Reactivarea herpesvirusurilor

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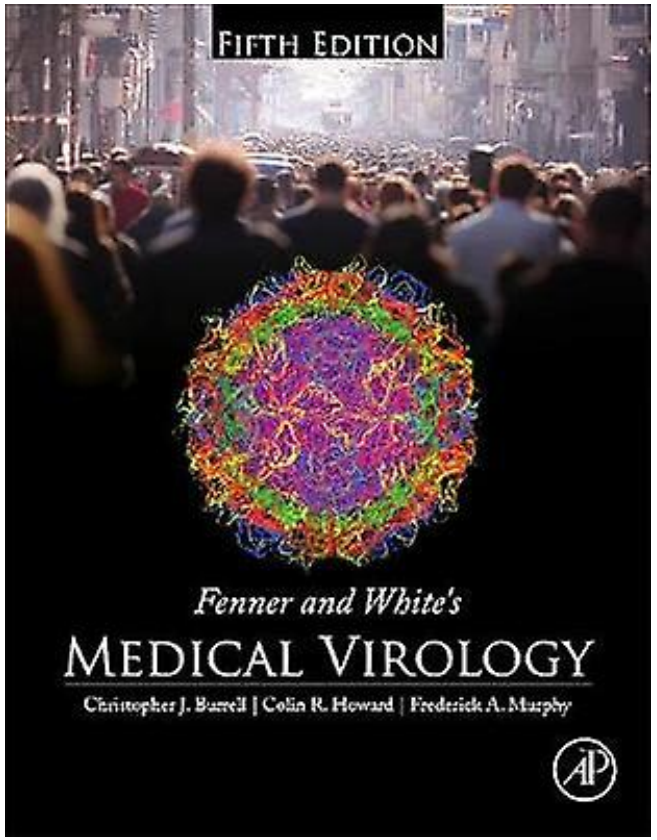
Chapter 17

Herpesviruses



PROPERTIES OF THE VIRUSES

Classification

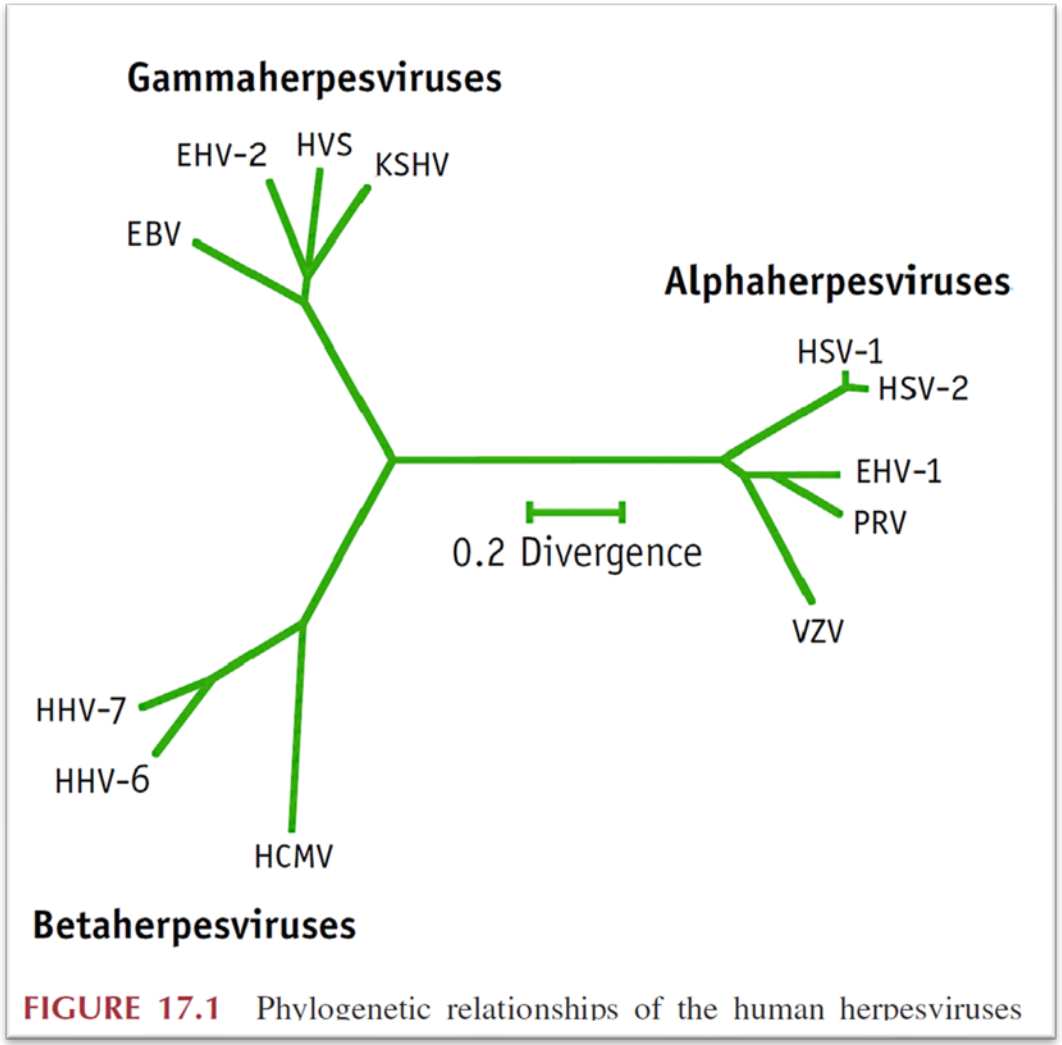


FIGURE 17.1 Phylogenetic relationships of the human herpesviruses

Burrell CJ, Howard CR, Murphy FA, eds. Fenner and White's Medical Virology. 5th ed. Academic Pr Inc; 2016.

