Infectious complications in SOT recipients

Magdalena Durlik

Risk factors for infection in SOT

- Epidemiologic exposures
- Patient's net state of immunesuppression
- Time from transplantation
- Type of transplantation
- Immune response is blunted, anatomy is altered, so signs and symptoms are subtle and atypical

Epidemiologic exposures

- Community acquired pathogens
  - Respiratory viruses (flu, paraflu, rsv, adeno)
  - Bacteria (strep, staph, mycoplasma, listeria, salmonella
  - Endemic fungi (histoplasma, cryptococcus, aspergillus, cryptosporidia)
- Reactivation of infection in patient (Were they known carriers? Were they immunized?)
  - HSV, CMV, VZV, HBV, HCV, HPV
  - TB, fungi, parasites
- Nosocomial infection (Ask about recent hospitalizations, previous antibiotic therapy)
  - MRSA, VRE, C diff
  - Legionella, pseudomonas, candida

Table 2: Factors contributing to the "net state of immunosuppression"

- Immunosuppressive Therapy: Type, Temporal Sequence, and Intensity
- Prior therapies (Chemotherapy or Antimicrobials)
- Mucocutaneous Barrier Integrity (catheters, lines, drains)
- Neutropenia, Lymphopenia, Hypogammaglobulinemia (often drug-induced)
- Technical complications (graft injury, fluid collections, wounds)
- Underlying immune defects (e.g. Genetic polymorphisms, autoimmune disease)
- Metabolic conditions: uremia, malnutrition, diabetes, alcoholism/cirrhosis, advanced age
- Viral infection (e.g., herpesviruses, hepatitis B and C, HIV, RSV, influenza)

Infections in SOT

- Fever and physical signs of infection are diminished; infection may be signaled by more subtle laboratory (e.g. liver function tests) or radiographic abnormalities. Antimetabolites (azathioprine and mycophenolate mofetil) are associated with lower leukocyte counts and lower maximum temperatures.
- Up to 40% of infections cause no fever, notably in fungal infections, and up to 22% of fevers are noninfectious in origin.
- Every effort must be made to establish specific microbiologic diagnoses to optimize the therapy for infection while minimizing antimicrobial resistance and associated toxicities.
- Reduction in immunosuppression may be a useful component of antimicrobial therapy but risks graft rejection.

Recurrence of infection, chronic infections, mixed infections

Infections in Solid Organ Recipient

Required:

- **prompt diagnosis**
- **intensive treatment**
- **prophylaxis**
  - **Pharmacoteraphy**
  - **IVIG**
  - **Vaccination**

Common problems

- Microorganisms refractory to the first line treatment anti-infectious medications

- Side effects and interactions with IS

Lab tests that can be useful

- Pancultures (mouth, urine, stool, blood, sputum, access, wound, fluid drainage).
- Antigen-based tests are more useful than serologic tests (ELISA or PCR)
- Medication levels (e.g. cyclosporin, tacrolimus)
- Test organ function (liver, renal, pulmonary, echo, EKG, chest x-ray..)
- Remember, signs and symptoms are limited.

Spectrum of pathogens

Table 1: Epidemiologic exposures relevant to transplantation[1]

- Virus
  - Herpes group (CMV, EBV, HHV6, 7, 8, HSV, VZV)
  - Hepatitis viruses (HAV, HBV, HCV, HEV)
  - Retroviruses (HIV, HTLV-1 and 2)
  - Others: West Nile (WNV), Chikungunya, Zika, Dengue, lymphocytic choriomeningitis virus, rabies
- Bacteria
  - Gram-positive and gram-negative bacteria (*Staphylococcus* spp., *Pseudomonas* spp., Enterobacteriaceae, antimicrobial-resistant organisms), *Legionella* spp.
  - Mycobacteria (Tuberculosis and nontuberculous)
  - *Nocardia* spp.
- Fungus
  - *Candida* spp.
  - *Aspergillus* spp.
  - *Cryptococcus* spp.
  - Geographic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides* species)
  - Opportunistic molds (*Scedosporium*, Agents of Mucormycosis, Phaeohyphomycoses)
- Parasites
  - *Toxoplasma gondii*
  - *Trypanosoma cruzi*
  - *Strongyloides stercoralis*
  - *Leishmania* spp.
  - *Balamuthia* spp.

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Opportunistic Infections

- **Opportunistic Infections (OIs) are defined as infections occuring due to bacteria, fungi, viruses, or parasites that normally do not cause a disease, but become pathogenic when the body's defense system is impaired.**
- **Many of these pathogens do not cause disease in a healthy host that has a non-compromised immune system, and can, in some cases, act as commensals until the balance of the immune system is disrupted. Opportunistic infections can also be attributed to pathogens that cause mild illness in healthy individuals but lead to more serious illness when given the opportunity to take advantage of an immunocompromised host.**

Opportunistic infections

Viral

- Herpes simplex virus (HSV)
- Varicella zoster virus (VZV)
- Cytomegalovirus (CMV)
- Epstein–Barr virus (EBV)
- Human papilloma virus (HPV)
- Human herpes virus-8 (HHV-8)
- JC polyomavirus Aspergillus
- BK polyomavirus

Bacterial

- *Clostridium difficile*
- *Nocardia*
- *Listeria*
- *Tubeculosis*

Parasites

Toxoplasma gondii

Fungal

Candida

Cryptococcus

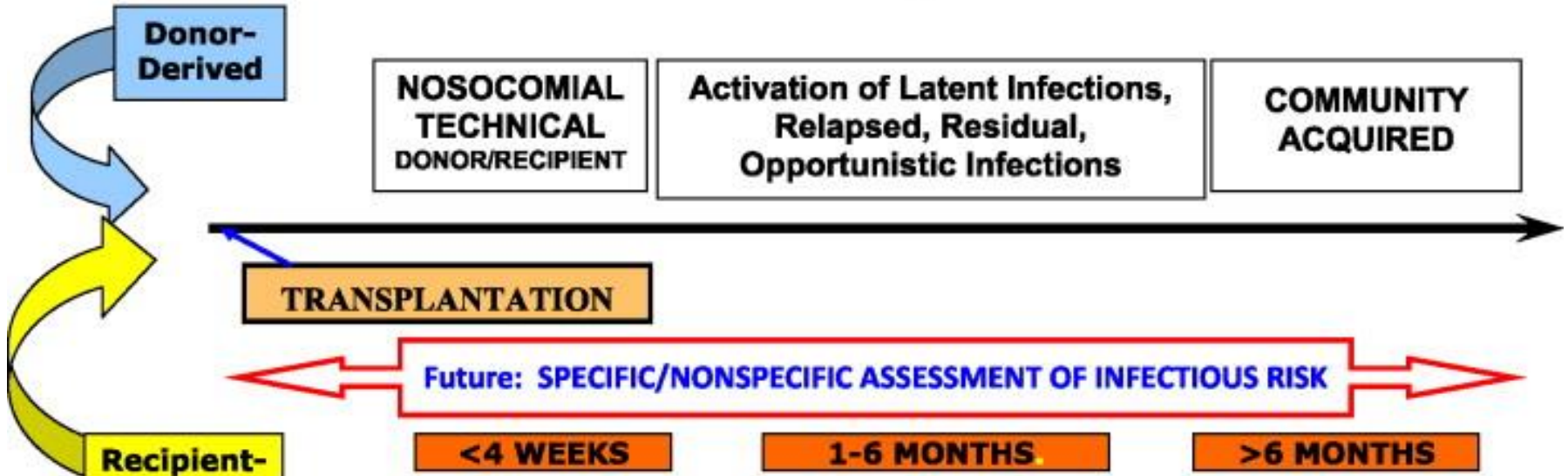
Pneumocysti jiroveci

TABLE 2 Pathogens reported to be transmitted with solid organ transplantation

Bacteria	**Mycobacteria**
Staphylococcus aureus	*Mycobacterium tuberculosis*
Klebsiella species	Non-tuberculous mycobacteria
Bacteroides fragilis	
Pseudomonas aeruginosa	**Parasites/Protozoa**
Escherichia coli	*Toxoplasma gondii*
Salmonella species	*Strongyloides stercoralis*
Yersinia enterocolitica	*Plasmodium* species
Treponema pallidum	*Trypanosoma cruzi*
Brucella species	*Pneumocystis jirovecii*
Enterobacter species	
Acinetobacter species	**Viruses**
Legionella species	Cytomegalovirus
Nocardia species	Epstein-Barr virus
Listeria monocytogenes	Herpes simplex virus
	Varicella-zoster virus*
Fungi	Human herpesvirus-6
Aspergillus species	Human herpesvirus-7
Candida species	Human herpesvirus-8
Coccidioides immitis	Hepatitis B, D
Cryptococcus neoformans	Hepatitis C
Histoplasma capsulatum	Human immunodeficiency virus
Scedosporium apiospermum	Parvovirus B19
Prototheca species	Rabies
Zygomycetes	Lymphocytic choriomeningitis virus
	West Nile virus
	BK virus
	Human T-cell lymphotropic virus (HTLV)- 1/2

Donor derived infections

The Timeline of Post-Transplant Infections



Common Infections in Solid Organ Transplantation Recipients

Antimicrobial-resistant species:
- MRSA
- VRE
- Candida species (non-albicans)

Aspiration
Line Infection
Wound Infection
Anastamotic Leaks/Ischemia
C. difficile colitis

Donor-Derived (Uncommon):
HSV, LCMV, rabies, West Nile

Recipient-Derived (colonization):
Aspergillus, Pseudomonas

With PCP and antiviral (CMV, HBV) Prophylaxis:
- BK Polyomavirus Nephropathy
- C. difficile colitis
- Hepatitis C virus
- Adenovirus, influenza
- *Cryptococcus neoformans*
- *M. tuberculosis*

Anastamotic complications

Without Prophylaxis Add:
Pneumocystis
Herpesviruses (HSV, VZV, CMV, EBV)
Hepatitis B virus
Listeria, Nocardia, Toxoplasma
Strongyloides, Leishmania, T. cruzi

Community Acquired Pneumonia
Urinary Tract Infection
Aspergillus, Atypical moulds, *Mucor* species
Nocardia, Rhodococcus species
Late Viral:
- CMV (Colitis/Retinitis)
- Hepatitis (HBV, HCV)
- HSV encephalitis
- Community acquired (SARS, West Nile)
- JC polyomavirus (PML)

Skin Cancer, Lymphoma (PTLD)

Phase I: 1 month posttransplantation

- During the first month after transplantation, infections result from surgical complications, donor-derived infections, preexisting recipient infections, and nosocomial infections including aspiration or C. difficile colitis.
- Early infections often reflect technical issues (bleeding, strictures, leaks, graft injury) or hospital environmental exposures (e.g. Aspergillus pneumonia with hospital construction).
- Drainage of fluid collections and early removal of lines and drains, limiting antimicrobial agents, and meticulous wound care are essential.
- Early opportunistic infections are uncommon as sustained administration of immunosuppressive agents is generally required to allow organisms of low native virulence to cause invasive disease.
- Majority of infections are of bacterial origin

Phase II: 1 to 6–12 months posttransplant

- **Viral infections including CMV, HSV, herpes zoster (VZV), EBV, HHV 6 or 7, BK polyomavirus, relapsed hepatitis (HBV, HCV), and the community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, respiratory syncytial virus RSV, and metapneumovirus)**
- **Opportunistic infections due to Pneumocystis jiroveci, L. monocytogenes, T. gondii, Nocardia species, Aspergillus species, endemic fungi.**

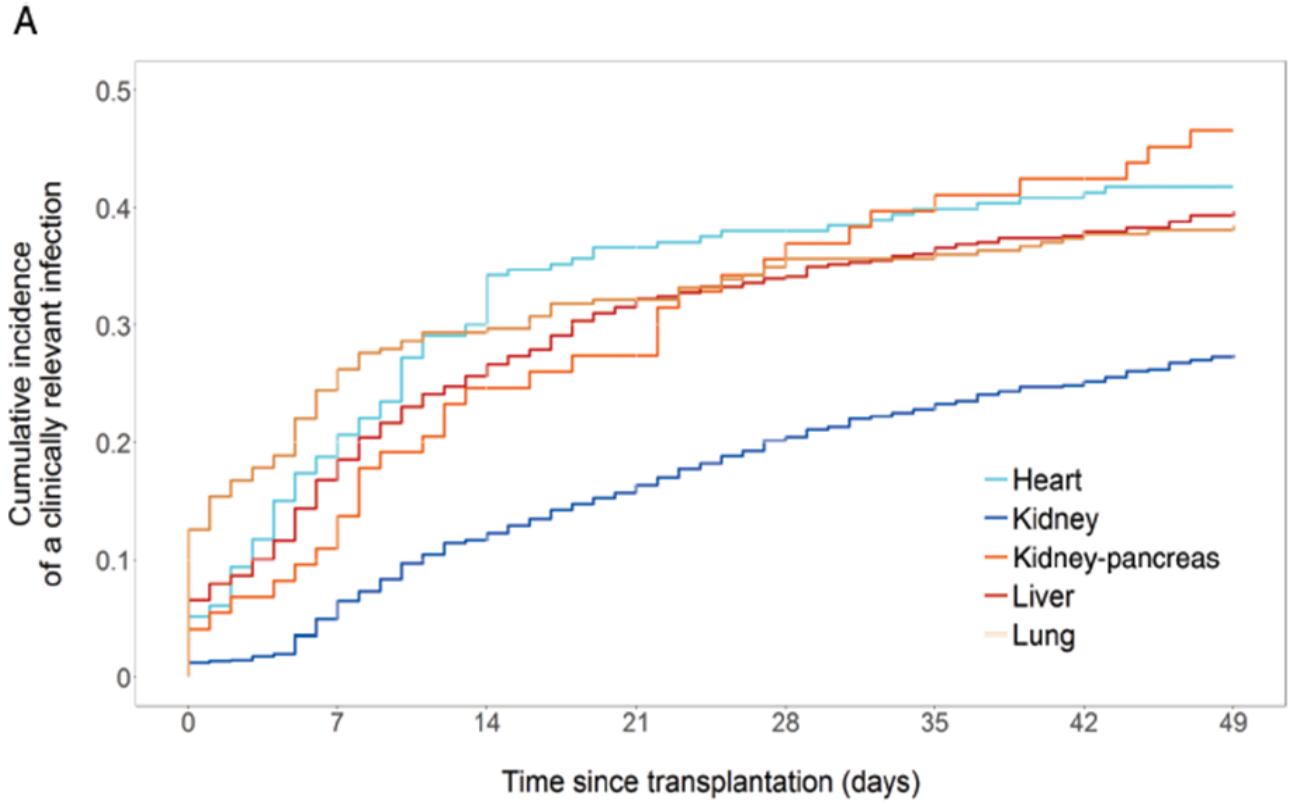
Phase III: more than 6–12 months posttransplant

- Later posttransplant, recipients with satisfactory allograft function will tolerate reduced maintenance immunosuppression with lowered risk of infection.
- Healthy recipients suffer community-based epidemiological exposures including “viruses,” foodborne gastroenteritis, or molds from work or gardening.
- Some recipients will develop relapsing viral infection. In the past, and in regions without access to antiviral therapies, this was driven by CMV, HBV,HCV, and HIV.
- At present, major challenges include late CMV (occasionally with antiviral resistance), EBV (as PTLD), BK polyomavirus infection, and HPV papillomavirus (anogenital cancers and warts).

Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study

Christian van Delden,[1] Susanne Stampf,[2] Hans H. Hirsch,[3,4] Oriol Manuel,[5] Pascal Meylan,[6] Alexia Cusini,[7] Cédric Hirzel,[7] Nina Khanna,[4] Maja Weisser,[4] Christian Garzoni,[7,8] Katja Boggian,[9] Christoph Berger,[10] David Nadal,[10] Michael Koller,[2] Ramon Saccilotto,[2] and Nicolas J. Mueller[11]; for the Swiss Transplant Cohort Study[a]

Infections After SOT • **cid 2020:71 (1 October)** • e159



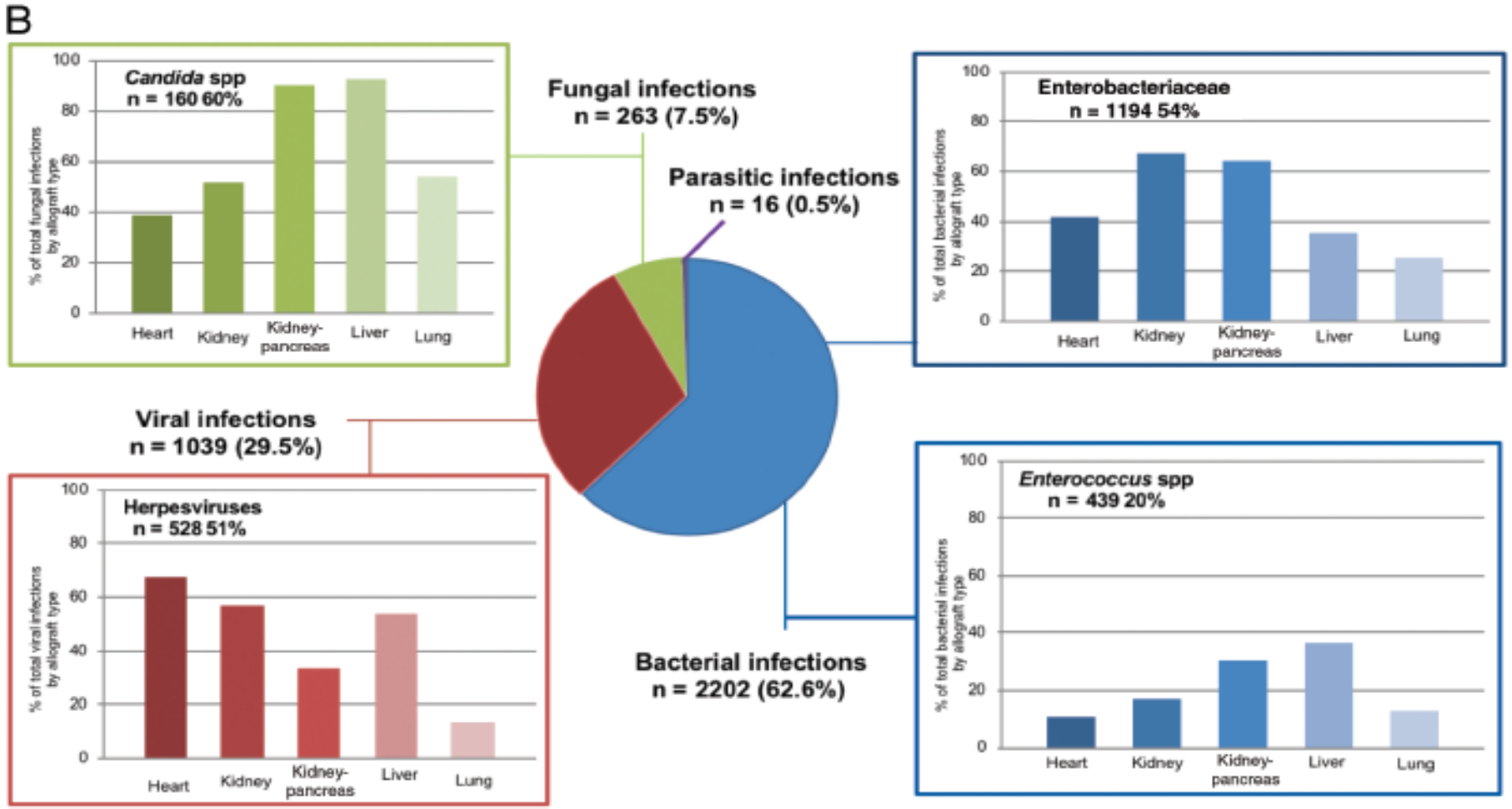


Figure 1. Incidence and distribution of clinically relevant infections by allograft type in 2761 solid organ transplant (SOT) recipients. *A*, Cumulative incidence censored for competing events (proven infection, graft loss, death, second transplantation) of first clinically relevant infections by allograft type until week 7 after SOT. *B*, Relative percentage of clinically relevant infections with predominant pathogens by allograft type.

