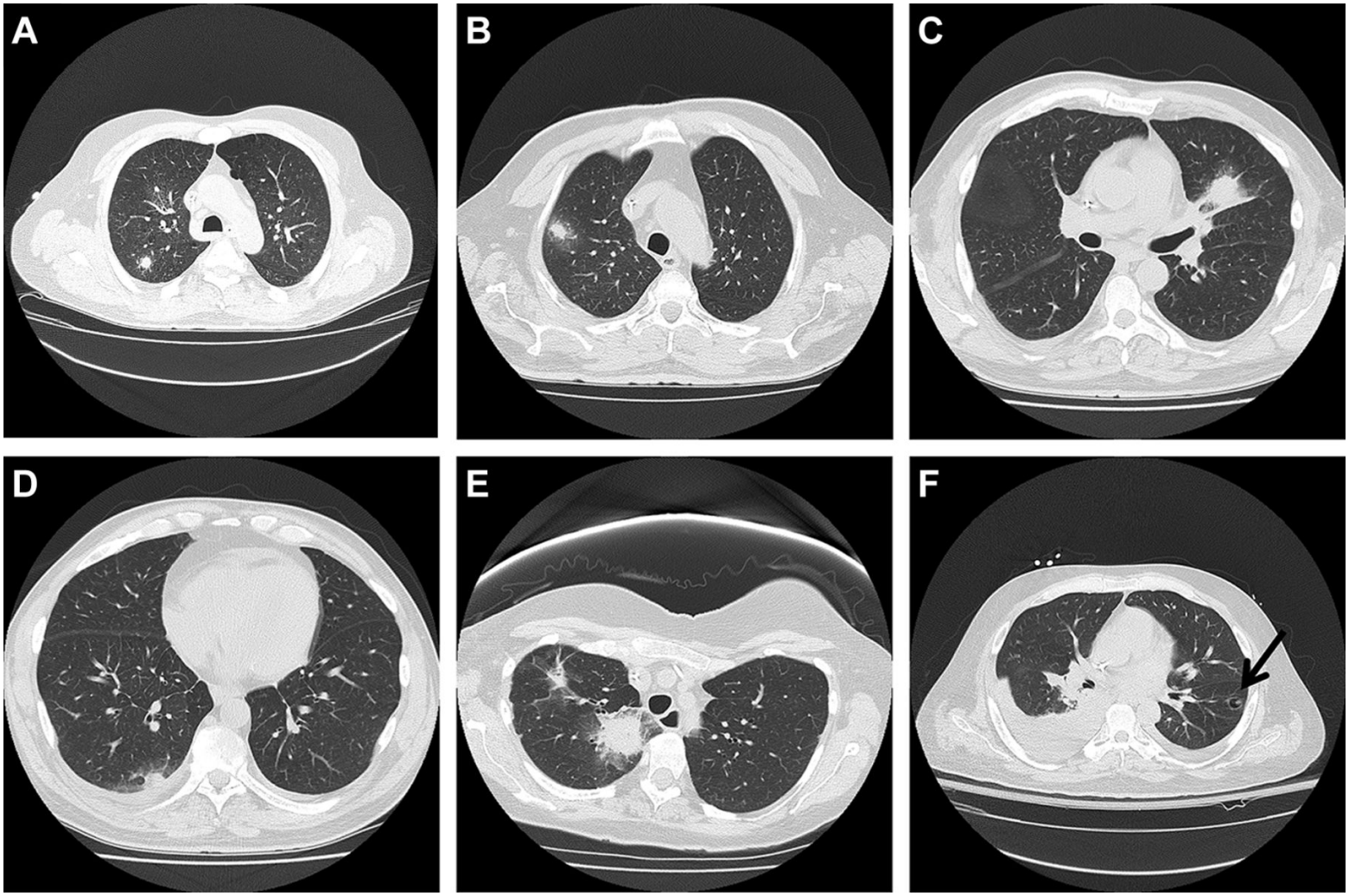
Marcio Nucci, and Elias Anaissie Blood 2014;124:3858-3869

Management of pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation



John R. Wingard et al. Blood 2012;120:1791-1800

Radiographs of different types of nodular pulmonary lesions



John R. Wingard et al. Blood 2012;120:1791-1800

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