Herpesvirus latency

Jeffrey I. Cohen

Published May 4, 2020 - More info

JCI The Journal of Clinical Investigation

Table 1. Features of latency and replication of human herpesviruses

Subfamily	Virus	Site of latency	Primary sites of replication	Proteins expressed during latency	RNAs expressed during latency	Disease in primary infection	Disease in immunocompromised host
Alphaherpesvirus	HSV-1	Neuron	Epithelial cells in and around mouth and genital area	None	LATs, miRNAs	Cold sores, genital herpes	Visceral infections (esophagitis, retinitis, hepatitis, encephalitis, etc.)
	HSV-2	Neuron	Epithelial cells in and around genital area	None	LATs, miRNAs	Genital herpes, neonatal herpes	Visceral infection (esophagitis, retinitis, hepatitis, encephalitis, etc.)
	VZV	Neuron	Epithelial cells in skin	None	VLT, IE63, miRNAs	Chickenpox	Visceral infection (disseminated rash, pneumonitis, hepatitis, encephalitis, etc.)

Cohen JI. J Clin Invest. 2020

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Betaherpesvirus	HCMV	$CD34^+$ myeloid progenitors, $CD14^+$ monocytes	Epithelial cells of salivary glands, kidneys, genital tract	None; IE1x4?[A]	Multiple RNAs of all classes at low level, miRNAs	Infectious mononucleosis, congenital HCMV in neonates	Visceral infection (pneumonitis, hepatitis, retinitis, colitis, etc.)
	HHV-6	$CD34^+$ stem cells, monocytes	Epithelial cells of salivary glands, lymphocytes	None reported	Not reported	Roseola; infantile fever and seizures	Encephalitis
	HHV-7	$CD4^+$ cells	Epithelial cells of salivary glands	None reported	Not reported	Roseola; infantile fever and seizures	Encephalitis
Gammaherpesvirus	EBV	B cells	Epithelial cells in oropharynx	EBNA1[A], others in tumors[B]	EBERs, miRNAs, others in tumors[B]	Infectious mononucleosis	B cell lymphoma
	KSHV	B cells	Epithelial cells in oropharynx, genital tract	LANA[A], others in tumors[C]	miRNAs, others in tumors[C]	Fever and rash	Primary effusion lymphoma, Kaposi sarcoma, multicentric Castleman disease

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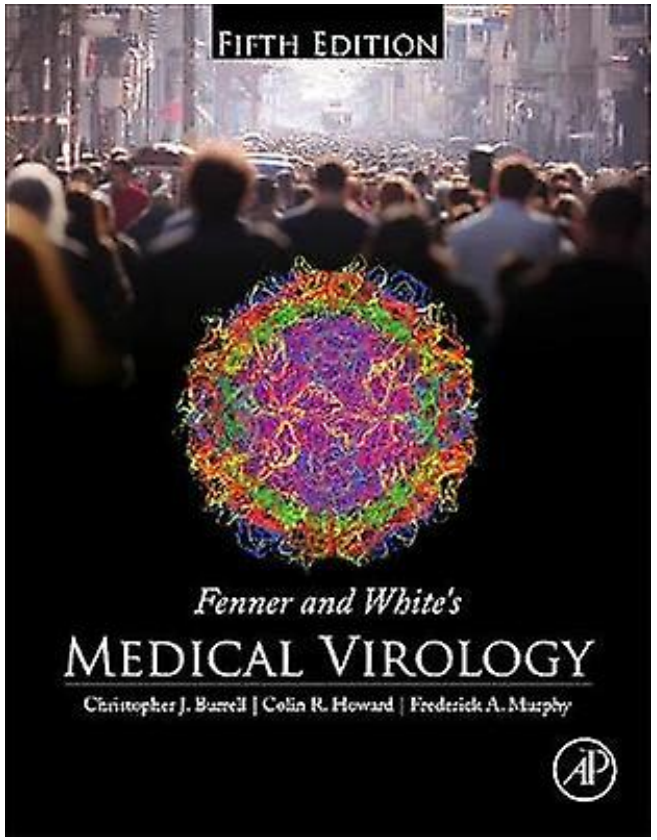
Herpesviruses