Heart

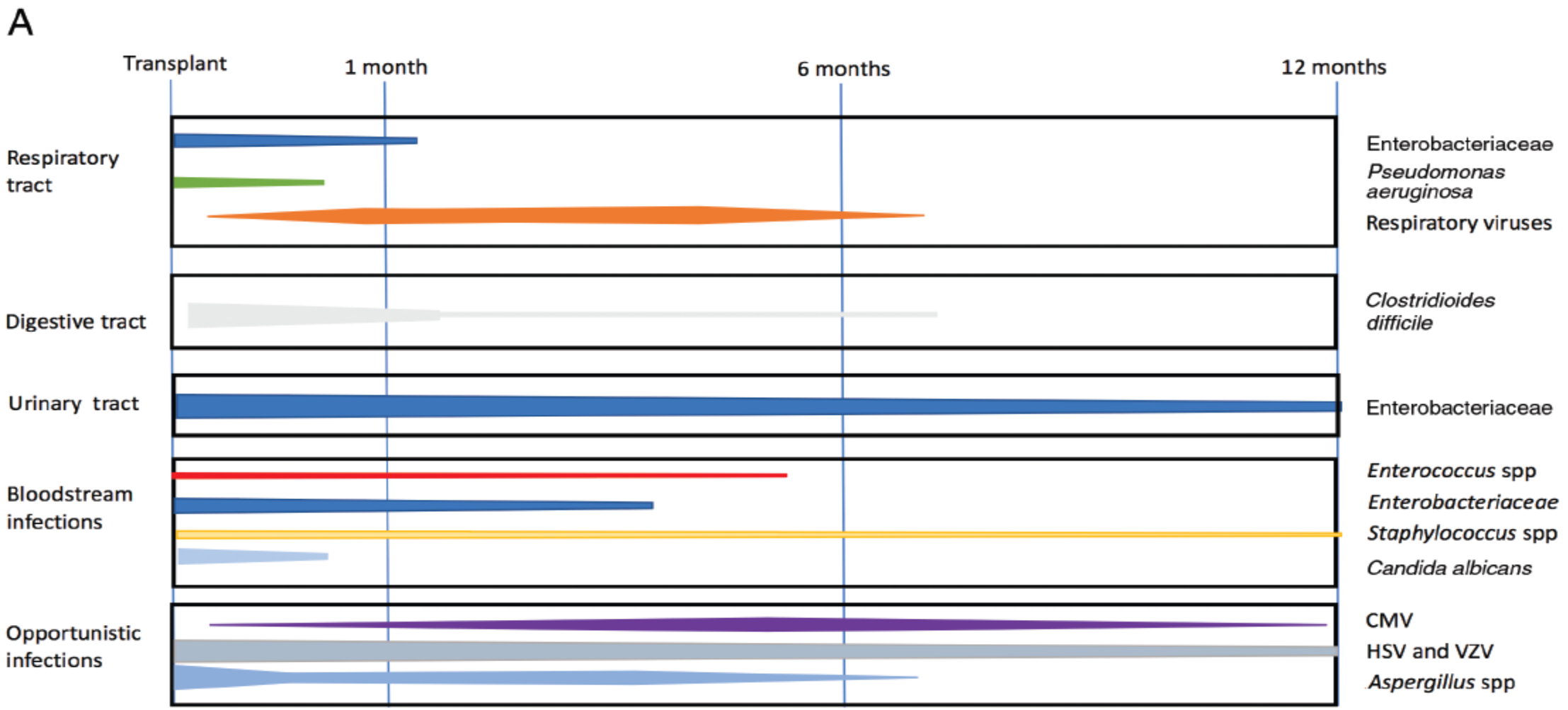
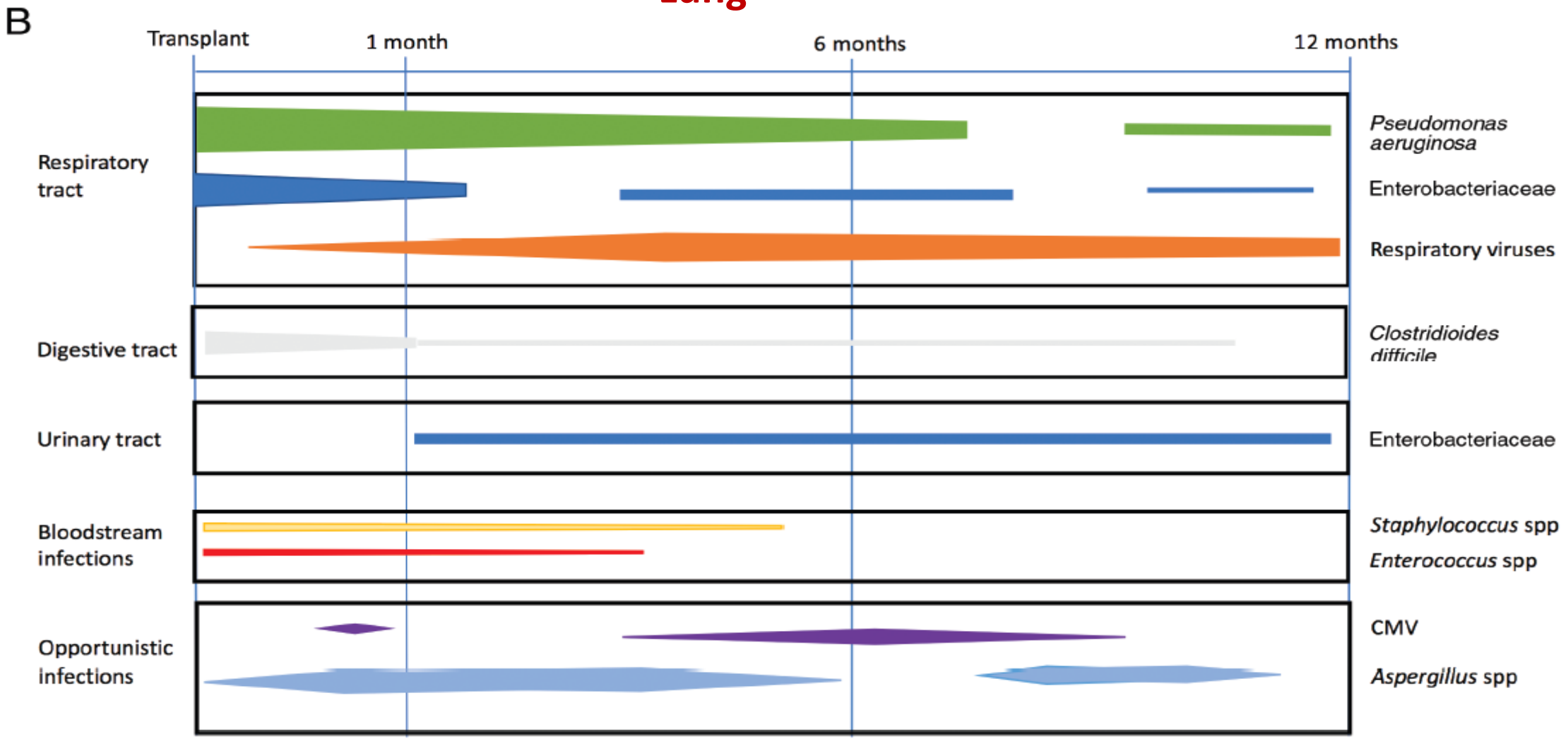


Figure 3. Timelines of the most significant clinically relevant infections for heart (*A*) and lung (*B*) transplant recipients according to predominant infection sites. The timeline and relative burden are based on the temporal distribution of 278 infections in 213 heart transplant recipients and 463 infections in 286 lung transplant recipients. Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella zoster virus.

Lung



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Kidney

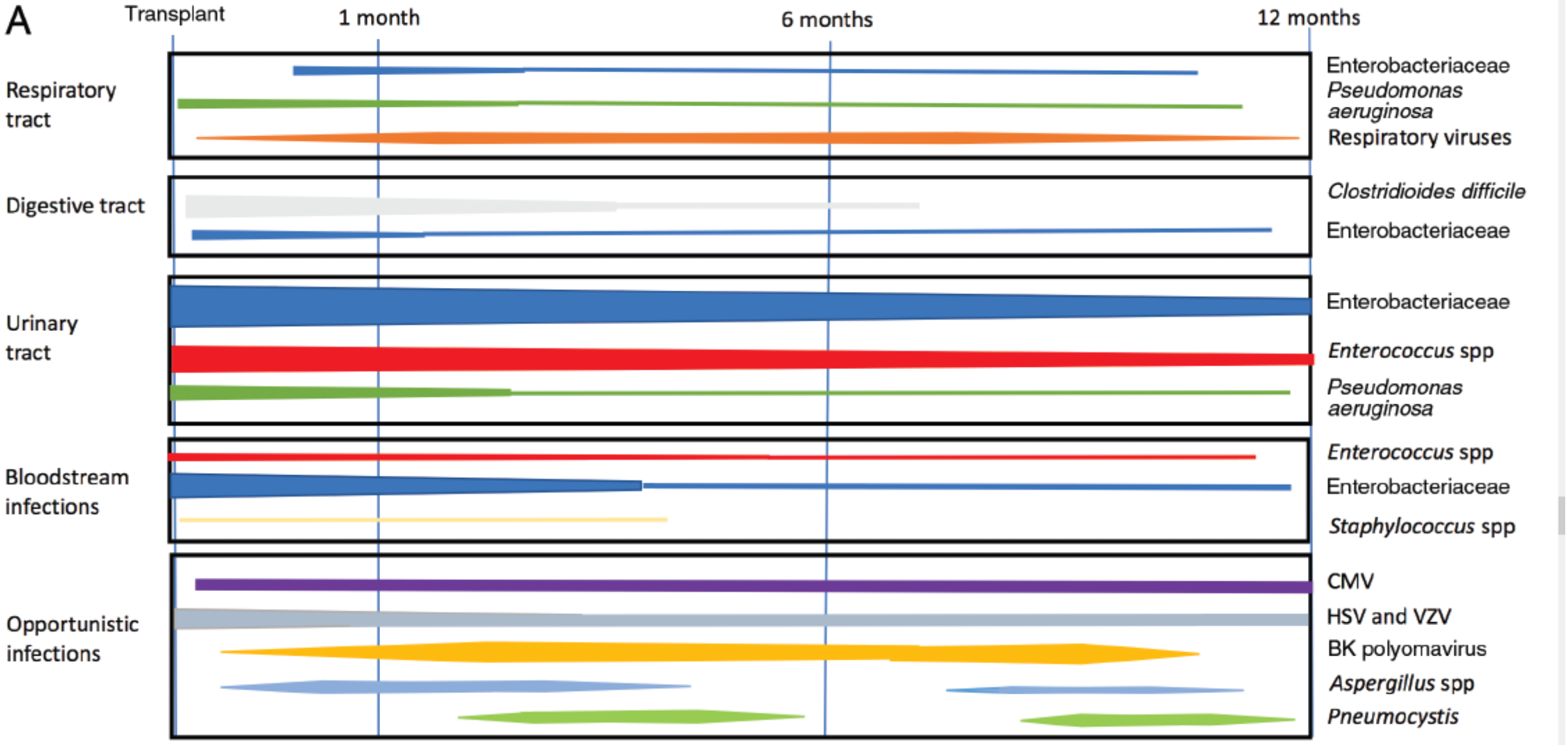
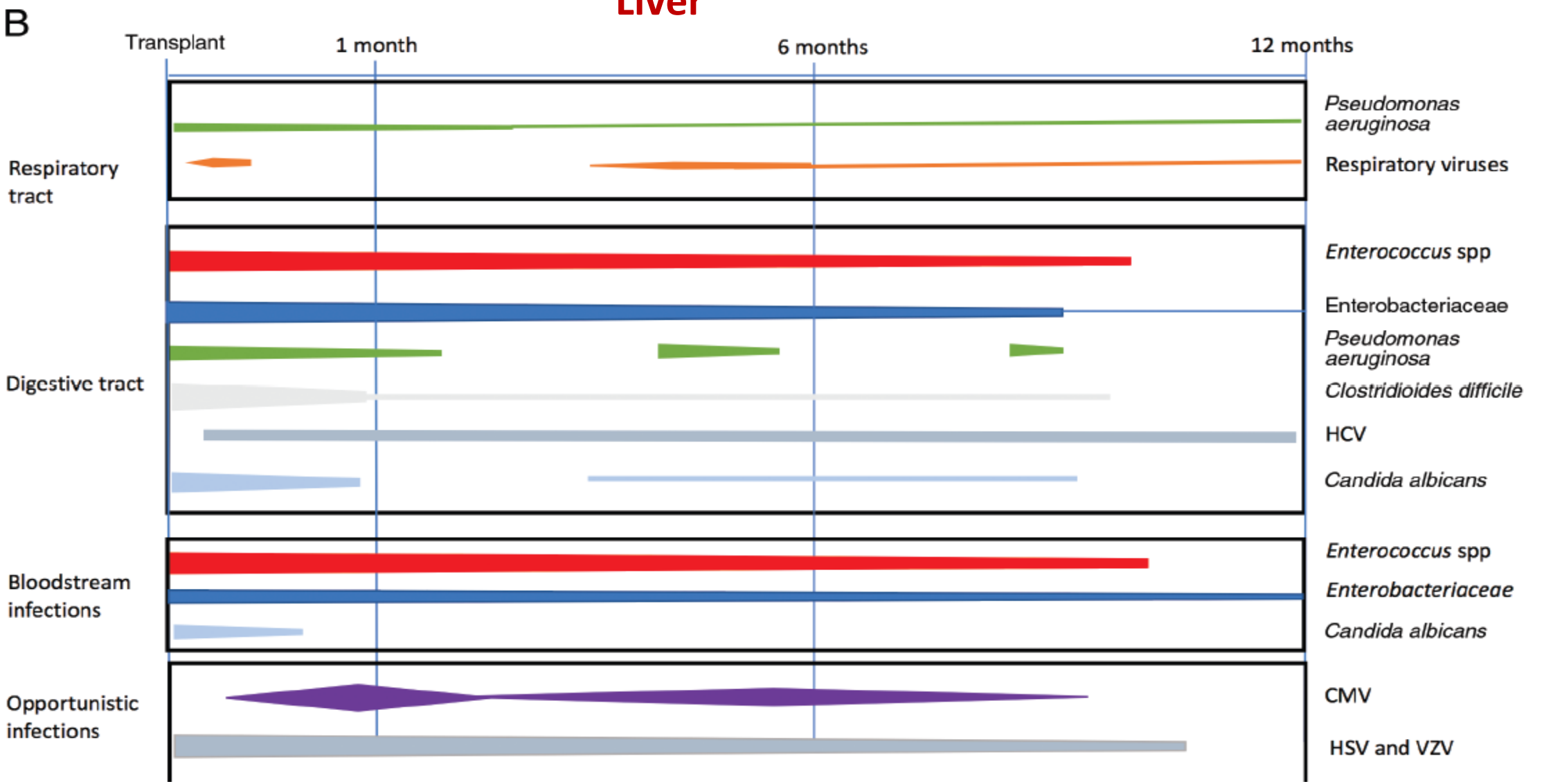


Figure 4. Timelines of the most significant clinically relevant infections for kidney (*A*) and liver (*B*) transplant recipients according to predominant infection sites. The timeline and relative burden are based on the temporal distribution of 1964 infections in 1612 kidney and 725 infections in 577 liver transplant recipients. Abbreviations: BKPyV, BK polyomavirus; CMV, cytomegalovirus; HCV, hepatitis C virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

Liver



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Results. Among 3541 SOT recipients, 2761 (1612 kidney, 577 liver, 286 lung, 213 heart, and 73 kidney-pancreas) had ≥12 months of follow-up; 1520 patients (55%) suffered 3520 infections during the first year posttransplantation.
Burden and timelines of clinically relevant infections differed between transplantations. Bacteria were responsible for 2202 infections (63%) prevailing throughout the year, with a predominance of Enterobacteriaceae (54%) as urinary pathogens in heart, lung, and kidney transplant recipients, and as digestive tract pathogens in liver transplant recipients. *Enterococcus* spp (20%) occurred as urinary tract pathogens in kidney transplant recipients and as digestive tract pathogens in liver transplant recipients, and *Pseudomonas aeruginosa* (9%) in lung transplant recipients. Among 1039 viral infections, herpesviruses predominated (51%) in kidney, liver, and heart transplant recipients. Among 263 fungal infections, *Candida* spp (60%) prevailed as digestive tract pathogens in liver transplant recipients. Opportunistic pathogens, including *Aspergillus fumigatus* (1.4%) and cytomegalovirus (6%), were rare, scattering over 12 months across all SOT recipients.
Conclusions. In the current era of immunosuppression and prophylaxis, SOT recipients experience a high burden of infections throughout the first year posttransplantation, with rare opportunistic pathogens and a predominance of bacteria.

Viral infections in SOT

- **Herpes: HSV 1, 2, VZV, CMV, EBV, HHV 6, HHV 7, HHV 8**
- **Hepatitis B, C**
- **Enteroviruses: Coxaci, Adenoviruses, Rotaviruses**
- **Respiratory: influenza, parainfluenza, RSV**
- **Retroviruses: HIV, HTLV 1, HTLV 2**
- **Papovaviruses: Human Papilloma Virus HPV, Polyoma JC, BK**
- **Parvovirus B 19**
- **SARS viruses: Sars-CoV-2**

Direct and indirect effects of viral infections

Each virus produces a set of clinical syndromes or "direct effects" (e.g. fever, pneumonitis, hepatitis, leukopenia) as well as a variety of "indirect" or cellular effects including

- **local or systemic immunosuppression predisposing to subsequent opportunistic infections;**
- **stimulation of innate immune responses that may augment alloreactivity;**
- **cellular proliferation including malignancies (posttransplant lymphoproliferative disorder [PTLD], anogenital cancers) and organ-specific injuries including accelerated atherogenesis (hearts) or chronic lung allograft dysfunction (CLAD) with bronchiolitis obliterans syndrome (lungs)**

The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation

Camille N. Kotton, MD,[1] Deepali Kumar, MD,[2] Oriol Manuel, MD,[3] Sunwen Chou, MD,[4] Randall T. Hayden, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] Anders Asberg, PhD,[7] Helio Tedesco-Silva, MD,[8] and Atul Humar, MD[2]; on behalf of The Transplantation Society International CMV Consensus Group*

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SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION

Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Raymund R. Razonable[1] | Atul Humar[2,3]

Clinical Infectious Diseases®
2024;79(3):787–94

Consensus Definitions of Cytomegalovirus (CMV) Infection and Disease in Transplant Patients Including Resistant and Refractory CMV for Use in Clinical Trials: 2024 Update From the Transplant Associated Virus Infections Forum

Per Ljungman,[1,2] Roy F. Chemaly,[3] Fareed Khawaya,[3] Sophie Alain,[4] Robin Avery,[5] Cyrus Badshah,[6] Michael Boeckh,[7,8] Martha Fournier,[9] Aimee Hodowanec,[10] Takashi Komatsu,[10] Ajit P. Limaye,[11] Oriol Manuel,[12] Yoichiro Natori,[13] David Navarro,[14,15] Andreas Pikis,[10] Raymund R. Razonable,[16,17] Gabriel Westman,[18,19] Veronica Miller,[20] Paul D. Griffiths,[21] and Camille N. Kotton[22]; for the CMV Definitions Working Group of the Transplant Associated Virus Infections Forum

Cytomegalovirus

Primary infection in childhood, 80% adults CMV-seropositive

CMV infection after Tx -CMV replication (60-90% recipients)

- **Primary infection (D+/R-)**
- **Secondary**
  - **reactivation (D-/R+, D+/R+)**
  - **reinfection (D+/R+)**

- **CMV infection: evidence of CMV replication regardless of symptoms (differs from latent CMV); defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen**

- **CMV disease: evidence of CMV infection with attributable symptoms.**

CMV disease can be further categorized as a viral syndrome (ie, fever, malaise, leukopenia, and/or thrombocytopenia), or as tissue invasive ("end organ") disease.