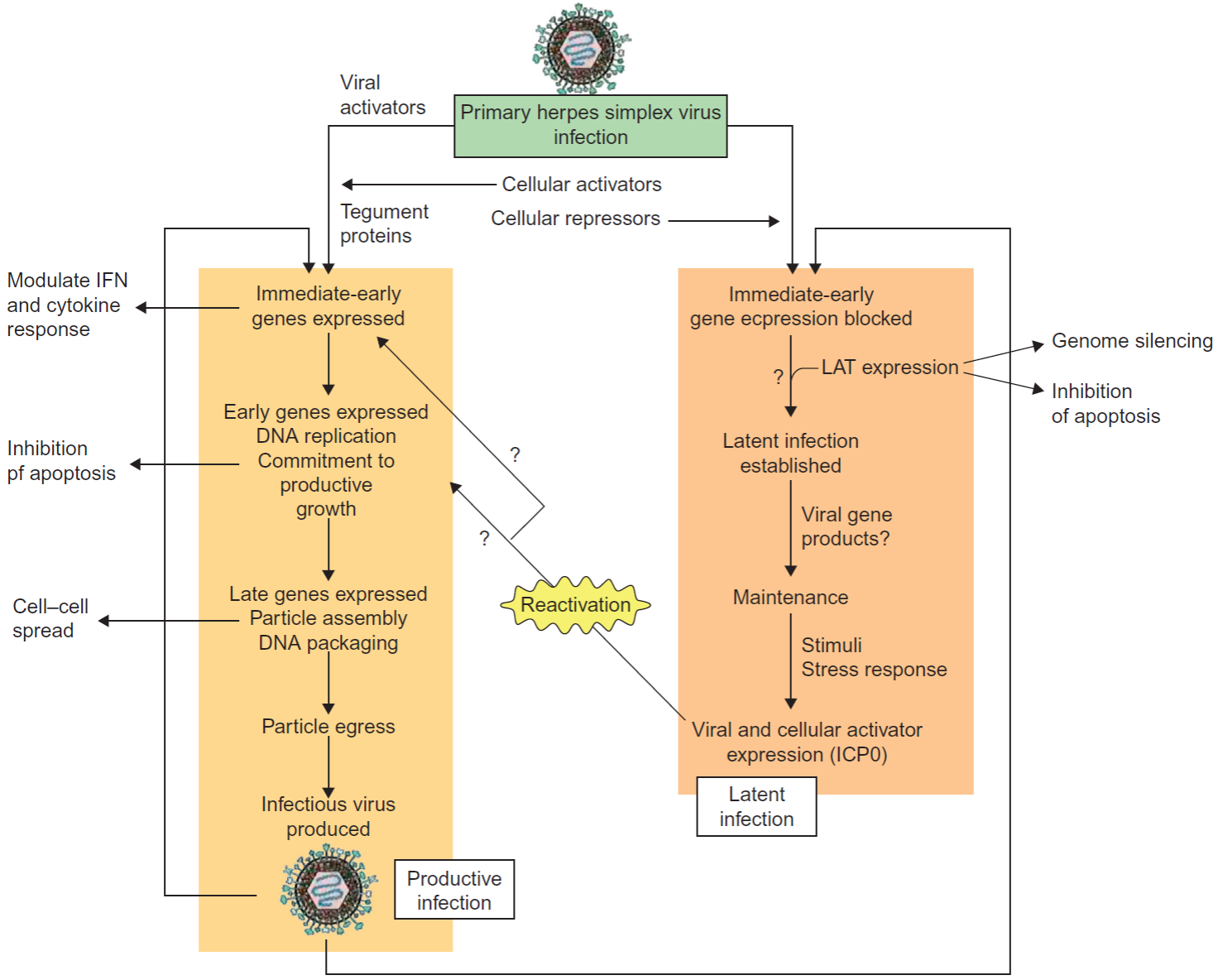


FIGURE 17.4 General strategies for the establishment of productive or latent infection with herpes simplex virus. The productive infection is shown by the pathway on the left, and the latent infection by the pathway on the right. Infectious particles produced by the productive pathway may infect other cells

Burrell CJ, Howard CR, Murphy FA, eds. Fenner and White's Medical Virology. 5th ed. Academic Pr Inc; 2016.

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Herpesviruses

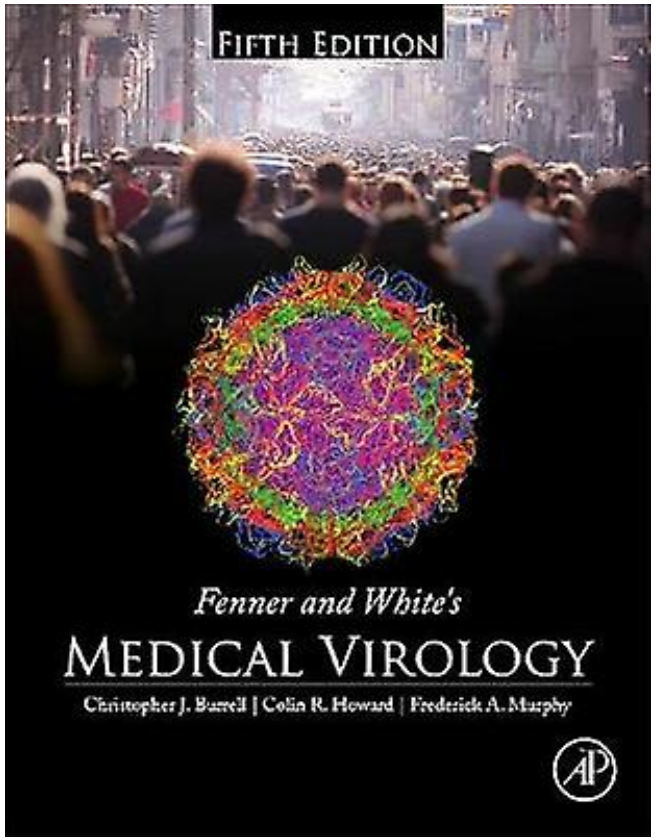

TABLE 17.4 Syndromes Caused by Cytomegalovirus Infections

Age or Immunocompetence	Route of Acquisition	Disease Caused by Primary Infection
Prenatal	Transplacental	Encephalitis, hepatitis, thrombocytopenia
		Long-term sequelae brain damage, nerve deafness, retinopathy
Perinatal	Cervical secretions, breast milk, saliva	Nil
Any age	Blood transfusion	Pneumonitis, disseminated disease
	Saliva or sexual intercourse	Mononucleosis, mild hepatitis
	Blood transfusion	Mononucleosis
Immunocompromised[a]	Saliva, sex, organ graft, blood transfusion	Pneumonia, hepatitis, retinitis, encephalitis, myelitis, gastrointestinal disease

[a]*Diseases shown occur less commonly after reactivation of a latent infection.*

Burrell CJ, Howard CR, Murphy FA, eds. Fenner and White's Medical Virology. 5th ed. Academic Pr Inc; 2016.

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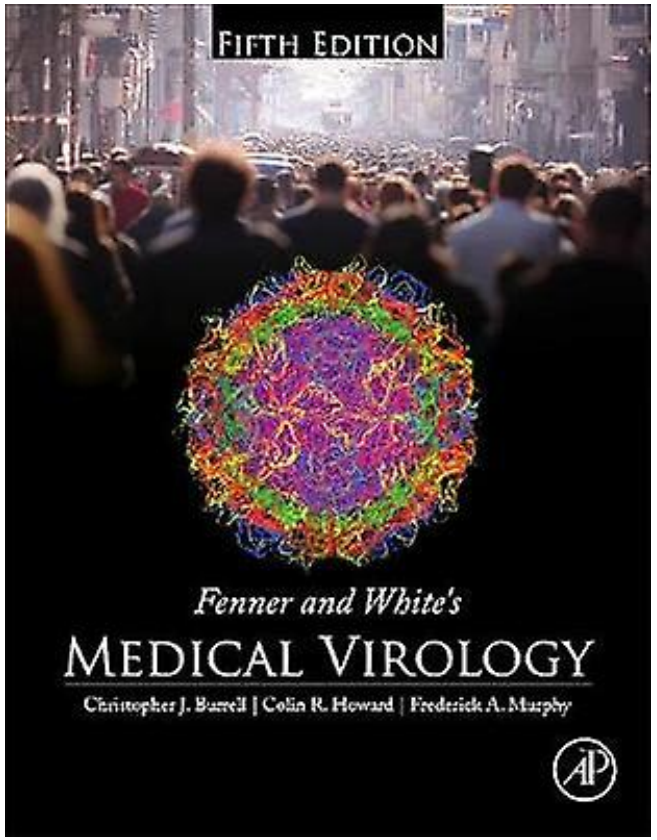