CMV syndrome

Table 4. Definition of Probable Cytomegalovirus (CMV) Syndrome in Solid Organ Transplant Patients Based on Clinical and Laboratory Criteria (at Least 2 Criteria are Required) and Detection of CMV DNA or Antigen in Whole Blood or Plasma Within 1 Week of Symptoms

a. Fever ≥38°C for at least 2 days of which at least 1 measurement is documented in a healthcare setting and without another identified cause of the fever
b. New or increased malaise CTCAE toxicity grade 2, including muscle aches or general achiness, headache, or new or increased fatigue (CTCAE toxicity grade 3)
c. A WBC count of <3500/μL if the WBC count prior to the development of clinical symptoms was ≥ 4000/μL or a WBC decrease of >20% if the WBC count prior to the development of clinical symptoms was <4000/μL; the corresponding neutrophil counts are <1500/μL or a decrease of more than 20% if the neutrophil count before the onset of symptoms was below 1500/μL
d. ≥5% atypical lymphocytes
e. A platelet count of <100 000/μL if the platelet count prior to the development of clinical symptoms was ≥ 115 000/mL or a decrease of >20% if the platelet count prior to the development of clinical symptoms was <115 000/ μL
f. Elevation of hepatic transaminases (alanine aminotransferase or aspartate aminotransferase) to >2 × upper limit of normal or >2×baseline value (if abnormal at baseline); baseline defined as last value before cytomegalovirus viremia was documented (applicable to non-liver transplant recipients)

Abbreviations: CTCAE, National Cancer Institute, Common Terminology Criteria for Adverse Events (version 4.0); WBC, white blood cell.

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CMV disease, organ involvment

Disease Entity	Proven
Pneumonia	Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with CMV documented in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques
GI disease	Proven disease requires upper and/or lower GI symptoms plus macroscopic mucosal lesions plus CMV documented in tissue by histopathology, virus isolation, rapid culture, immunohistochemistry, or in situ nucleic acid hybridization techniques; studies should give information regarding the presence or absence of gut GVHD in HCT recipients
Hepatitis	Abnormal liver function tests *plus* CMV documented in tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques *plus* the absence of other documented cause of hepatitis
Encephalitis and ventriculitis	CNS symptoms *plus* detection of CMV in CNS tissue by virus isolation, rapid culture, immunohistochemical analysis, in situ hybridization, or preferably quantitative polymerase chain reaction
Nephritis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a kidney allograft biopsy specimen obtained from a patient with renal dysfunction together with the identification of histologic features of CMV infection

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Cystitis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a bladder biopsy specimen obtained from a patient with cystitis together with the identification of conventional histologic features of CMV infection
Myocarditis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a heart biopsy specimen obtained from a patient with myocarditis together with the identification of conventional histologic features of CMV infection
Pancreatitis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a pancreatic biopsy specimen obtained from a patient with pancreatitis together with the identification of conventional histologic features of CMV infection
Other end-organ disease	CMV can also cause disease in other organs, and the definitions of these additional disease categories include the presence of compatible symptoms and signs and documentation of CMV by biopsy by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization

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Direct and indirect CMV effects

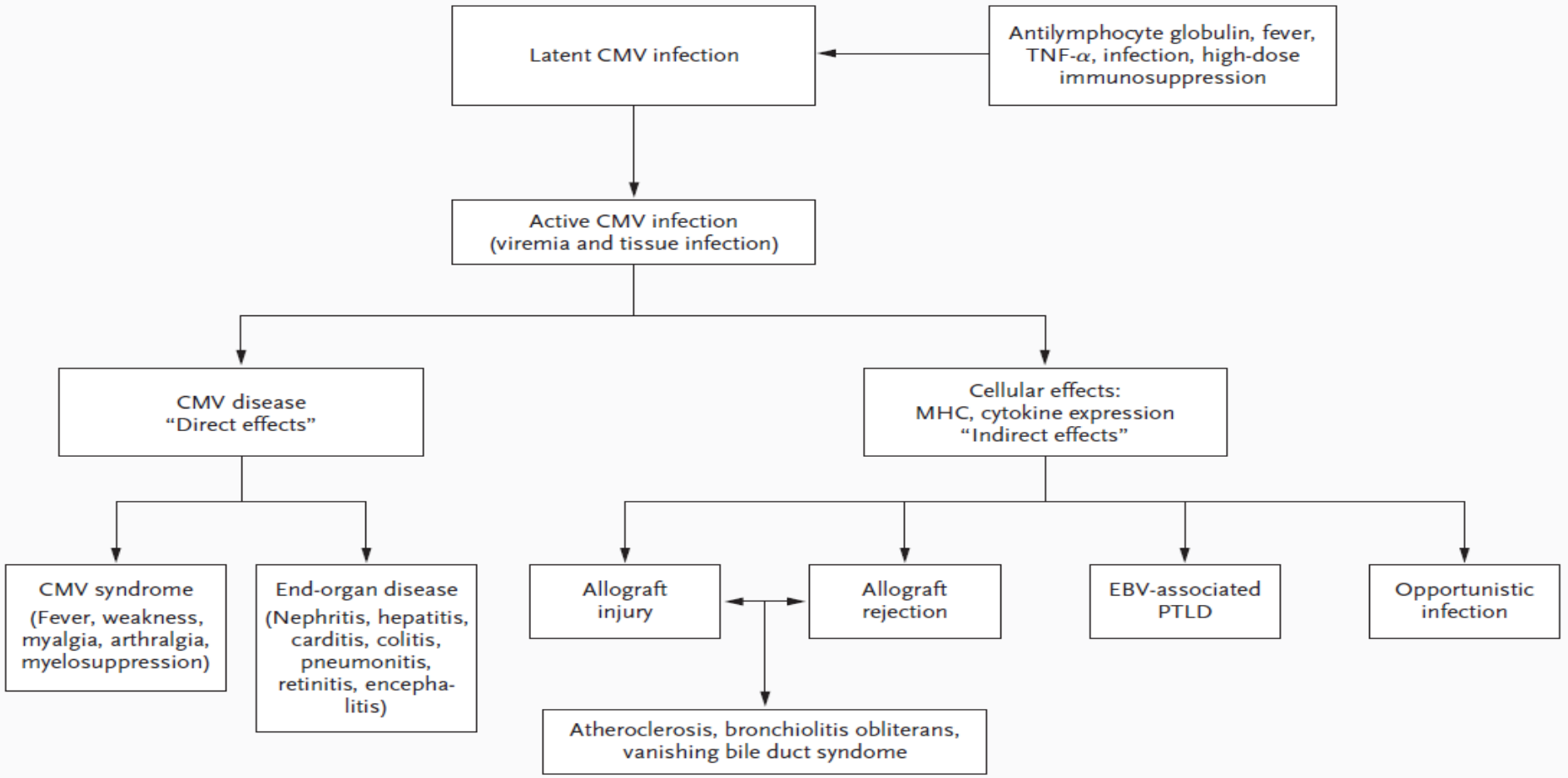


Figure 5. Cytomegalovirus Infection.

Cytomegalovirus (CMV) causes both invasive disease ("direct effects") and immunologic phenomena ("indirect effects"), including graft rejection and a predisposition to opportunistic infections. CMV may be activated by febrile illness (through the release of tumor necrosis factor α [TNF-α]), by depletion of antilymphocyte antibodies, or during treatment for graft rejection. MHC denotes major histocompatibility complex, EBV Epstein–Barr virus, and PTLD post-transplantation lymphoproliferative disorder.

Diagnosis

- CMV QNAT is the laboratory method of choice for rapid diagnosis of CMV infection in blood after SOT. CMV QNAT is the preferred laboratory method for CMV surveillance to guide preemptive therapy.
- pp65 antigenemia is an alternative laboratory method for surveillance and diagnosis of CMV infection after SOT.
- CMV QNAT assays should be calibrated using the WHO International Reference Standard.
- Pretransplant donor and recipient serology should be performed
- CMV-IgM and -IgG serology should not be used for the diagnosis of CMV disease after SOT.
- Immunologic monitoring after SOT may be used to stratify the risk of CMV disease. Measures of global (nonspecific) and CMV-specific CD8+ and/ or CD4+ T cells may be used to stratify the risk of CMV disease after SOT.

Anti-CMV drugs

- **Ganciclovir, Valganciclovir, Foscarnet, and Cidofovir:**

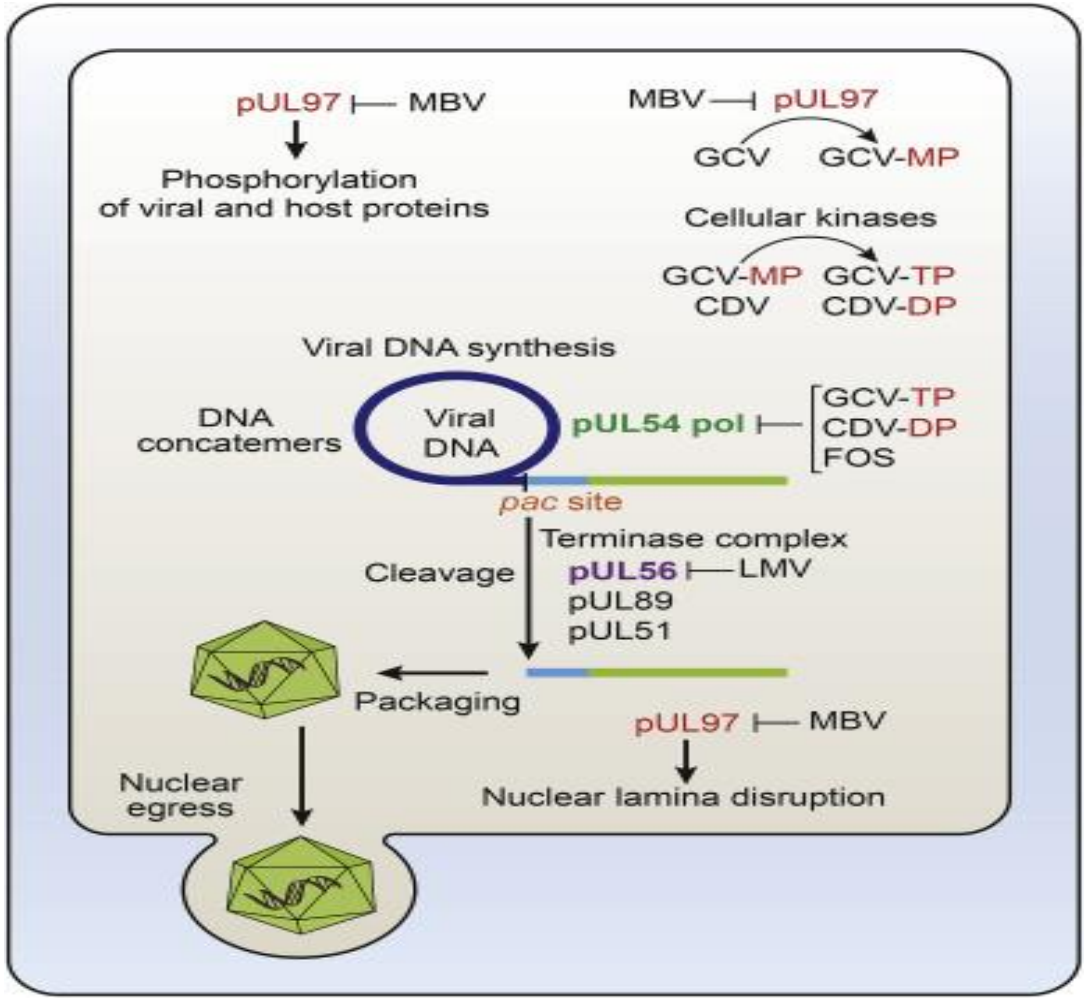
These drugs primarily target the viral DNA polymerase, interfering with the virus's ability to replicate.

- **Maribavir:**

Inhibits the UL97 kinase, a viral protein involved in DNA replication and viral capsid nuclear egress.

- **Letermovir:**

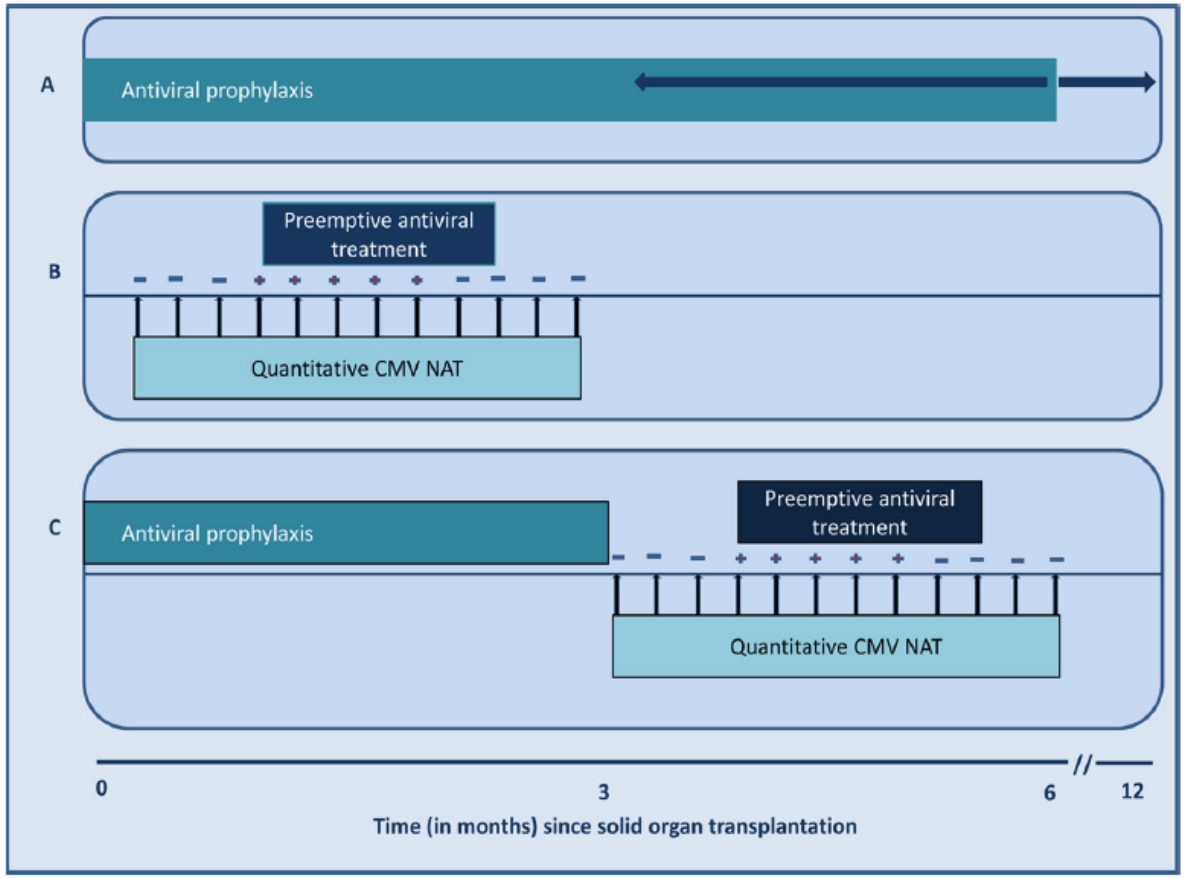
Inhibits viral terminase, a protein involved in viral DNA replication and packaging.



Treatment of CMV disease

- CMV disease should be treated with intravenous ganciclovir (5 mg/kg every 12 hours) or oral valganciclovir (900 mg twice daily), adjusted based on renal function.
- Intravenous ganciclovir is the recommended initial treatment for severe or life-threatening CMV disease, those with very high viral load, and those with questionable gastrointestinal absorption.
- Antiviral treatment of CMV disease should be continued until the following criteria are met:
  - Resolution of clinical symptoms, AND
  - Virologic clearance below a threshold negative value based on laboratory monitoring with CMV QNAT or pp65 antigenemia once a week, AND
  - Minimum 2 weeks of antiviral treatment
- The addition of IVIg or CMV-Ig to antiviral treatment of CMV disease may be considered for patients with life-threatening disease, CMV pneumonitis and possibly other severe forms of disease, drug-resistant virus, and those with hypogammaglobulinemia

Prevention of CMV



Universal prophylaxis

Preemptive therapy

Hybrid approach

FIG 1 Strategies for prevention of cytomegalovirus disease in transplant recipients. (A) Antiviral prophylaxis. An antiviral drug, most commonly valganciclovir, is given to all at-risk patients for a defined period after transplantation. In general, the duration is 3 to 6 months, although it can be shortened (backward arrow) or prolonged (forward arrow) depending on the risk profile. (B) Preemptive therapy. This strategy entails routine cytomegalovirus surveillance by nucleic acid testing (often on a weekly basis, as indicated by arrows). Upon detection of a positive viral load threshold, antiviral treatment is initiated and continued until the viral level falls below the clinically relevant threshold. Viral load monitoring for patients is usually conducted during the first 3 months after transplantation. (C) Hybrid approach, wherein antiviral prophylaxis is followed by a preemptive strategy. This is an approach to reduce the incidence of late-onset cytomegalovirus disease in high-risk transplant patients who start off with antiviral prophylaxis as the primary method of cytomegalovirus prevention.

Stratification in respect of the serostatus

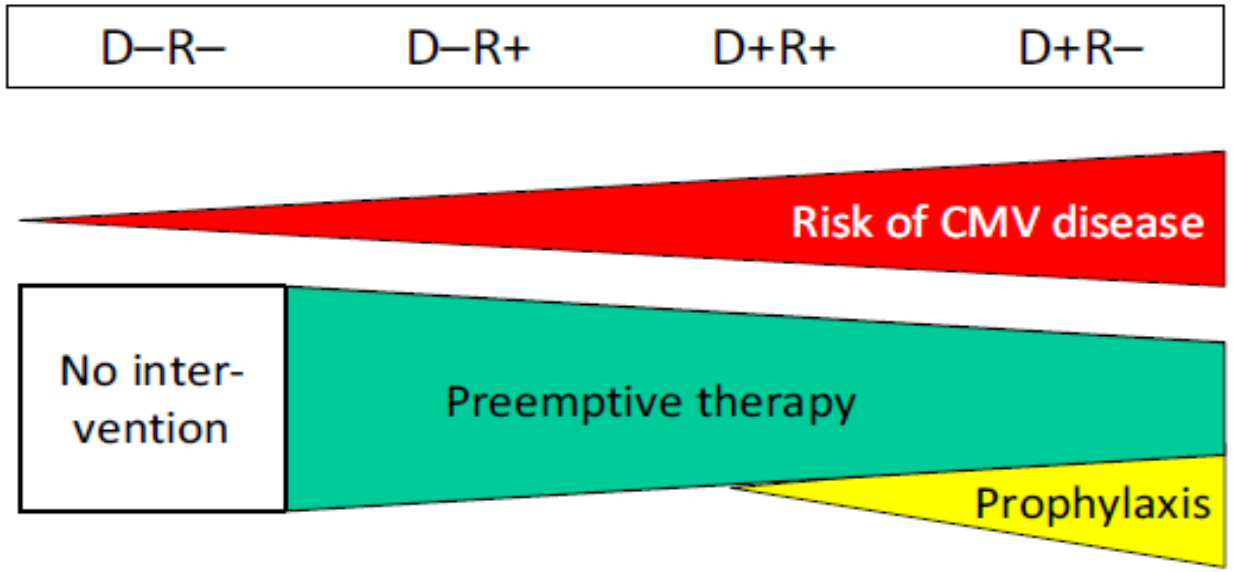


Figure 2 Proposal for use of pre-emptive therapy and anti-CMV prophylaxis. The risk of CMV disease is highly influenced by the serostatus of donor and recipient prior to transplantation. Here, we propose a risk-adapted use of pre-emptive therapy and antiviral prophylaxis with respect to the serostatus.

Duration of prophylaxis depneds on transplanted organ and D/R serostatus

TABLE 3.