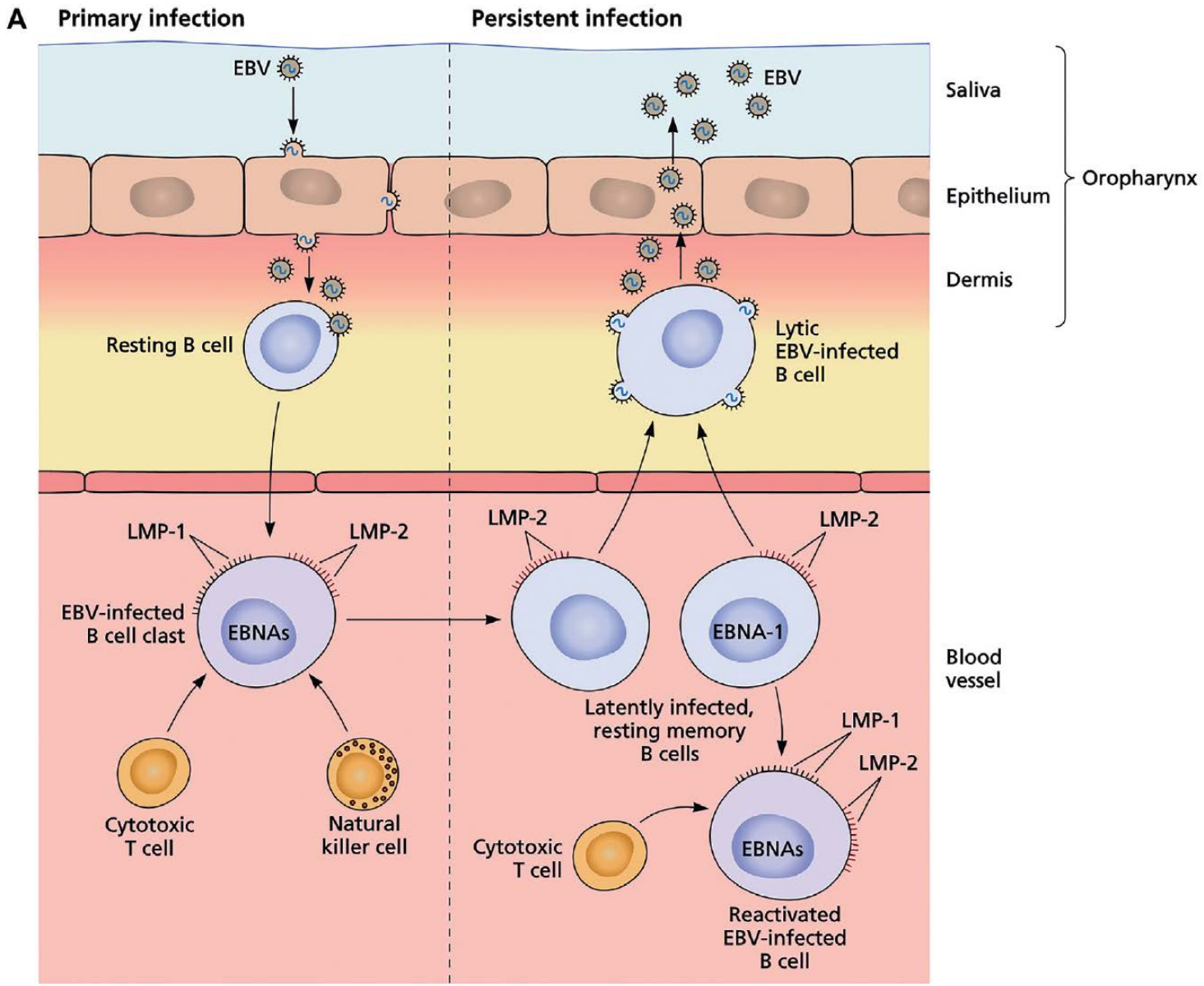

Burrell CJ, Howard CR, Murphy FA, eds. Fenner and White's Medical Virology. 5th ed. Academic Pr Inc; 2016.

Novel Therapeutics for Epstein–Barr Virus

by Graciela Andrei * , Erika Trompet and Robert Snoeck

molecules

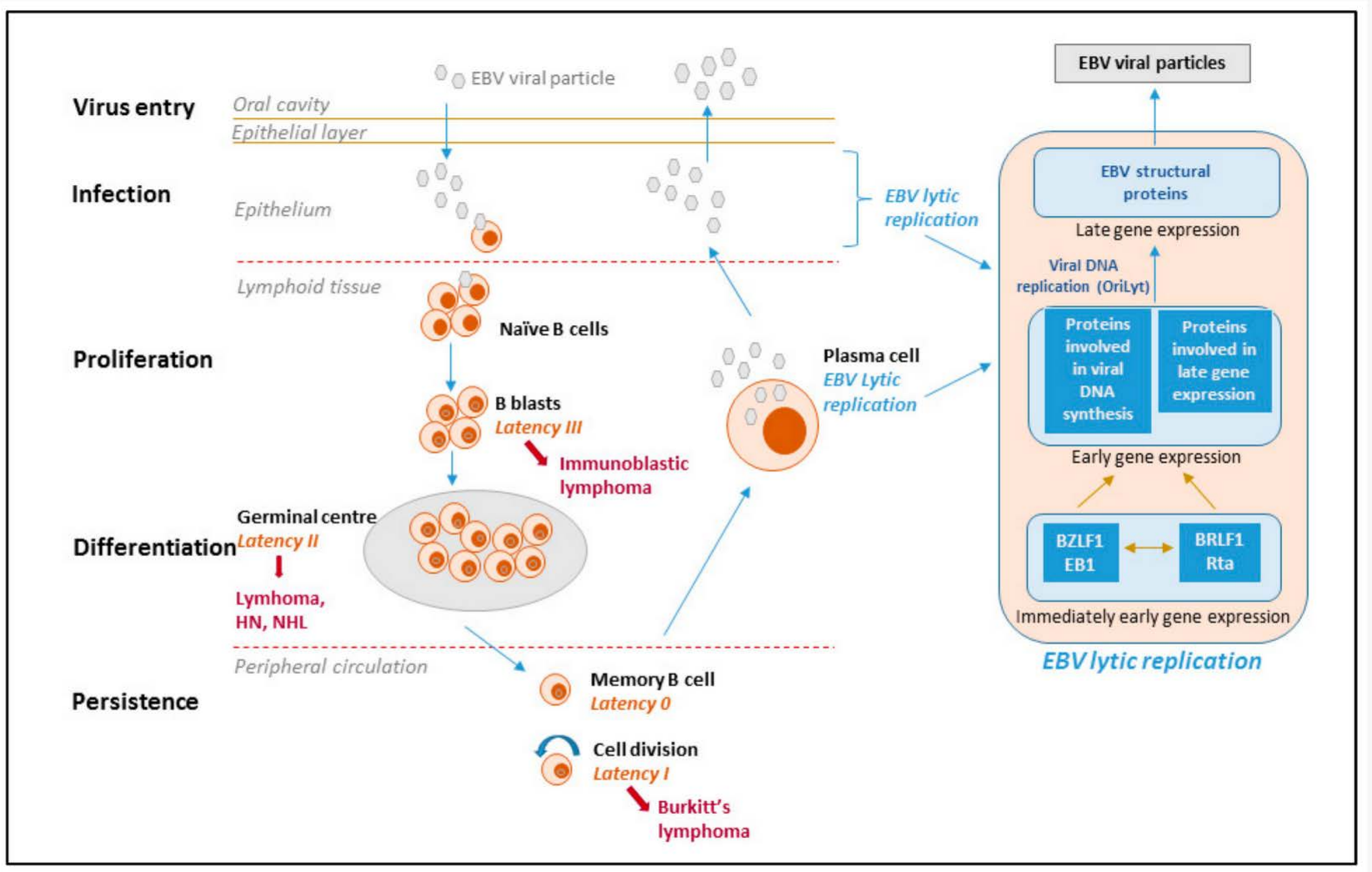

Figure 1. EBV life cycle, latency stages and derived lymphomas. The viral life cycle includes at least five different stages (virus entry, infection, proliferation, differentiation and persistence), and four of them are associated with EBV diseases. The virus is transmitted through the saliva and infects naïve B-cells in the

Andrei G et al. Molecules 2019.

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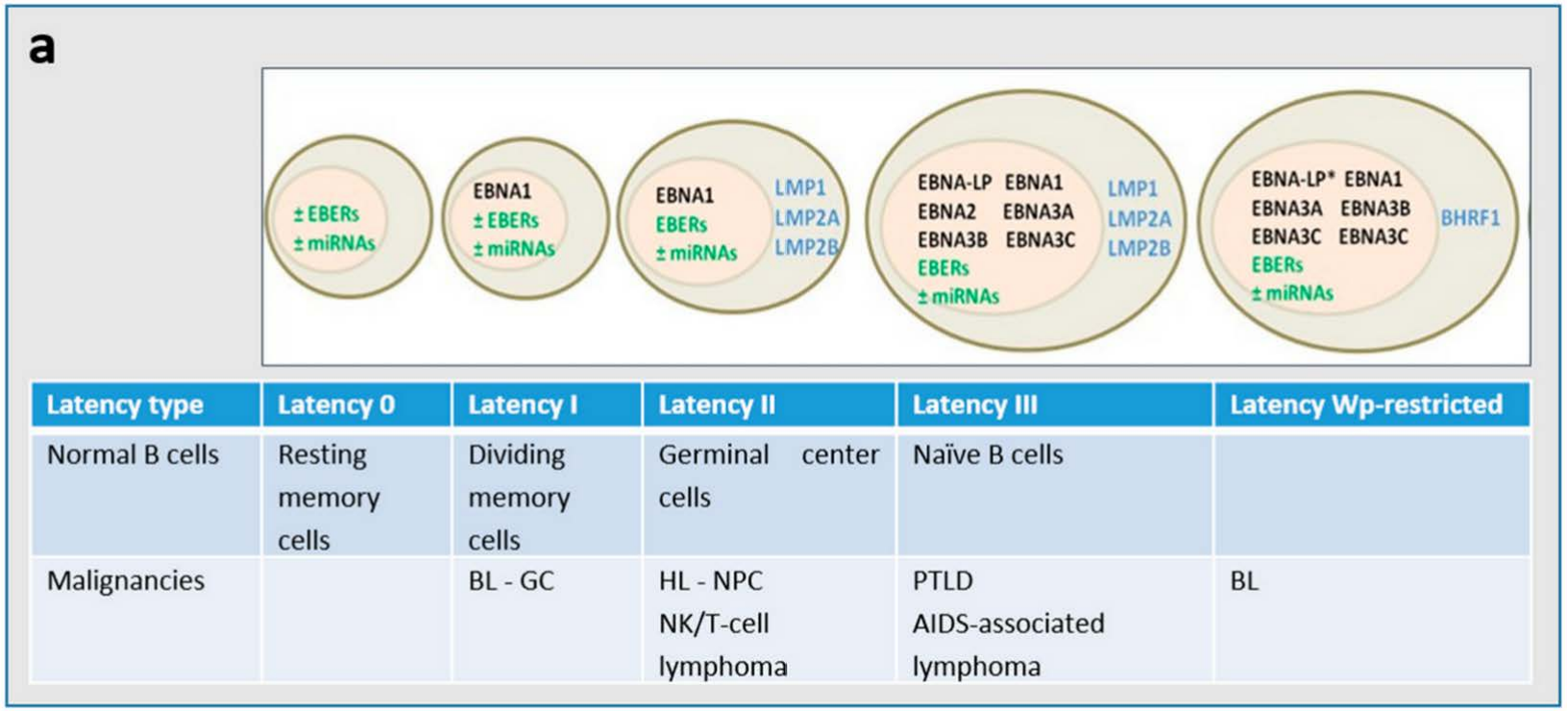

Latency type	Latency 0	Latency I	Latency II	Latency III	Latency Wp-restricted
Normal B cells	Resting memory cells	Dividing memory cells	Germinal center cells	Naïve B cells	
Malignancies		BL - GC	HL - NPC NK/T-cell lymphoma	PTLD AIDS-associated lymphoma	BL

Figure 2. (**a**) Patterns of gene expression during EBV latency.

EBV-associated malignancies. PEL: primary effusion lymphoma; HL: Hodgkin lymphoma; BL: Burkitt lymphoma; NHL: non-Hodgkin lymphoma; PTLD: post-transplant lymphoproliferative disorder; NPC: nasopharyngeal carcinoma; GC: gastric carcinoma.

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Anti-EBV therapy remains a major unmet medical need, in particular for patients with an impaired immune system. Antivirals approved for other herpesviruses that have been evaluated for EBV-associated diseases have delivered disappointing results. A few candidate anti-EBV drugs are available but much work remains to be done to

A novel strategy that could potentially be used to combat both productive and latent EBV infections is the targeting of viral genetic elements required for viral fitness by CRISPR/Cas9 genome editing techniques. Lebbink's group demonstrated that by simultaneous targeting of EBV genome with multiple guided RNAs (gRNAs), almost complete clearance of the virus from latently infected EBV-transformed cells was achieved. This opens new avenues for the development of therapeutic approaches to manage pathogenic human herpesviruses by means of novel genome-engineering technologies [117].

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Prevention of viral infections in hematopoietic cell transplant recipients

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Topic Graphics

Author: John R Wingard, MD

Infection in HCT recipients is associated with high morbidity and mortality. Viruses of major importance in HCT recipients include herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, respiratory viruses (eg, influenza, parainfluenza, respiratory syncytial virus, adenovirus, severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), human herpes virus 6, hepatitis B, and hepatitis C. Antiviral prophylaxis or pre-emptive therapy against some of these viruses is recommended for HCT recipients and will be discussed here.