Recommended approaches for CMV prevention in different organs for adult solid organ transplant recipients

Organ	Serostatus	Risk level	Recommended[a]	Alternate
All	D-/R-	Low	Monitoring for clinical symptoms; consider antiviral prophylaxis against other herpes infections	Preemptive therapy (if higher risk, ie, significant transfusions)
Kidney	D+/R-	High	6 mo of (V)GCV or 6 mo of LET or preemptive therapy	High-dose VALACY
	R+	Intermediate	3 mo of VGCV or preemptive therapy	High-dose VALACY. If on mTOR-based immunosuppression, preemptive therapy or close clinical monitoring recommended
Liver	D+/R-	High	3–6 mo of VGCV or preemptive therapy	
	R+	Intermediate	3 mo of VGCV or preemptive therapy	
Pancreas	D+/R-	High	3–6 mo of VGCV	Preemptive therapy
	R+	Intermediate	3 mo of VGCV or preemptive therapy	
Islet	D+/R-	Intermediate	3 mo of VGCV	Preemptive therapy
	R+	Intermediate	3 mo of VGCV or preemptive therapy	
Heart	D+/R-	High	3–6 mo of (V)GCV	-Preemptive therapy -Some experts add CMVIG to prophylaxis
	R+	Intermediate	3 mo of (V)GCV or preemptive therapy	
Lung	D+/R-	High	12 mo of (V)GCV	-Preemptive therapy
	R+	Intermediate	6–12 mo of (V)GCV	-Some experts add CMVIG to prophylaxis
Intestinal, composite tissue	D+/R-	High	Minimum 6 mo (V)GCV	-Preemptive therapy
	R+	High	3–6 mo (V)GCV	-Some experts add CMVIG to prophylaxis

Gancyclovir is effective against HSV, VZV, EBV , HHV 6, HHV7

HSV 1, 2 infections

- Occurs 1 - 3 months following transplant.
- Primary infection more severe than recurrent infection.
- Kerato-conjunctivitis, orofacial HSV.
- More severe forms of HSV disease include disseminated mucocutaneous

or visceral disease, esophagitis, hepatitis, and pneumonitis. Fever, leukopenia, and hepatitis are the common presenting signs of disseminated disease.

Treatment and prevention: acyclovir

- For limited mucocutaneous lesions, oral therapy can be used and

therapy should be continued for a minimum of 5-7 days or until

complete healing of the lesions depending on the clinical circumstances.

- For severe, disseminated, visceral or CNS involvement, doses of up to 10 mg/kg every 8 hours intravenously should be initiated (with adjustment for reduced GFR) and continued for at least 14 days.

• Suppressive therapy can be safely continued for many years and is associated with less frequent acyclovir-resistant HSV than episodic therapy in immunocompromised patients and thus is the preferred approach.

VZV

- **Primary infection: chickenpox**
- **Reactivation: herpes zoster (5-13%)**
- **Organ lesions**
- **Generalized form**
- **Prophylaxis and treatment: acyclovir**
- **Contact with chickenpox - acyclovir prophylaxis for 7-10 days**

EBV and PTLD

- Seroprevalence rates over 90% in adults worldwide, latency in oral epithelial cells and in B-cells
- Primary EBV infection may be asymptomatic or cause a febrile mononucleosis syndrome with B cell lymphocytosis with or without lymphadenopathy, atypical lymphocytosis, exudative pharyngitis, meningitis, hepatitis, or pancreatitis.

Clinical presentation of EBV-associated disease

- Asymptomatic
- Unexplained fever or weight loss.
- Mononucleosis-like syndromes or tonsillar swelling.
- Gastrointestinal bleeding, obstruction, perforation, or abdominal mass lesions
- Infiltrative disease of the allograft (often donor-derived; confused with rejection)
- Focal CNS dysfunction or meningitis
- Pulmonary or other organ infiltration

We recommend EBV viral load surveillance and preemptive interventions (reduction in immunosuppression) in patients who are EBV-seronegative pre-transplant. In patients who receive seropositive donor organs, monitoring should occur weekly to biweekly, when possible over the first post-transplant year.

Parvovirus B 19

Prevalence 1-2%, red cel aplasia, treatment: IVIG 0.4g/kgbw/d 5 days

TABLE 1 Clinical manifestations of parvovirus B19 in immunocompromised hosts

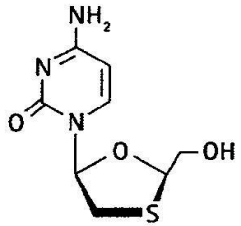
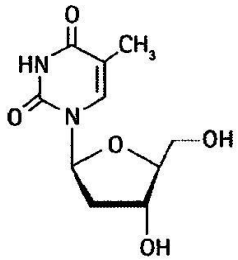
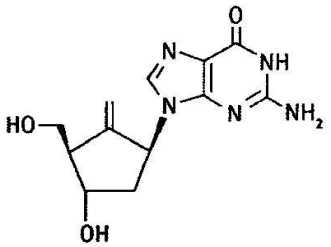
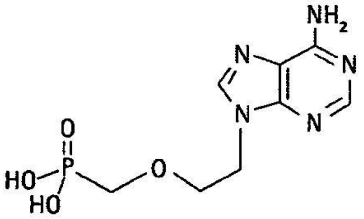
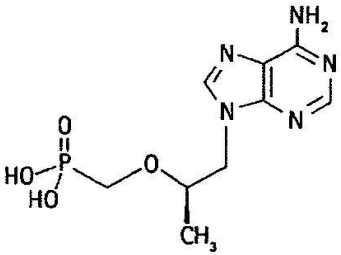
Anemia: severe or persistent • Lack of reticulocyte response • Lack of response to erythropoietin
Lacy skin rash • Not always present because of lack of antigen-antibody complexes[37,42]
Arthropathy • Not always present because of lack of antigen-antibody complexes[37,42]
Pancytopenia • A subset of patients will manifest concomitant leukopenia or thrombocytopenia with the anemia[9,22,78] • The causative etiology is speculated to be non-specific cytopathic effects in the bone marrow[9] or restricted non-structural protein expression in megakaryocytes, which leads to cytotoxicity but not viral progeny[79]
Graft loss or dysfunction[33]
Organ-invasive disease (ie, carditis, hepatitis, pneumonitis, glomerulonephropathy, vasculitis, and neurologic disease)[33]

HBV and HCV infecitons in solid organ recipients

- Increase morbidity and mortality in SOT → diminished organs survival
- Late complications associated with infection
  - Chronic hepatitis
  - Cirrosis
  - HCC (0.1-3%, 38 x risk increment)
  - Extra hepatic manifestations
  - Deep immunodeficiency → icreased risk of infections

Drugs inhibiting HBV proliferation

Table 2. Nucleos(t)ide analogues for treatment of hepatitis B infection

	Nucleoside analogues			Nucleotide analogues	
	Lamivudine (LAM)	**Telbivudine (TBV)**	**Entecavir (ETV)**	**Adefovir (ADV)**	**Tenofovir (TDF)**
Chemical structure					
Dose	100 mg	600 mg	0.5 mg[a]/1 mg[b]	10 mg	300 mg
Resistance conferring mutations[d]	L80I/V, V173L, L180M, M204I/S/V	L80I/V, L180M, M204I	V173L[a], T184G[a], S202C/G/I, M250I/V *in vitro:* L180M, M204V/I (*significance unclear*)	A181T/V N236T	*in vitro* (*significance unclear*): A181T/V, N236T, V191I, A194T
Development of resistance (virological breakthrough)[d]					
Week 48/52	10–32%	3–5%	<0.5%[a]/1%[c]	0%	0%
Week 96/104	22–42%	9–22%	<0.5%[a]/11%[c]	3–20%	
Year 3	−53%		<1%[a]/27%[c]	11%	
Year 4	−70%		<1%[a]/41%[c]	18%	
Year 5			<1%[a]/43%[c]	29%	
Options for management in case of HBV resistance	add on ADV, add on TDF, switch to TDF, (switch to ETV)	add on ADV, add on TDF, (switch to ETV)	add on ADV, add on TDF	LAM-naive: add on ETV, add on TBV, add on LAM	add on ETV, add on TBV, add on LAM
Cost/year	1554.77 €	6452.68 €	7704.79 €[a]/8288.18 €[b]	8290.00 €	6104.50 €

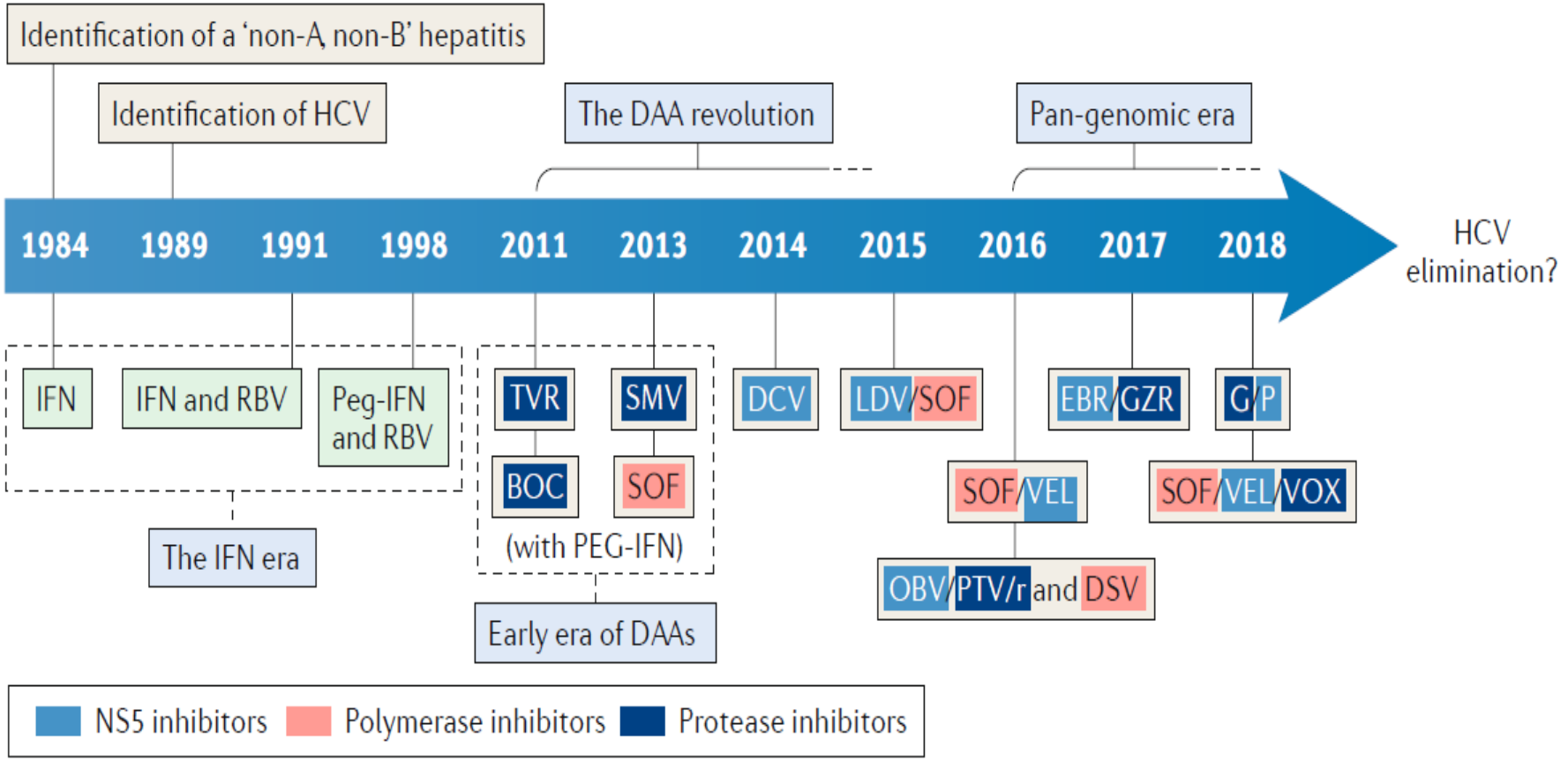
[a]LAM-naive patients; [b]LAM-experienced patients; [c]LAM experienced HBeAg$^+$ patients; [d][15,21–23].

HBV

- Administration of ETV, TDF, or TAF, with HBIg, is recommended after LT for prevention of HBV recurrence in recipients who are HBsAg positive, regardless of HBV DNA level or HBeAg status at time of LT.
- HBIG - 10 000 IU in ahepatic phase than daily for 1 week

  treatment goal anty-HBs > 100 IU/L (500 IU/L) , than once in 1-2 months.
- Due to the high risk of reactivation, non-hepatic SOT recipients with chronic HBV (ie, HBsAg positive) who did not require antiviral therapy prior to transplant should be initiated on potent NA therapy at the time of transplant and be continued indefinitely post-transplant. This is independent of the HBV DNA levels.
- ETV or TDF is recommended as first-line therapy
- HBIg is not recommended in the prevention of HBV peri-transplant in non-hepatic recipients
- Transplant candidates or recipients who are not immune to HBV, including those with isolated HBcAb positivity, should be vaccinated

Direct-acting antivirals for the treatment of hepatitis C virus infection DAA



DAA

inhibitory NS3 (proteazy)	glekaprewir (GLE) grazoprewir (GZR) parytaprewir (PTV) woksylaprewir (VOX)
inhibitory NS5B (polimerazy)	dazabuwir (DSV) sofosbuwir (SOF)
inhibitory NS5A	daklataswir (DCV) elbaswir (EBR) ledipaswir (LDV) ombitaswir (OBV) ibrentaswir (PIB) welpataswir (VEL)

(GLE/PIB, SOF/VEL/VOX, SOF/VEL, SOF/LDV, EBR/GZR, OBV/PTV/r), >97% efficacy.

HCV liver transplantation

- **Viral eradication rates with DAA in LT recipients are as good as in non-transplant recipients**
- **The most effective prevention for hepatitis C recurrence is viral eradication before LT. However, the decision to treat LT candidates should be individualized to the candidate's indication for LT (whether HCC is an indication or not), access to a donor organ and comorbidities that may impact treatment safety and efficacy**
- **Patients with post-transplant HCV recurrence without cirrhosis or with compensated (Child-Pugh A) cirrhosis should be treated with either: (i) the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (without the need for immunosuppressant drug dose adjustments), or (ii) the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (with the need to monitor immunosuppressant drug levels and adjust as needed during and after the end of treatment)**

HCV non-liver SOT

- **All non-hepatic transplant recipients with chronic HCV should be considered for treatment.**
- **For those with genotype 1 or 4 infection, options for therapy include glecaprevir/pibrentasvir for 12 weeks or sofosbuvir/ledipasvir for 12 weeks.**
- **For those with genotype 2, 3, 5, or 6 infection, glecaprevir/pibrentasvir for 12 weeks is recommended, with daclatasvir plus sofosbuvir plus ribavirin considered and alternative.**

Polyoma BK Virus

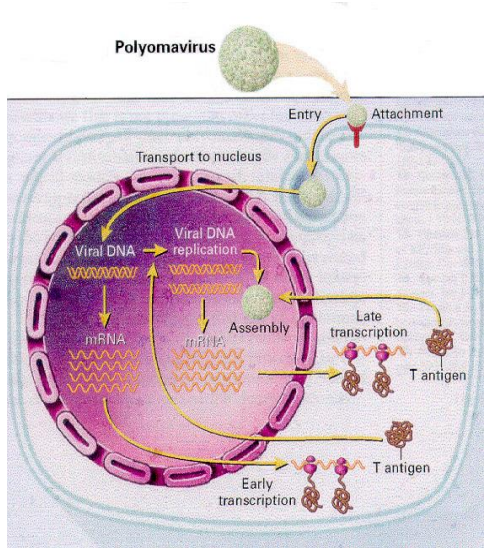
- Primary infection in childhood- >80% seropositivity
- Latent infection- uroepithelium, renal tubular epithelial cells
- Renal transplant recipient- reactivation 60%
- Viruria- 30-40%
- Viremia- 10%-20%
- BKV nephropathy- 1-10%- tublointerstitial nephritis
- Graft loss- 15%-80%

Polyoma JC virus- demyelinating disease of the brain (JCV - progressive multifocal encephalopathy PML)

BKV infection evolution

Viruria
↓
Viremia
↓
BKN

Reactivation
↓
Low replication
↓
High viral load
↓
Renal tissue invasion
↓
Inflammation- renal injury
↓
Renal failure
↓
Graft loss



The Second International Consensus Guidelines on BK Polyomavirus in Kidney Transplantation

Background

BK polyomavirus (BKPyV) impairs kidney transplantation outcomes.

Method

In 2022-2023, 55 experts from all TTS regions reviewed current evidence in 6 working groups and up-dated recommendations using GRADE.

Expect higher rates for older or male recipients, donor BKPyV-viruria, tacrolimus, acute rejection and treatment, or high steroid exposure.

Screen all recipients monthly until 9 months, 3 monthly until 2 years (for children 3 years).

Integrate all clinical, virology and pathology data; *add* BKPyV-DNAemia if planning graft biopsy.

Reduce immunosuppression using predefined protocols and *monitor* BKPyV-DNAemia loads (no biopsy unless high risk or failing function)

Expect in children higher rates of BKPyV-D+/R-, later-onset BKPyV-DNAemia, delayed functional failure, higher drug metabolism

Follow screening rates to save costs, to reduce graft failure and maintain QALY.

Consider retransplant if eligible and BKPyV-DNAemia cleared; if persisting, nephrectomy.

Conclusion

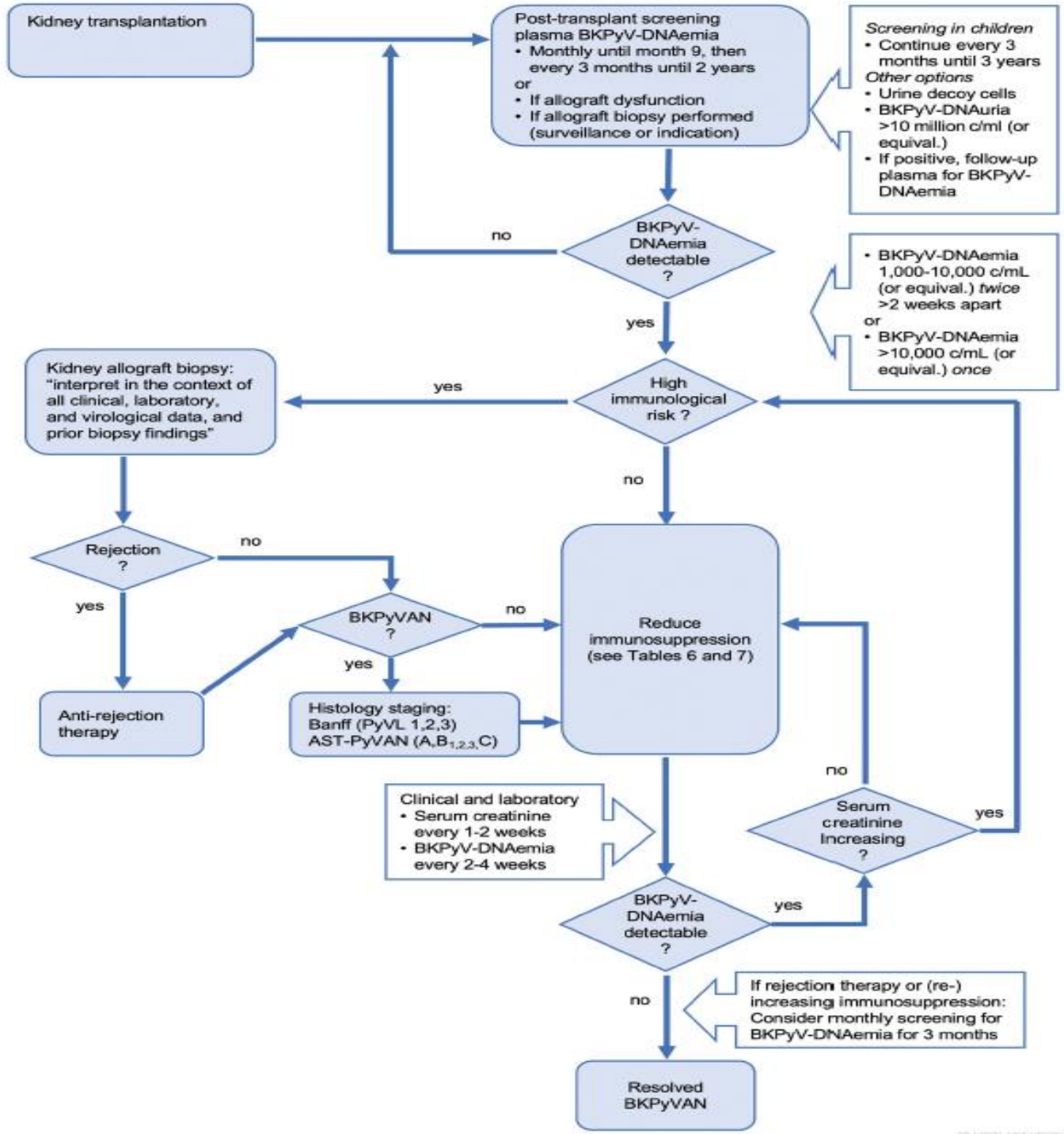
Reduce impact of BKPyV-DNAemia/Nephropathy by proactive screening & monitoring, clinically integrated histopathology evaluation, and timely reduction of immuno-suppression after careful considering individual risks.