Prevention of viral infections in hematopoietic cell transplant recipients

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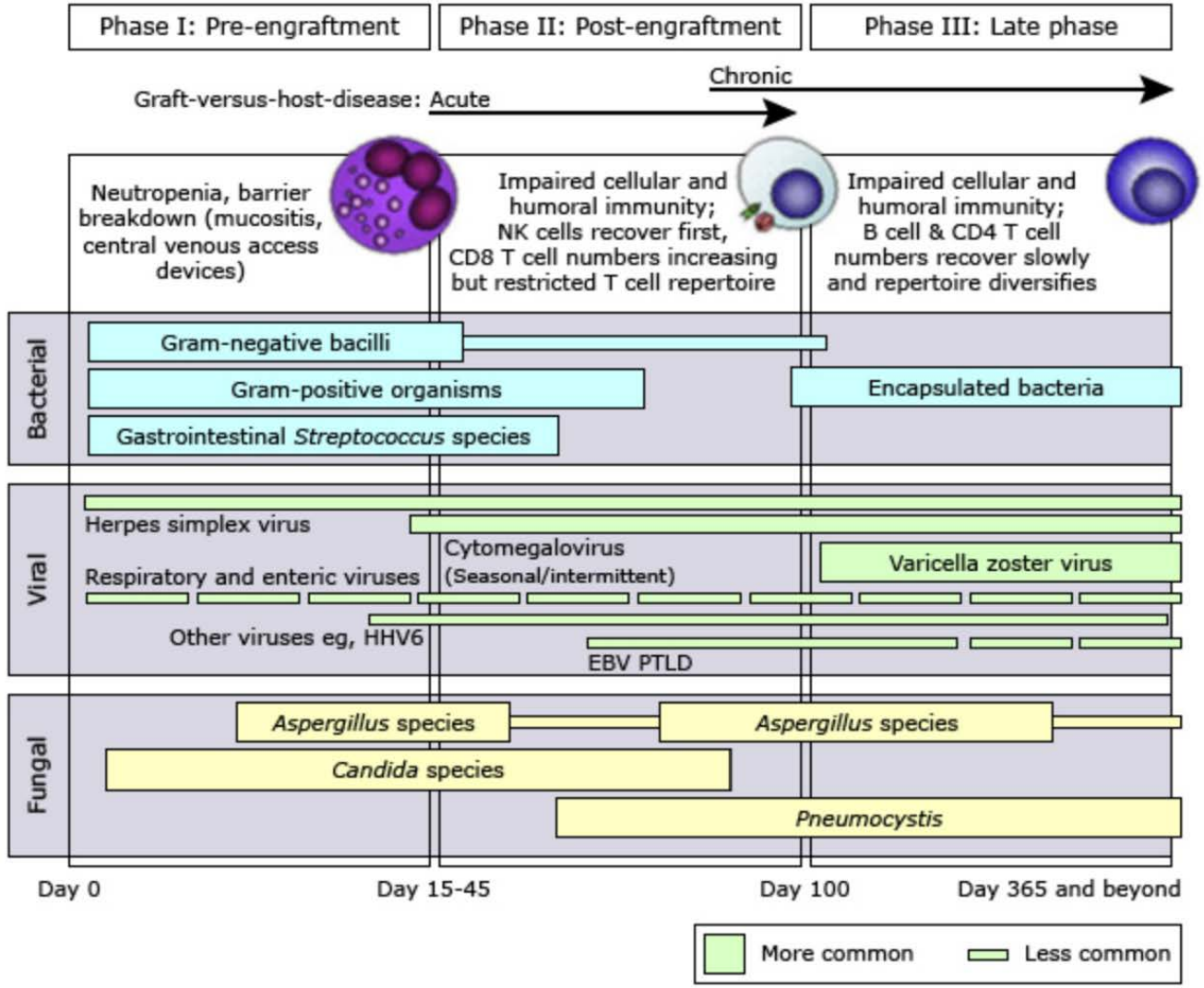
Phases of opportunistic infections among allogeneic hematopoietic cell transplant recipients



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Prevention of viral infections in hematopoietic cell transplant recipients

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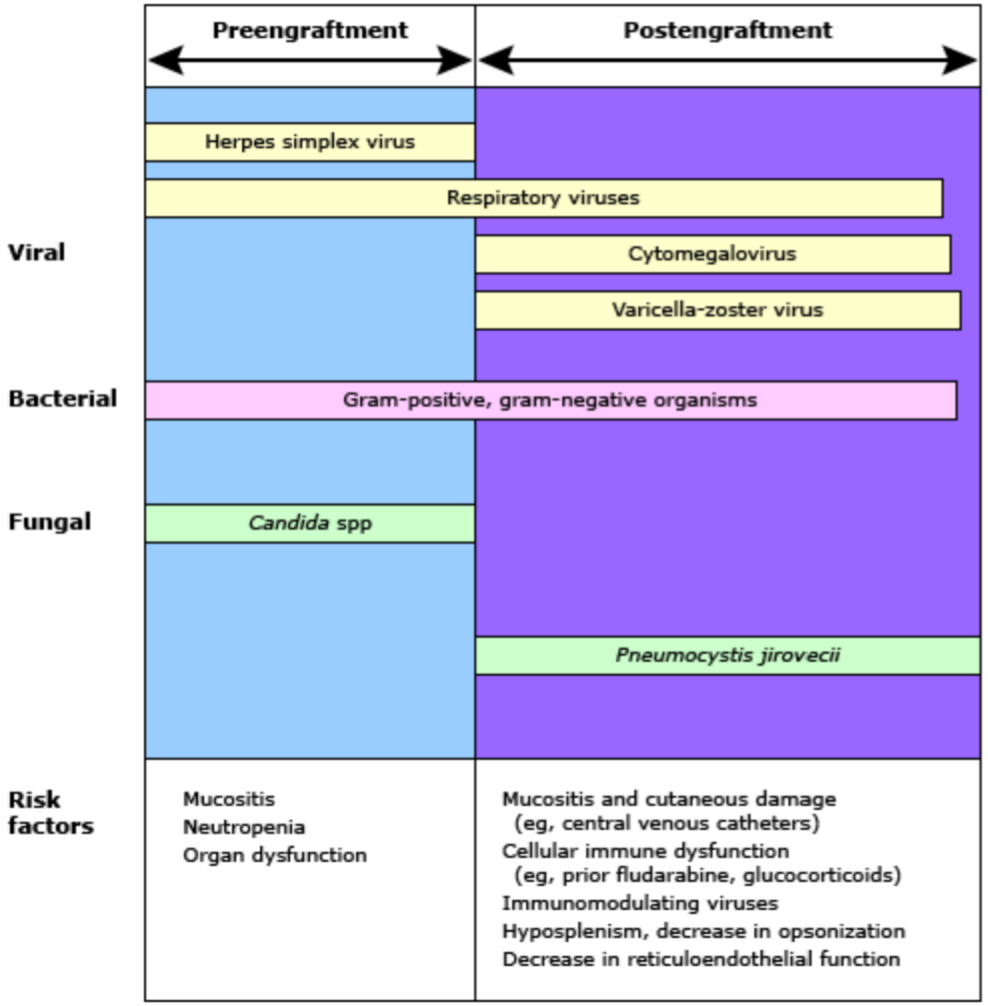
Typical timing of infections among autologous hematopoietic cell recipients receiving antimicrobial prophylaxis



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Prevention of viral infections in hematopoietic cell transplant recipients

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DEFINITIONS OF PROPHYLAXIS AND PRE-EMPTIVE THERAPY

Approaches to the prevention of infection in HCT recipients include primary prophylaxis, secondary prophylaxis, and pre-emptive therapy.

- **Primary prophylaxis** – Primary prophylaxis involves the administration of an antimicrobial drug to prevent infection in patients at increased risk.
- **Secondary prophylaxis** – Secondary prophylaxis involves the administration of prophylactic doses of an antimicrobial drug to prevent recurrent infection.
- **Pre-emptive therapy** – Pre-emptive therapy involves starting antimicrobial therapy based upon screening with a sensitive assay (eg, polymerase chain reaction) in an attempt to detect early infection. The goal of pre-emptive therapy is to avoid progression to invasive disease. Pre-emptive therapy may be favored over prophylaxis when the antimicrobial therapy is particularly toxic (eg, for cytomegalovirus). (See 'Pre-emptive therapy' below.)

Prevention of viral infections in hematopoietic cell transplant recipients

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Patient profile	Recommendations	Timing and duration
CMV+/- with heterologous HCT	• letermovir (480 mg orally or IV QD or, in patients taking cyclosporine, 240 mg QF) plus • prophylaxis for HSV/VZV, if needed or • ganciclovir from day -8 to day -2, followed by high-dose valacyclovir (2 g p.o. Q8h) with Q2W qPCR	From HCT until week 14 week. From HCT until engraftment or longer in patients on glucocorticoids
CMV+ with autologous HCT	Risk/benefit assessment	
EBV in high-risk	QW EBV DNA qPCR for three months after transplant. Pre-emptive strategies for high EBV viral loads to prevent post-transplantation lymphoproliferative disorder (PTLD): • reduction of immunosuppression, • anti-CD20 mAb (rituximab) • EBV-specific cytotoxic T cells.	

Prevention of viral infections in hematopoietic cell transplant recipients

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Patient profile	Recommendations	Timing and duration
VZV IgG-	VZV Ig as PEP	
VZV IgG+	• valacyclovir (500 mg p.o. Q12h) or • oral acyclovir (800 mg p.o. Q12h)	At least 1y. Continue for 6 mo after discontinuation of immunosuppressive therapy.
HSV IgG+	• i.v. acyclovir (5 mg/kg IV Q12h or 250 mg/m^2 IV Q12h) or • oral acyclovir (400 or 800 mg p.o., Q12h) or • valacyclovir (500 mg p.o. Q12h)	From conditioning until engraftment or until mucositis resolves.

Wingard JR. UpToDate 2022.

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Anti-herpesvirus prophylaxis, pre-emptive treatment or no treatment in adults undergoing allogeneic transplant for haematological disease: systematic review and meta-analysis

O. Beyar-Katz • R. Bitterman • T. Zuckerman • Y. Ofran • D. Yahav • M. Paul

Open Archive • Published: September 16, 2019 • DOI: https://doi.org/10.1016/j.cmi.2019.09.003

- Antiviral prophylaxis compared with no treatment/placebo or pre-emptive treatment, reduced:
  - all-cause mortality (RR 0.83, 95% CI 0.7–0.99; 15 trials, I^2 = 0%),
  - CMV disease (RR 0.54, 95% CI 0.34–0.85; *n* = 15, I^2 = 20%)
  - HSV disease (RR 0.29, 95% CI 0.2–0.43; *n* = 13, I^2 = 18%)

  all with high-certainty evidence.

- Antiviral prophylaxis did not result in increased adverse event rates overall or more discontinuation due to adverse events.

Beyar-Katz O. Clin Microbiol Infect. 2019

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