Future Directions

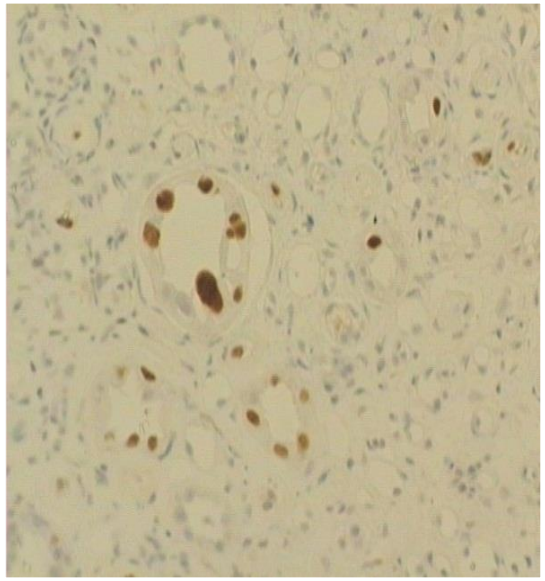
Randomized clinical trials needed to validate novel molecular and immune diagnostics, antivirals and vaccines to prevent and treat BKPyV-DNAemia/Nephropathy without causing acute rejection

Kotton CN, Kamar N, Wojciechowski D, et al. *Transplantation*. January 2024
@TransplantJrnl

Transplantation

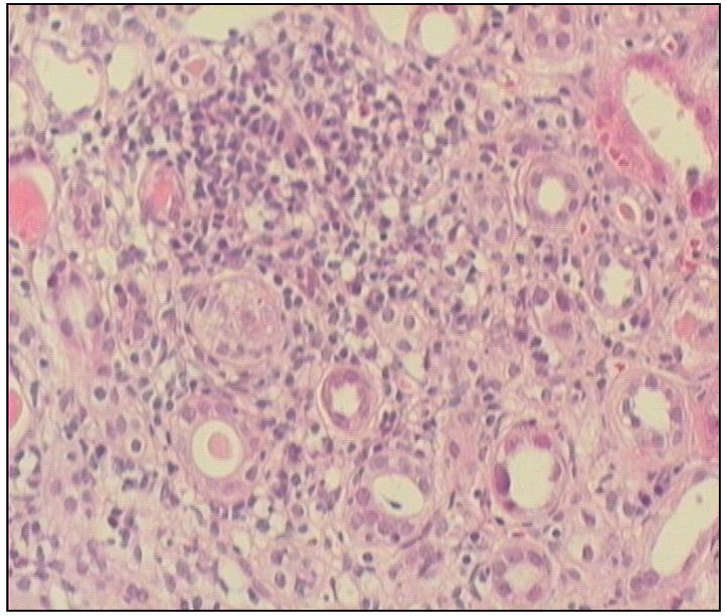

Kidney transplantation
Post-transplant screening plasma BKPyV-DNAemia
• Monthly until month 9, then every 3 months until 2 years
or
• If allograft dysfunction
• If allograft biopsy performed (surveillance or indication)
Screening in children
• Continue every 3 months until 3 years
Other options
• Urine decoy cells
• BKPyV-DNAuria >10 million c/ml (or equival.)
• If positive, follow-up plasma for BKPyV-DNAemia
BKPyV-DNAemia detectable ?
no
yes
• BKPyV-DNAemia 1,000-10,000 c/mL (or equival.) twice >2 weeks apart
or
• BKPyV-DNAemia >10,000 c/mL (or equival.) once
High immunological risk ?
yes
Kidney allograft biopsy: "interpret in the context of all clinical, laboratory, and virological data, and prior biopsy findings"
no
Rejection ?
no
yes
BKPyVAN ?
no
yes
Anti-rejection therapy
Histology staging: Banff (PyVL 1,2,3) AST-PyVAN (A,B1,2,3,C)
Reduce immunosuppression (see Tables 6 and 7)
Clinical and laboratory
• Serum creatinine every 1-2 weeks
• BKPyV-DNAemia every 2-4 weeks
no
Serum creatinine Increasing ?
yes
BKPyV-DNAemia detectable ?
yes
no
If rejection therapy or (re-) increasing immunosuppression: Consider monthly screening for BKPyV-DNAemia for 3 months
Resolved BKPyVAN

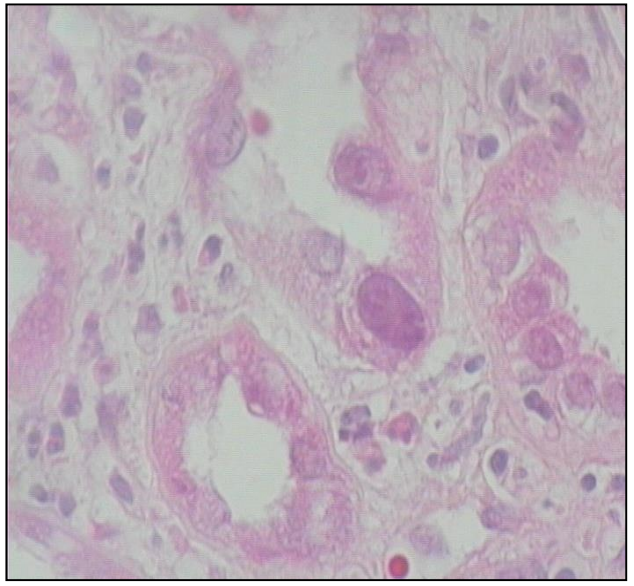
Diagnosis



- Gold standard- renal biopsy with SV40 staining – proven BKN
- Blood- BKV DNA PCR – high sensitivity and specifity
  - Persistent high viral load –greatest risk of BKN
  - Low viral load- does not predict BKN

- Urine
  - Decoy cells
  - BKV DNA- PCR





Management of BKV

- Kidney transplant recipients should be screened for BKPyVDNAemia by QNAT to identify patients to be considered for preemptive treatment for PyVAN.
- Screening for BKPyV-DNAemia by QNAT should be performer monthly until month 9, then every 3 months until 2 years posttransplant .
- Kidney transplant recipients should be tested for BKPyVDNAemia by QNAT when undergoing renal allograft biopsy for surveillance or for cause/indication.
- The primary treatment of sustained BKPyV-DNAemia/probable PyVAN, presumptive PyVAN, or proven PyVAN in kidney transplant patients without concurrent acute rejection is reducing maintenance immunosuppression.
- Tacrolimus trough levels are commonly targeted to <6 ng/mL, cyclosporine trough levels to <150 ng/mL, mycophenolate mofetil/mycophenolic acid daily dose equivalents of less or equal than half of the daily maintenance dose.
- Additional strategies have been switching from tacrolimus to low dose

cyclosporine-A, or switching from the calcineurin inhibitors to mTORi, or switching from mycophenolic acid to low-dose mTORi

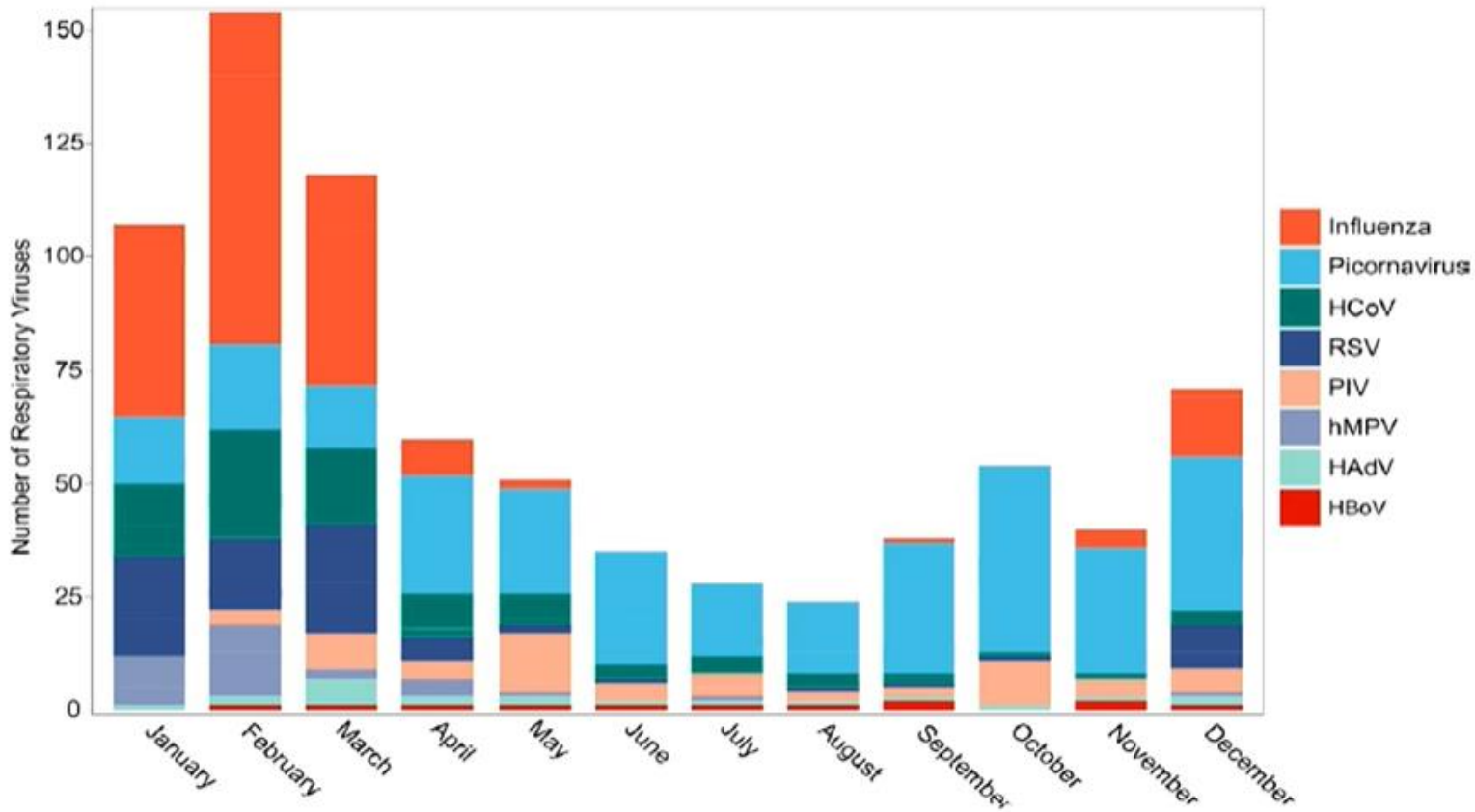
- High doses of IVIG

Distribution of major respiratory virus in SOT before the pandemic

Virus	Family	Genome	Diversity	Distribution (%)
Rhinovirus	Picornaviridae	RNA	A, B, C, >100 types	21–62 %
Coronavirus	Coronaviridae	RNA	OC43, E229, HKU1, NL63	13–29 %
Influenza virus	Orthomyxoviridae	RNA	A, B, C / H3N2, H1N1pdm	2-16 %
Respiratory syncytial virus	Paramyxoviridae	RNA	A and B	6–20 %
Parainfluenza virus	Paramyxoviridae	RNA	1, 2, 3 and 4	3–18 %
Metapneumovirus	Paramyxoviridae	RNA	A1, A2, B1, B2	4–7 %
Adenovirus	Adenoviridae	DNA	7 species, > 50 serotypes	1–25 %

Ison et al. Clin Microbiol Rev. 2019

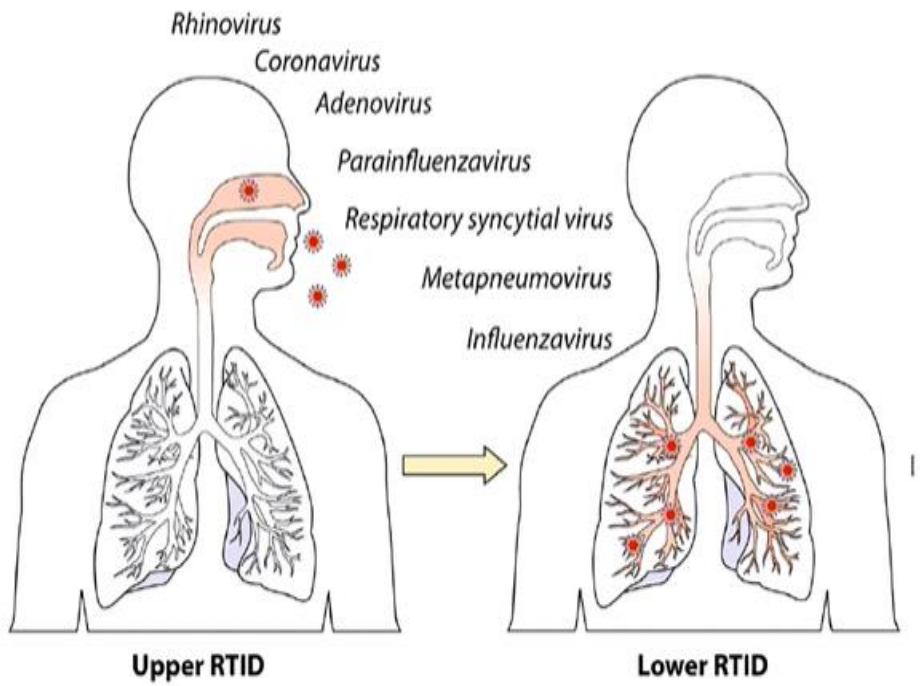
Seasonality in SOT follows that of general population



ATC2024

Peghin et al. Am J Transplant. 2017
Mombelli et al. Am J Transplant. 2021

Direct, cytopathic and tissue-invasive effects in organ transplantation more than just a cold



Upper Respiratory Tract Infection, URTI

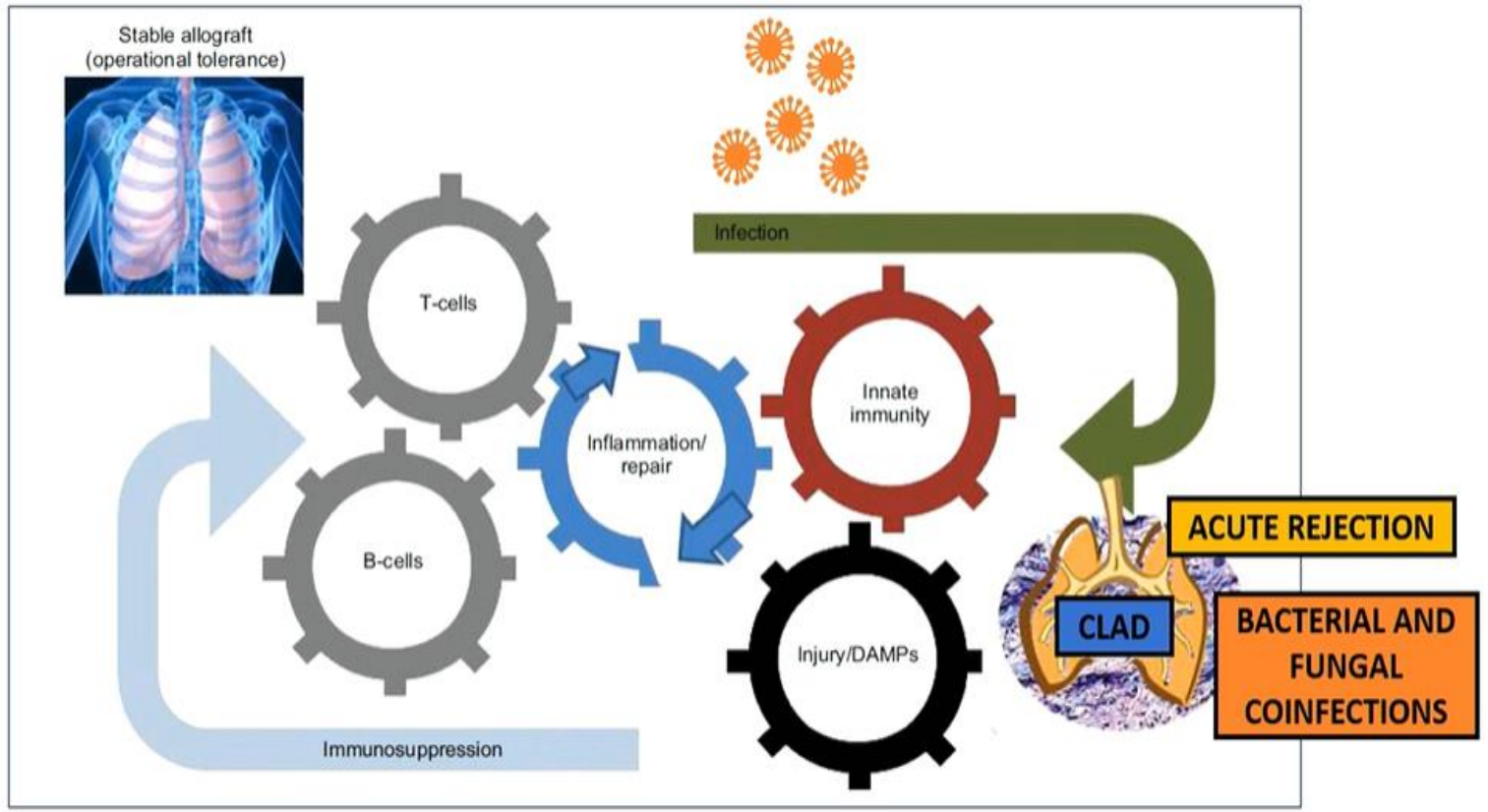
Greater risk of progression

6-56%

Lower Respiratory Tract Infection, LRTI
- Tracheobronchitis
- Bronchiolitis
- Pneumonia

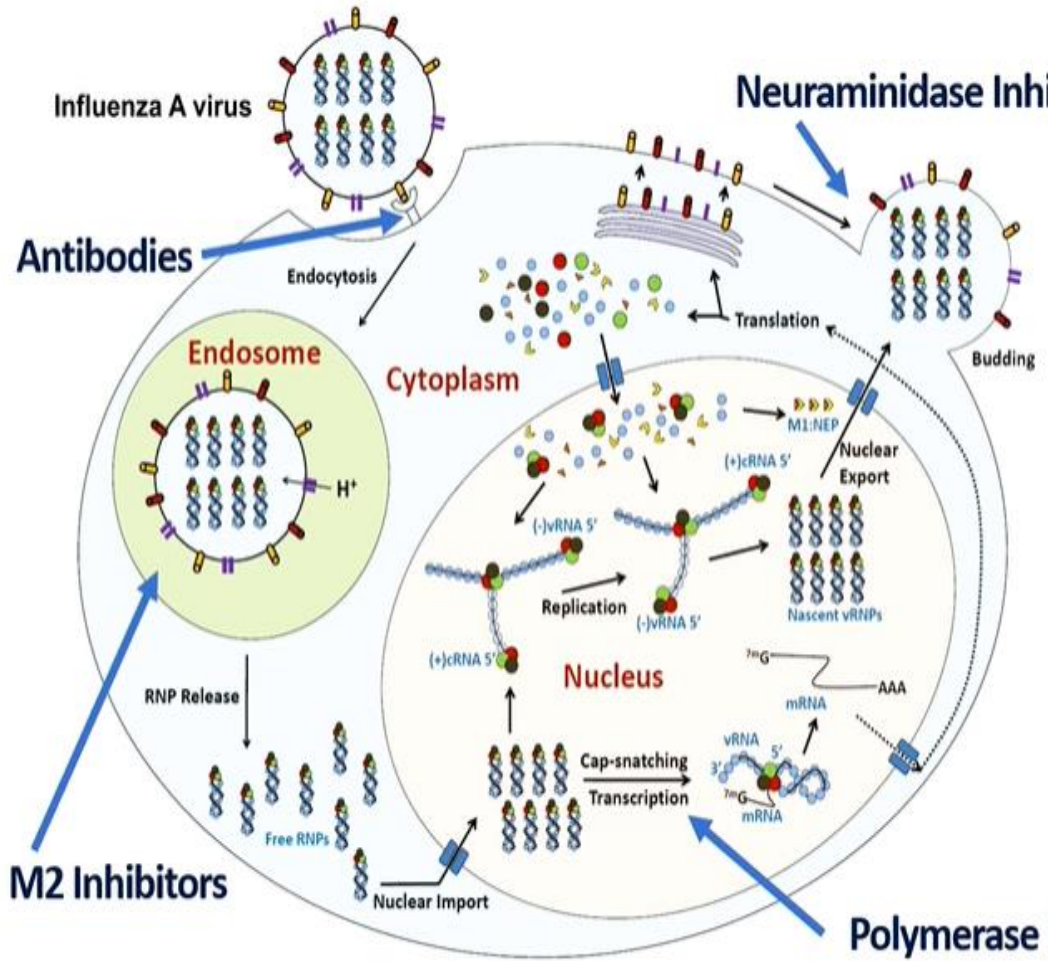
- **Hospital admission and ICU admission**
- **Respiratory failure**
- **Mechanical ventilation**
- **Increased mortality**

RV and local and systemic microbially determined immune modulation



Fishman JA Clin Microbiol Infect. 2014
Kotsimbos et al. Eur Respir Rev. 2012

Available Agents for Treatment of Influenza



Available Influenza Antivirals
M2 Ion Channel Inhibitors: Amantadine, Rimantadine
Neuraminidase Inhibitors: Laninamivir, Oseltamivir, Peramivir, Zanamivir
Polymerase Inhibitors: Baloxavir, Favipirivir, Ribavirin

National Institute of Allergy and Infectious Diseases

Zheng W, Tao YJ. ***FEBS Letters***. 2013; 587: 1206-1214.

Table 1. Common causes of post-transplant diarrhea

Infectious	Noninfectious
Bacterial	IS medications
Clostridium difficile	Mycophenolate
Campylobacter spp.	Tacrolimus
Salmonella spp.	Cyclosporine
Bacterial overgrowth	Sirolimus
Aeromonus spp.	
Escherichia coli	
Viruses	Non-IS medications
CMV	Antibacterial
Norovirus	Antiarrhythmic
Sapovavirus	Antidiabetic
Rotavirus	Laxatives
Adenovirus	Proton pump inhibitors
	Protease inhibitors
Parasitic	Other
Giardia	GVHD
Cryptosporidium	PTLD
Isosopora Cyclospora	IBD
Microsporidium	Colon cancer
Entameoba	Malabsorption

Fungal infections

- ***Candida*:**
  - **albicans**
  - ***glabrata, krusei, parapsilosis, lusitaniae***
- ***Aspergillus species***
- ***Cryptococcus neoformans***
- ***Pneumocistis jiroveci***
- **Sporadic: *Mucor spp, Fusarium spp, Penicillium spp***

Post-Transplant IFIs

SOT

Common Fungal Pathogens

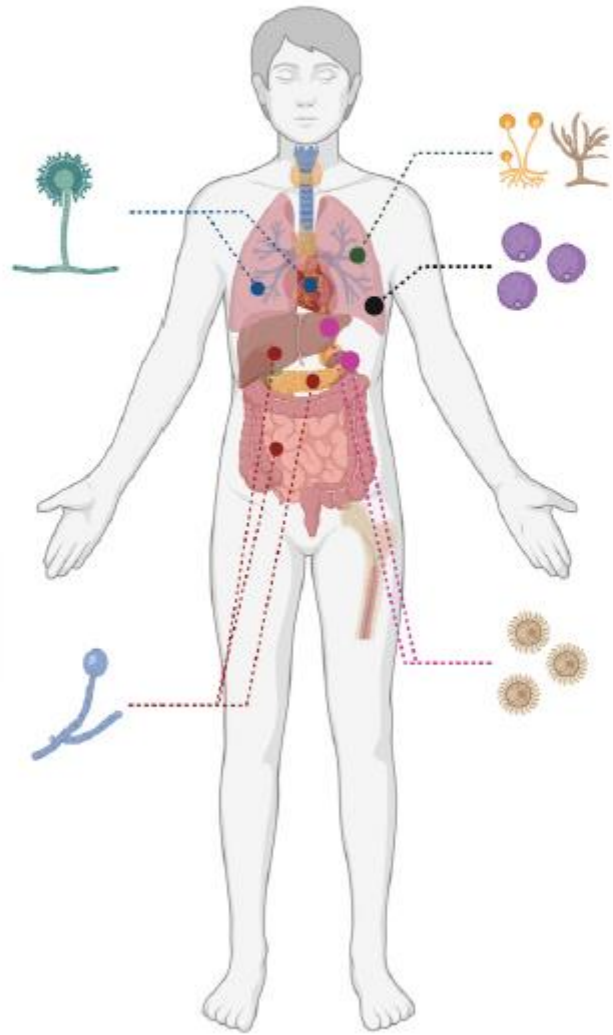
Candidiasis
- *Candida albicans*
- *Candida glabrata*
- *Candida parapsilosis*
- *Candida krusei*

Aspergillosis
- *Aspergillus fumigatus*
- *Aspergillus flavus*
- *Aspergillus niger*
- *Aspergillus terreus*

Other mold infections
- Mucorales
- *Fusarium* spp.

Cryptoccocosis
- *Cryptococcus neoformans*
- *Cryptococcus gattii*

PCP
- *Pneumocystis jirovecii*



HSCT

Common Fungal Pathogens

Aspergillosis
- *Aspergillus fumigatus*
- *Aspergillus terreus*
- *Aspergillus niger*
- *Aspergillus flavus*

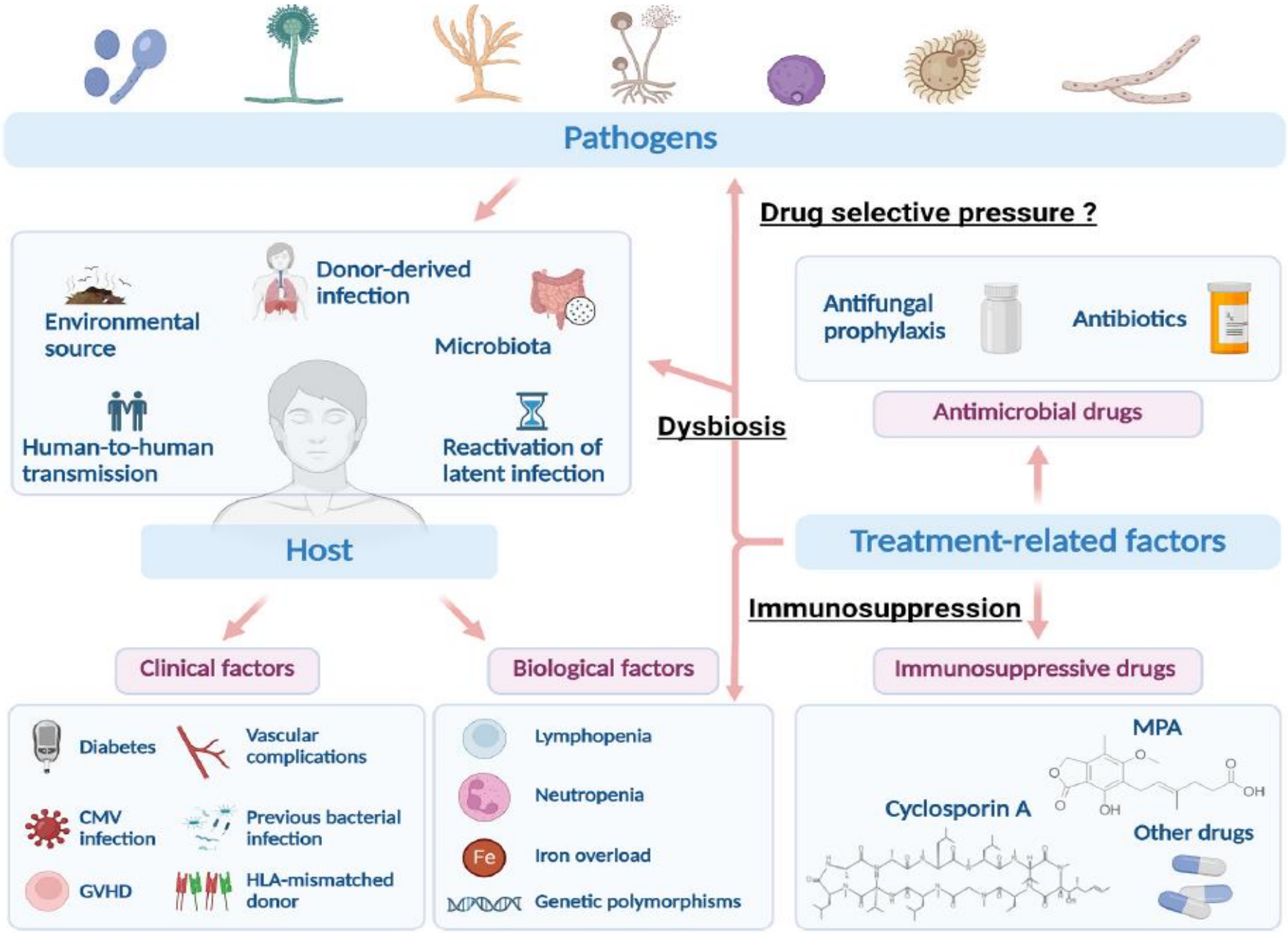
Candidiasis
- *Candida glabrata*
- *Candida albicans*
- *Candida parapsilosis*
- *Candida tropicalis*

Mucormycosis
- *Rhizopus* spp.
- *Mucor* spp.
- *Rhizomucor* spp.

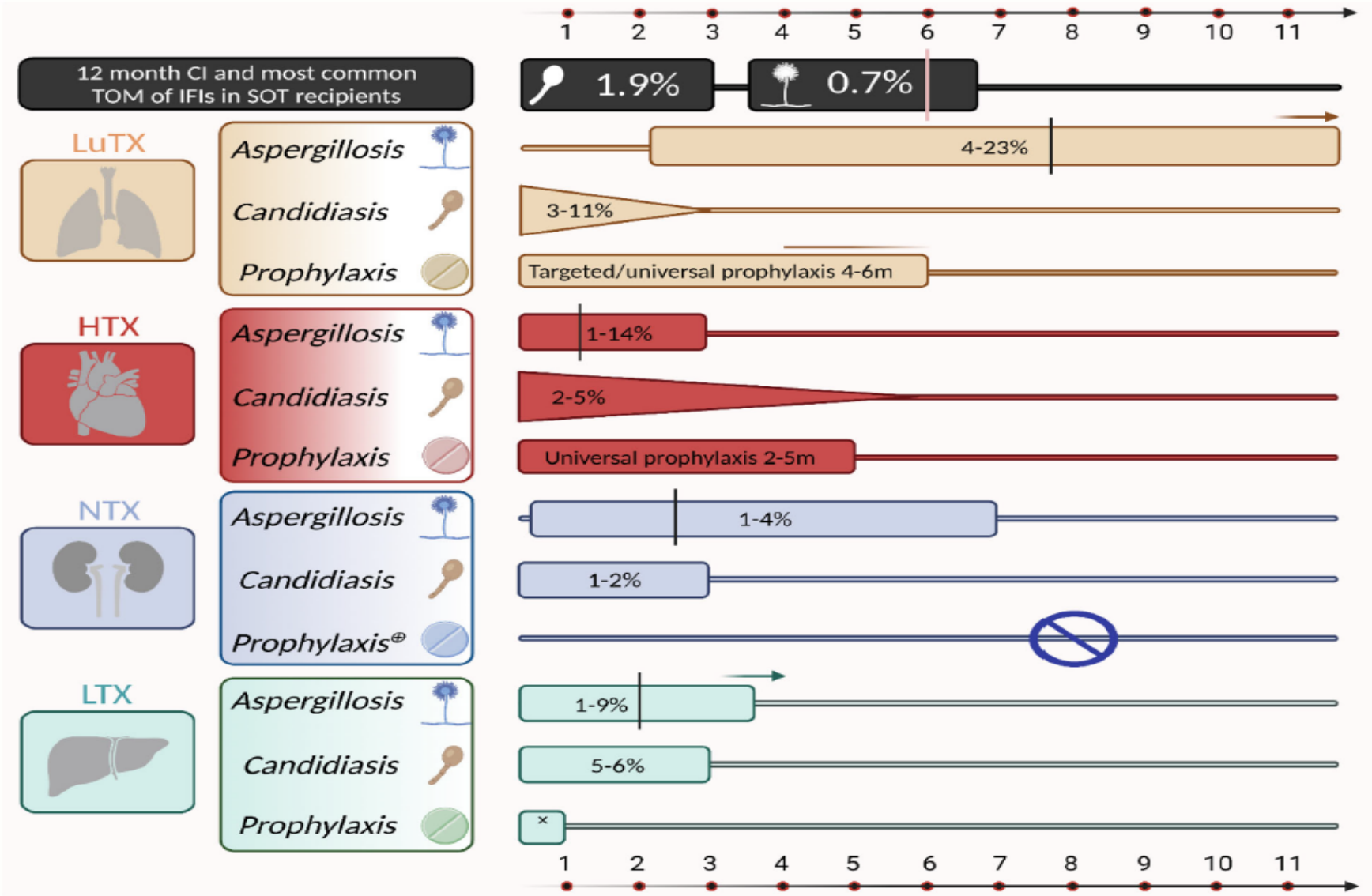
Other mold infections
- *Fusarium* spp.
- *Scedosporium* spp.

PCP
- *Pneumocystis jirovecii*

Risk factors

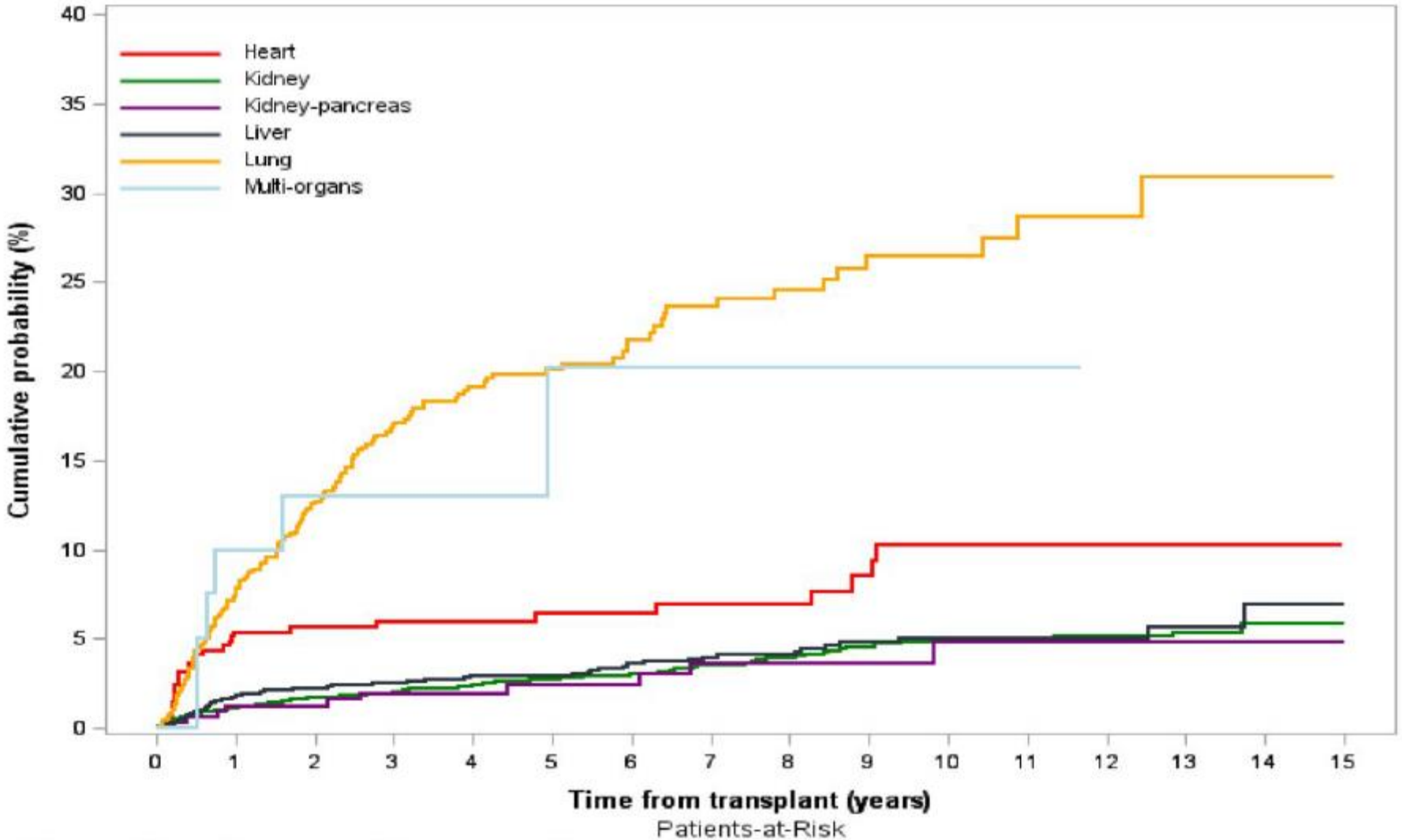


Fungal infections



Transpl Infect Dis. 2022;24:e13855.
https://doi.org/10.1111/tid.13855

FIGURE 1 Summary of IFI prevalence and timing when those fungal infections normally occur as well as prophylaxis recommendations for selected organ transplantations and fungal pathogens.



Patients-at-Risk

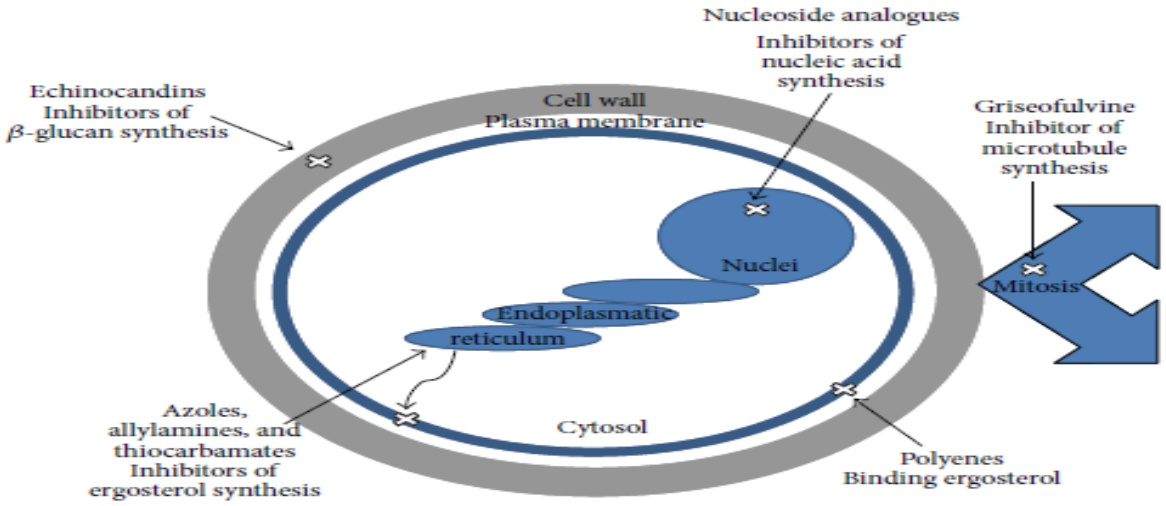
Heart	453	378	281	220
Kidney	5685	5479	4271	3281
Kidney-pancreas	333	323	244	194
Liver	1869	1676	1239	950
Lung	942	754	458	299
Multi-organs	44	36	17	11

FIGURE 3 Cumulative probability of IFI in recipients of different organ allografts

Diagnosis

- Lack of specific symptoms
- Lack of specific and sensitive laboratory tests
  - Serology is not reaiable
  - Fungal antigens- Candida, Aspergillus, Cryptococcus
    - 1-3βD glucan (sensivity 70%, specifity 87%)
    - Galactmannan (ELISA) –aspergillus sensivity 22%, specifity 84%
  - PCR DNA – not viable- risk of contamination

Antifungal agents



Antifungal class	Mode of action	Drugs
Azoles	Inhibitors of lanosterol 14-α-demethylase	Miconazole Econazole Clotrimazole Ketoconazole Fluconazole Itraconazole Voriconazole Posaconazole
Echinocandins	Inhibitors of (1,3)-β-D-glucan synthase	Caspofungin Micafungin Anidulafungin
Polyenes	Binding ergosterol	Nystatin Amphotericin B
Nucleoside analogues	Inhibitor of DNA/RNA synthesis	Flucytosine
Allylamines	Inhibitors of squalene-epoxidase	Terbinafine Amorolfine Naftifine
Thiocarbamates	Inhibitors of squalene-epoxidase	Tolnaftate Tolciclate
Antibiotic	Interaction with β-tubulin	Griseofulvin

FIGURE 1: Primary targets and mode of action of several antifungal agents.

Aspergillus infection

- **Clinical manifestations of aspergillosis range from asymptomatic colonization to invasive presentations including sinusitis, tracheobronchitis, pnumonia, and empyema. In a majority of cases of pneumonia, the clinical symptoms are subtle with cough, pleuritic chest pain, or fever.**
- **Sites of infection beyond the respiratory tract include the following: mediastinitis, the musculoskeletal system, thyroid, skin, rhinocerebral disease, ocular, organ specific, endocarditis, central nervous system (CNS), and disseminated disease forms.**

Treatment IA

- Early initiation of antifungal therapy in patients with strongly suspected IA is warranted while a diagnostic evaluation is conducted
- Voriconazole is the drug of choice to treat all forms of IA .
- Isavuconazole and lipid formulations of AmB, preferably L-AmB, can be considered as alternative agents .
- Posaconazole can be considered for salvage therapy in patients who fail or do not tolerate first-line antifungals.
- Combination therapy can be considered in select cases such as in patients with disseminated or CNS disease.
- Inhaled AmB (in conjunction with systemic antifungal therapy) may be used in the setting of tracheobronchial aspergillosis associated with anastomotic endobronchial ischemia, or ischemic reperfusion injury due to airway ischemia associated with lung transplant.
- Duration of treatment should be guided by clinical and radiological response; most cases will require a minimum of 12 weeks, if tolerated .
- Prophylaxis: liver, lung recipients.

Candida infection

- ***Candida*** **may cause a wide spectrum of infections ranging from superficial mucocutaneous infections to less common life-threatening invasive infections.**
- **Invasive candidiasis (IC) presents predominantly as *Candida* bloodstream infections (candidemia) that is most typically associated with central venous catheters or gastrointestinal or genitourinary tract pathology.**
- **The clinical presentation of *Candida* infection in a SOT recipient is not specific and may range from no symptoms with only laboratory markers of infection such as an elevated white blood cell count to septic shock manifested by fever, chills, hypotension, oliguria, and multi-organ dysfunction.**

Treatment and prophylaxis

- **Early initiation of antifungal therapy in SOT recipients with**

suspected or confirmed IC is recommended.

- **An echinocandin is recommended for initial treatment of candidemia**

and invasive candidiasis in SOT recipients.

- **Fluconazole is recommended as acceptable alternative therapy if the pathogen is likely to be fluconazole susceptible, and the patient is not critically ill.**
- **Routine *Candida* prophylaxis is not recommended for heart and kidney transplant recipients**
- **Targeted prophylaxis in liver, pancreas, small bowel transplant recipients with azoles or echinocandins is preferred over lipid formulations of amphotericinB.**

Cryptoccocus infection

- The clinical symptoms of cryptococcal infections in SOT recipients are often non-specific;
- In patients with meningitis, prolonged headache, altered mental status, fevers, and malaise are usually prominent symptoms compared to photophobia and nuchal rigidity.
- In patients with pulmonary infection, manifestations range from asymptomatic colonization or infection to severe pneumonia with respiratory failure. Symptoms are often non-specific and include fever, chills, cough, malaise, night sweats, dyspnea, and weight loss.
- Radiographic findings of pneumonia are frequently solitary (33% of patients) or multiple nodules, so the differential for causative agents should include other fungal infections. Other less common radiographic findings include mass lesions, lobar consolidations, or effusions.
- Among SOT patients, cryptococcal infections are usually disseminated (extrapulmonary) at time of presentation with both pulmonary and neurologic findings being common. Approximately 50%-75% of SOT recipients with cryptococcosis have extrapulmonary or disseminated disease.

Treatment

Induction	Duration
CNS disease, disseminated disease, or moderate-to-severe pulmonary disease	
Preferred therapy	
Liposomal amphotericin B 3-4 mg/kg/d or amphotericin B lipid complex 5 mg/kg/d plus 5-flucytosine 100 mg/kg/d[a]	Minimum of 2 wk
Alternative therapy	
Liposomal amphotericin B 3-4 mg/kg/d or amphotericin B lipid complex 5 mg/kg/d	Minimum of 4-6 wk
Consolidation	
Fluconazole 400-800 mg/d	8 wk
Maintenance	
Fluconazole 200-400 mg/d	Minimum of 6-12 mo
Pulmonary disease	
Asymptomatic or mild-to-moderate disease[b]	
Fluconazole 400 mg/d	6-12 mo
Severe pulmonary disease, or azole use not an option	
Same as for CNS disease	

Epidemiology of PCP

Pneumocystis **is transmitted by the airborne route. Acquisition of new infections in humans can most likely occur by person-to-person spread. Individuals with normal immune systems may have asymptomatic lung colonization and may serve as a reservoir for spread of *Pneumocystis* to immunocompromised hosts.**

Approximately 5 to 15 % of patients who undergo solid organ transplantation develop PCP in the absence of prophylaxis. The rates are lowest in renal transplant recipients and highest among lung and heart-lung transplant recipients. The period of highest risk for PCP following solid organ transplantation is from one to six months postoperatively when prophylaxis is not given. The risk is greatest in patients receiving the most intensive immunosuppressive regimens.

PCP signs and symptoms

TABLE 2 Signs and symptoms of *Pneumocystis* pneumonia

Sign or Symptom of PJP	Incidence
Fever	81%-87%
Dyspnea	66%-68%
Cough	71%-81%
Chest pain	23%-24%
Abnormal lung auscultation on examination	30%-34%
Abnormal chest radiography	92%-96%
Hypoxemia	78%-91%

Diagnosis

TABLE 3 Recommended diagnostic approach to PJP in patients with haematological malignancies, stem cell transplant, and solid organ transplant recipients*

Specimen/Technique	Recommended usage	Strength of recommendation	Quality of evidence
Diagnostic specimen			
Bronchoalveolar lavage	Allows detection of multiple etiologies; yield ≥80%[43,91]	Strong	High
Transbronchial biopsy	Increases yield of BAL, other lung pathology	Strong	Moderate
Open Lung biopsy or video-assisted thoracoscopy (VATS)	Gold standard for diagnosis, generally not required[92-94]	Strong	Low
Induced Sputum	Alternative specimen to BAL, yield ≥50%[94,95]	Strong	High
Other Respiratory specimens[a]	Not a good alternative, low organism burden[96]	Strong	Low
Diagnostic technique			
Immunofluorescence assays	Most sensitive microscopic diagnostic method; increased yield over other stains	Strong	High
Real-time quantitative PCR, nucleic acid testing	Quantification in BAL; cannot distinguish infection from carriage[40,46,97]	Strong	Low
Silver, polychrome, or calcofluor stains	Exclusion of PJP by negative BAL only	Strong	High
Serum			
Lactic dehydrogenase (LDH)	Not specific, generally positive in PJP[98]	Weak	Low
β-D-glucan	Not specific, useful as adjunctive diagnostic tool; β-D-Glucan is component of *P jiroveci* cell wall[40,98]	Weak	Moderate
Genotyping, sequencing	Investigation of suspected outbreaks	Strong	Low

PCP treatment

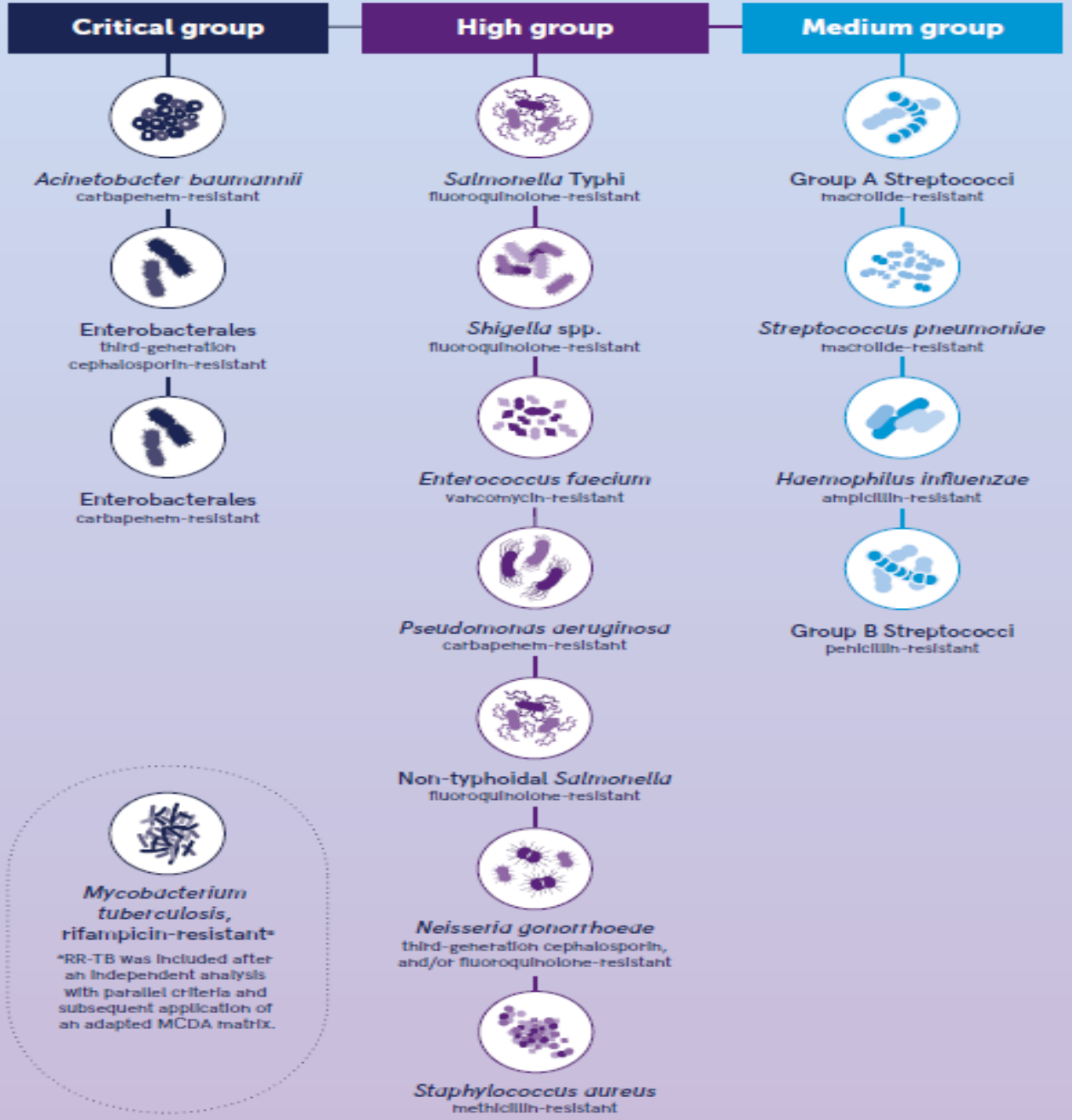
- Trimethoprim-sulfamethoxazole (TMP-SMX) is the first-line therapeutic agent and drug of choice for documented PJP (strong, high).
- Alternative agents are less effective and include intravenous pentamidine isethionate, atovaquone, primaquine and clindamycin (strong, high).
- Pentamidine therapy may cause pancreatitis, hypo- and hyperglycemia, and electrolyte disturbances and should generally be avoided in pancreas recipients (strong, moderate).
- Adjunctive corticosteroids are best administered within 72 hours of presentation in the setting of hypoxia (pAO_2 < 70 mm Hg) (strong, low).
- The duration of antimicrobial therapy should be at least 14 days; longer courses are often required (strong, low).

Trimethoprim-sulfamethoxazole (TMP-SMX)	Adults/Adolescents: 15-20 mg/kg/day of the TMP component given IV in divided doses every 6-8 h; lower doses may be sufficient. In milder disease, two double-strength tablets can be given po tid	TMP-SMX remains the drug of choice; most effective systemic therapy for PJP. Correct for renal function and maintain hydration. May consider adjunctive corti-

Bacterial infections

< 1 month	6. 2- 12 months	>12 months
MRSA, VRE *Pseudomonas aeruginosa,* *Burkholderia spp.* *Clostridium difficile*	*Clostridium difficile* *Pseudomonas aeruginosa* *Burkholderia spp.* *Mycobacterium tbc* *Listeria monocytogenes* *Nocardia spp.* *Legionella spp.* *Mycoplasma spp.* *Chlamydia spp.*	*Streptococcus pneumoniae* *Haemophilus influenzae* Gram-ujemne pałeczki *Mycobacterium non-tbc*

Fig. 1. WHO Bacterial Priority Pathogens List, 2024 update



World Health Organization

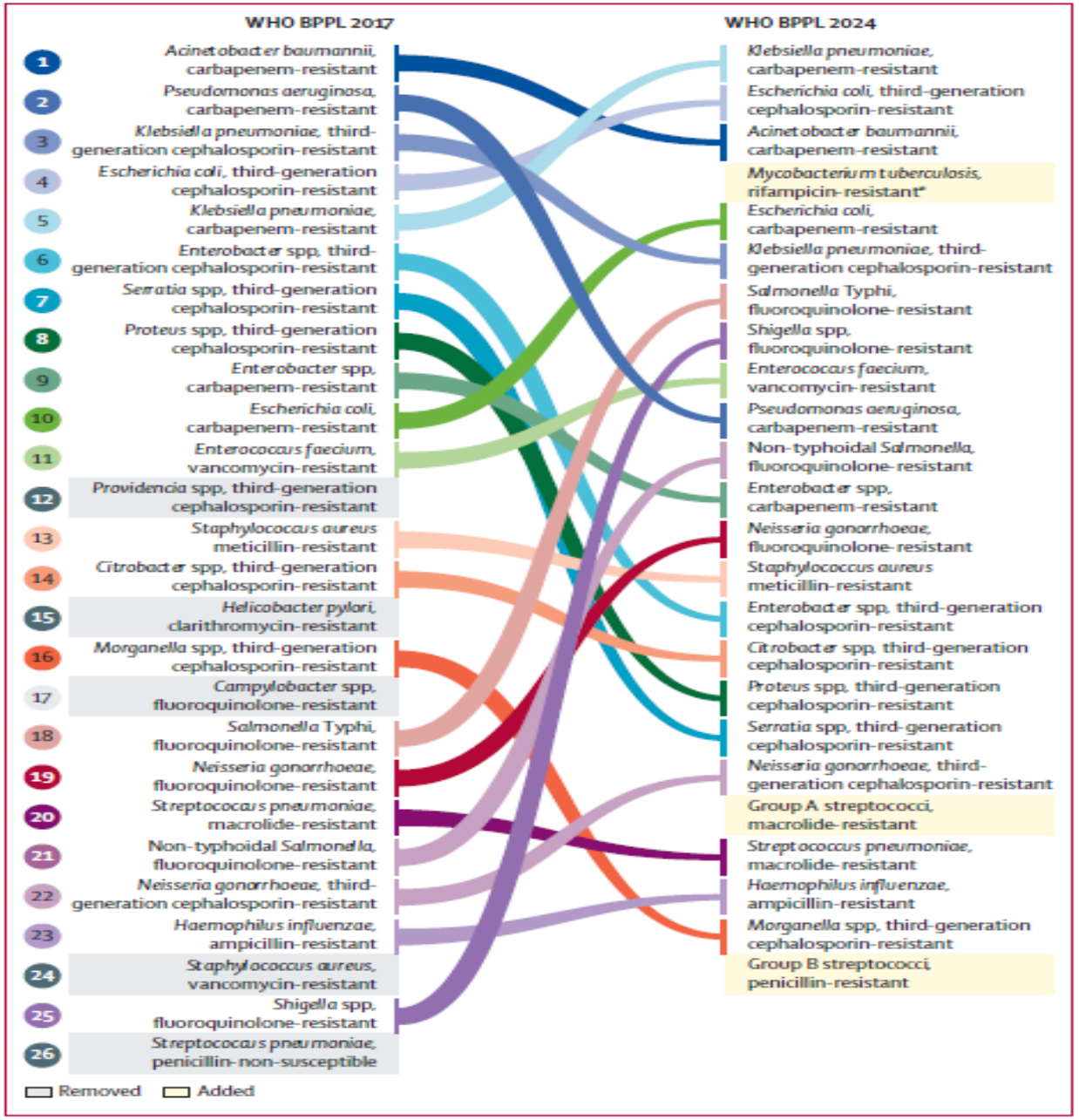


Figure 3: **Comparative overview of WHO BPPL, 2017 versus 2024**
Pathogens are ranked by position on the BPPL. Figure reproduced from the 2024 WHO BPPL report.[35] BPPL=Bacterial Priority Pathogens List. *Salmonella* Typhi=*Salmonella enterica* serotype Typhi. *Rifampicin-resistant *M tuberculosis* was included after an independent analysis with parallel criteria and subsequent application of the multicriteria decision analysis matrix.

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Multidrug-resistant organism bloodstream infections in solid organ transplant recipients and impact on mortality: a systematic review

Alice J. Liu [1], Adelaide S. M. Dennis [1], Zarin Fariha[1], Rekha Pai Mangalore[1] and Nenad Macesic [1,2,3]*

[1]Department of Infectious Diseases, The Alfred Hospital and School of Translational Medicine, Monash University, Melbourne, Australia; [2]Centre to Impact AMR, Monash University, Clayton, Australia; [3]Infection Prevention & Healthcare Epidemiology, Alfred Health, Melbourne, Australia

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Six MDROs were selected from the WHO Bacterial Priority Pathogens (2024 update) due to their relevance for SOT recipients: carbapenem-resistant Enterobacterales (CRE); carbapenem-resistant *Acinetobacter baumannii* (CRAB); carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), third-generation cephalosporin-resistant Enterobacterales (3GCR-E), vancomycin-resistant *Enterococcus faecium* (VRE) and MRSA.

Table 1. Proportions of BSIs caused by resistant organisms in SOT recipients by time period and region

	Pooled (*n* = 49)	2002–10 (*n* = 10)	2011–15 (*n* = 15)	2016–20 (*n* = 12)	2021–24 (*n* = 12)	Europe (*n* = 16)	North America (*n* = 12)	South America (*n* = 4)	Asia (*n* = 17)
3GCR-E (% of Enterobacterales), median (IQR)	38.2 (27–49)	42.3 (33.6–50.9)	30.0 (27.6–56.5)	33.8 (20.8–40.8)	40.0 (35.0–47.5)	29.3 (21.2–40.5)	33.5 (30.4–36.2)	43.4 (41.9–44.9)	63.1 (45.2–72.9)
CRE (% of Enterobacterales), median (IQR)	13.6 (8.7–37.0)	9.5[a]	45.5[a]	28.6 (14.3–61.9)	6.3 (3.6–9.1)	14.3[a]	12.9 (7.8–13.6)	NR	35.7 (8.3–63.1)
CRAB (% of *A. baumannii*), median (IQR)	59.2 (50.0–77.4)	60.0[a]	54.2 (48.2–73.3)	72.4 (6.2–83.6)	84.6[a]	50.0 (50.0–61.4)	NR	53.6 (42.9–64.3)	60.0 (54.2–88.7)
CRPA (% of *P. aeruginosa*), median (IQR)	33.3 (24.3–43.8)	NR	33.3 (33.3–74.3)	32.4 (27.9–36.8)	17.0 (6.8–29.9)	45.2 (25.0–61.4)	38.9 (36.1–41.7)	87.5[a]	27.5 (21.0–32.8)
MRSA (% of *Staphylococcus aureus*), median (IQR)	50.4 (36.4–86.7)	77.8 (47.40–100)	56.0 (35.5–84.3)	77.9 (73.9–81.8)	31.5 (15.6–47.4)	31.7 (22.0–46.6)	50.5 (38.1–77.8)	64.3 (53.6–75.0)	86.2 (77.3–94.6)
VRE (% of *E. faecium*), median (IQR)	38.1 (3.0–67.6)	55.6 (27.88–77.8)	15.0 (0.0–36.1)	53.0 (28.4–76.0)	36.9 (8.9–62.2)	3.0 (0.0–23.5)	76.6 (57.2–89.4)	38.6[a]	32.3 (6.6–51.2)

[a]Only single studies available, unable to calculate IQR. NR, not reported.

Liver transplantation was the most frequently studied transplant type, with the following median MDRO resistance percentages: CRE 9.5% , 3GCR-E 40.4% , CRAB 72.3% , CRPA 33.3% , VRE 34.0% and MRSA 80.0% .
 Kidney transplantation had sufficient data for analysis of 3GCR-E resistance percentage [median 32.4%], but there were too few studies to determine these for other transplant type/MDRO combinations.
Crude mortality due to MDRO BSI ranged from 15.4% (VRE 30 day mortality in liver transplant recipients) to 82.4% (CRE mortality in liver transplant recipients admitted to intensive care).Excluding patients in the intensive care setting, crude mortality remained as high as 65.5% (CRAB 10 day and 30 day mortality in liver transplant recipients).Where mortality due to MDRO BSI was assessed alongside drug-susceptible BSI, MDRO BSIs were consistently associated with a higher mortality rate irrespective of MDRO or transplant type. For individual MDROs, MRSA- and VRE-associated mortality were most frequently reported, with a median crude mortality of 36.1% and 37.2% , respectively.

TABLE 2 Recently approved antibiotic agents with potential activity against extended-spectrum β-lactamase-producing (ESBL-E) and carbapenem-resistant Enterobacterales (CRE)

Agent	Approved indications	Dose (normal renal function)	Experience in SOT recipients	Considerations
Cefiderocol	cUTI, HAP/VAP (FDA) Infections due to aerobic GNB with limited treatment options (EMA)	2 g IV every 8 h	Case reports	The only agent with activity against MBL-producing CRE FDA warning due to increased all-cause mortality in phase III RCT compared to best available therapy Potential for resistance selection
Ceftazidime-avibactam	cUTI, cIAI, HAP/VAP (FDA, EMA) Infections due to aerobic GNB with limited treatment options (EMA)	2/0.5 g IV every 8 h	Case reports, case series, comparative retrospective studies	Activity against OXA-48-producing CRE Potential activity against MBL-producing CRE in combination with aztreonam
Meropenem-vaborbactam	cUTI (FDA) cUTI, cIAI, HAP/VAP (EMA) Infections due to aerobic GNB with limited treatment options (EMA)	2/2 g IV every 8 h	Case reports	Lower potential for resistance selection than CAZ-AVI No additional activity beyond meropenem for MDR *Pseudomonas* No activity against OXA-48-type and MBL-producing CRE
Imipenem-cilastatin-relebactam	cUTI, cIAI, HAP/VAP (FDA) HAP/VAP, infections due to aerobic GNB with limited treatment options (EMA)	500/500/125 mg IV every 6 h	None	No activity against OXA-48-type, GES-type, and MBL-producing CRE
Plazomicin	cUTI (FDA)	15 mg/Kg IV every 24 h	None	Potential role of monotherapy Increased risk of nephrotoxicity with calcineurin inhibitors Not available in Europe
Eravacycline	cIAI (FDA, EMA)	1 mg/Kg IV every 24 h	Small case series	More potent activity, better tissue penetration, and lower potential for resistance selection than tigecycline Interaction with strong CYP3A4 inducers Unfavorable PK/PD profile for BSI Should be avoided in cUTI

Abbreviations: BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; cIAI, complicated intraabdominal infection; CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infection; EMA, European Medicines Agency; FDA, Food and Drug Administration; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; MBL, metallo-β-lactamase; PK/PD, pharmacokinetic/pharmacodynamic; RCT, randomized clinical trial; SOT, solid organ transplantation.

Urinary tract infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Accepted: 12 February 2019

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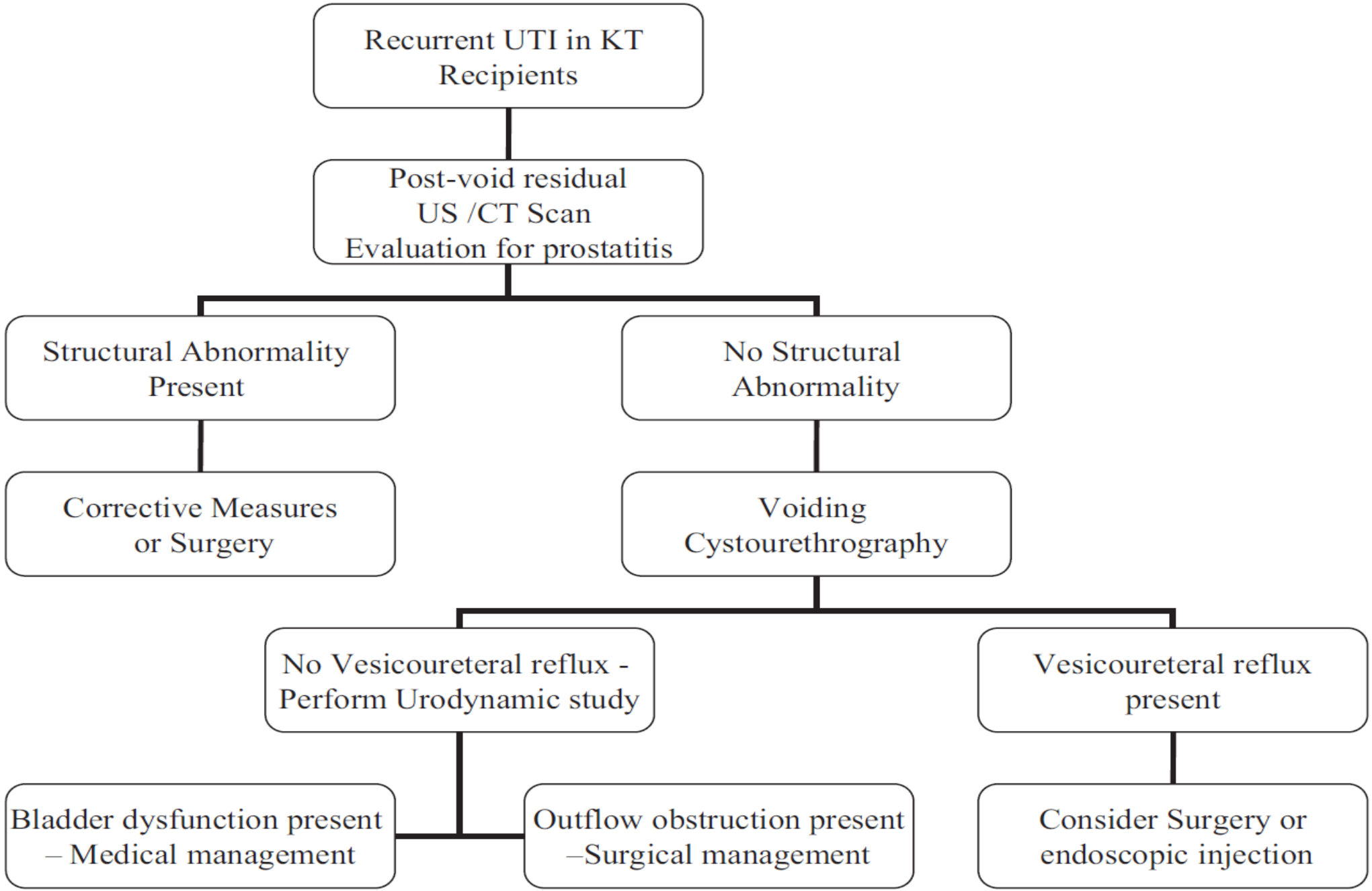
TABLE 1 Classification of asymptomatic bacteriuria (AB) and urinary tract Infection (UTI) in renal transplant recipients

Classification	Description	Laboratory investigations of urine
Asymptomatic bacteriuria	No urinary or systemic symptoms of infection	$>10^5$ CFU/mL uropathogen[ab]
Acute simple cystitis	Dysuria, urinary urgency/frequency, or suprapubic pain; but no systemic symptoms and no ureteral stent/nephrostomy tube/chronic urinary catheter	>10 WBC/mm^3[c] $>10^3$ CFU/mL uropathogen[b]
Acute pyelonephritis/Complicated UTI	Fever, chills, malaise, hemodynamic instability, or leukocytosis (without other apparent etiology); flank/allograft pain; or bacteremia with same organism as in urine Dysuria, urgency, frequency, suprapubic pain may or may not be present	>10 WBC/mm^3[c] $>10^4$ CFU/mL uropathogen[b]
Recurrent UTI	≥ 3 UTIs in prior 12-month period	As above

TABLE 2 Treatment of asymptomatic bacteriuria and urinary tract infection in transplant recipients

Clinical presentation[a]	Suggested management
Asymptomatic bacteriuria (AB)	Routine treatment of AB is not routinely recommended (see Treatment section). However, if two consecutive urine samples yield $>10^5$ of the same uropathogen in the first two months post-transplant, can *consider* treatment for 5-7 days. This practice may have no benefit and may promote antimicrobial resistance; this practice has not been studied in the early transplant period. Beyond the early transplant period, studies have been performed and do not support treatment of AB. There is no role for empiric treatment of AB—await culture susceptibility and select the most narrow-spectrum antibiotic available. Do not treat AB of multi-drug resistant bacteria.
Simple cystitis[b]	Third-generation oral cephalosporin OR amoxicillin-clavulanate OR ciprofloxacin OR levofloxacin. Nitrofurantoin is broad-spectrum but is not recommended if CrCl < 40—see text. (Especially if patient recently receiving TMP-SMX, anticipate uropathogen to be resistant to TMP-SMX. Routine use of fosfomycin is not recommended; limit fosfomycin to multi-drug resistant cystitis.) Treatment duration 5-7 days.
Pyelonephritis/Complicated UTI—moderate/severe[b]	Piperacillin-tazobactam OR cefepime OR carbapenem, ±fluoroquinolone. Once culture susceptibility results available, complete 14-21 days of therapy with the most narrow-spectrum antibiotic available.


Recurrent UTI in KT Recipients
Post-void residual US /CT Scan Evaluation for prostatitis
Structural Abnormality Present
No Structural Abnormality
Corrective Measures or Surgery
Voiding Cystourethrography
No Vesicoureteral reflux - Perform Urodynamic study
Vesicoureteral reflux present
Bladder dysfunction present – Medical management
Outflow obstruction present –Surgical management
Consider Surgery or endoscopic injection

Clostridium difficile

- **Mild-to-moderate CDI typically presents with diarrhea and possibly also with mild abdominal pain and minimal systemic symptoms.**
- **In CDI classified as severe, the number of unformed bowel movements exceeds 10 daily and patients have systemic symptoms of fever and severe abdominal pain along with laboratory parameters of leukocytosis, renal evidence of dehydration, and hypoalbuminemia.**
- **Patients classified as having severe disease with complications include those having the symptoms of severe disease accompanied by life-threatening conditions such as paralytic ileus, toxic megacolon, refractory hypotension, and/or multiorgan failure secondary to CDI. Disease severity may rapidly progress; therefore, clinicians should frequently reassess and adjust CDI therapy accordingly.**
- **Fever (>38.5°C), leukocytosis (WBC >15 000/mm3, and creatinine >1.5 mg/dL appear to be variables that most correlate with treatment failure.**
- **Testing of stool for *C difficile* and/or its toxins should only be performer in symptomatic patients who have clinically significant diarrhea, defined as new onset >3 unformed bowel movements in a 24-hour time period or diarrhea worse than otherwise expected based on the clinical scenario.**

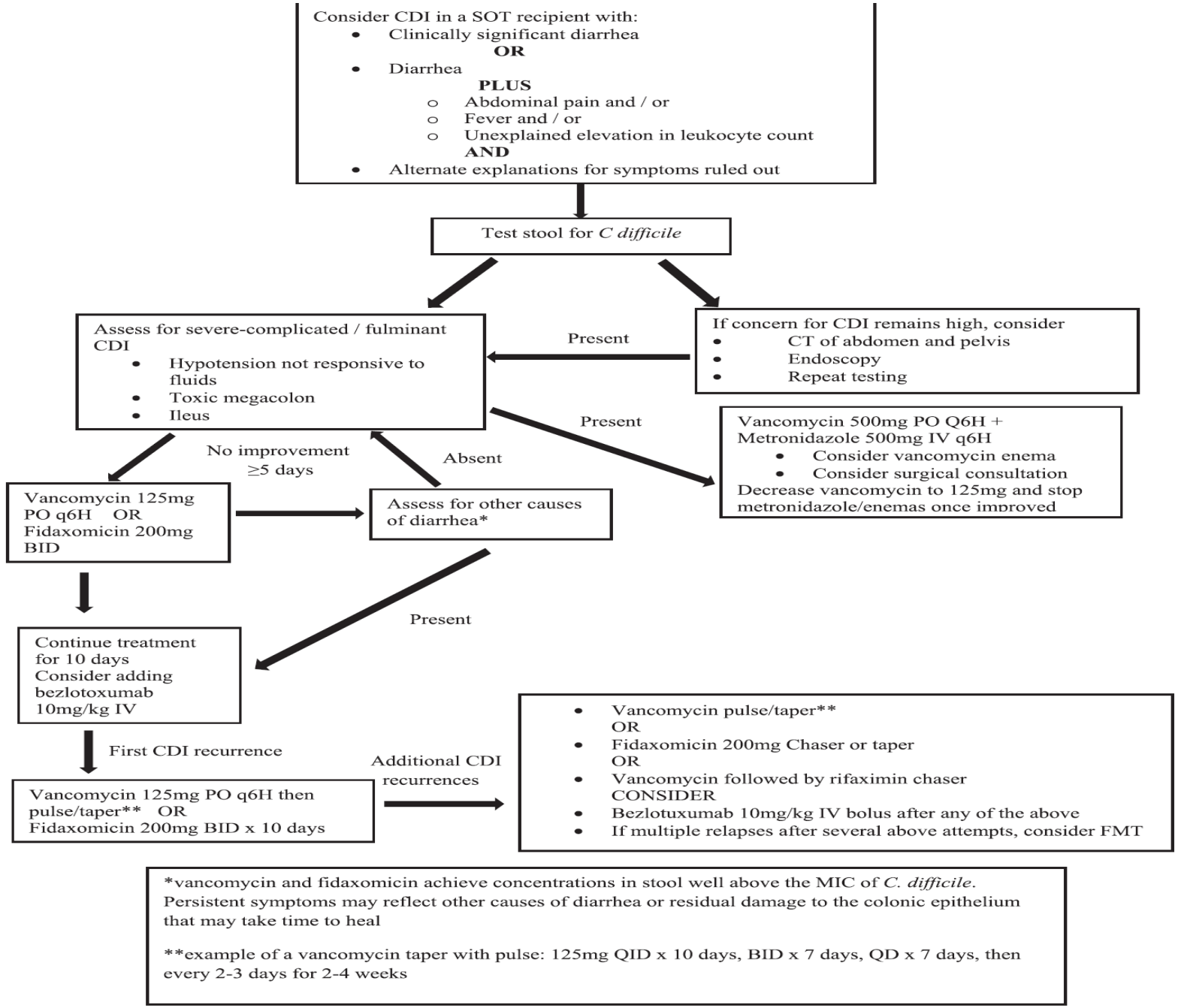


FIGURE 1 Recommended approach to the diagnosis and treatment of *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) presenting with diarrhea in adult solid organ transplant (SOT) recipients

Vaccination

General principles

- **Vaccination status should be reviewed and vaccination plan developed**
- **in all transplant candidates and recipients.**
- **All transplant candidates should be up to date on their routine vaccines as per national guidelines.**
- **Inactivated vaccines should be given at least 2 weeks prior to transplant where possible for an adequate immune response**
- **Live-attenuated vaccines should be given at least 4 weeks prior to transplant to ensure that vaccine-related viral replication has resolved prior to transplant**
- **In the post-transplant setting, inactivated vaccines can be administered starting at 3-6 months post-transplant except influenza vaccine which can be given as early as 1 month post-transplant**

TABLE 2 Recommendations for immunization of adult patients

Vaccine	Inactivated/live attenuated (I/LA)	Recommended before transplant	Recommended after transplant	Evaluate for serologic response
Influenza[48-52]	I	Yes	Yes	No
	LA	See text	No	No
Hepatitis B[19,23,24,53,56]	I	Yes	Yes	Yes
Hepatitis A[a] [57,58]	I	Yes	Yes	Yes
Tetanus[59-62]	I	Yes	Yes	No
Pertussis (Tdap)[b]	I	Yes	Yes	No
Inactivated Polio vaccine	I	Yes	Yes	No
H influenza type B[c]	I	Yes	Yes	Yes
S pneumonia (conjugate vaccine)[25,26,28,29,64,65]	I	Yes	Yes	No
S pneumonia (polysaccharide vaccine)[25,26,28,29,64,65]	I	Yes	Yes	No
Rabies[a,d]	I	Yes	Yes	Yes
Human papilloma virus (HPV)	I	Yes	Yes	No
MMR	LA	Yes	No	No
Varicella (live attenuated; Varivax)	LA	Yes	No	Yes
Varicella (live attenuated; Zostavax)[64]	LA	Yes	No	No
Varicella (subunit;Shingrix)	I	Yes	Yes	No
Measles/Mumps/Rubella[60,71-74]	LA	Yes	No	Yes
BCG[e]	LA	Yes	No	No
Smallpox[f75]	LA	No	No	No
Anthrax	I	No	No	No

[a]Monitoring indicated only if ongoing risk for exposure, for example with planned travel to high-risk areas.
[b]If no tetanus booster in the past 10 y, Tdap should be administered. At least one dose of acellular pertussis should be given in adulthood, with particular attention to women of child-bearing age and individuals with in contact with infants.
[c]Indicated before or after splenectomy. Serologic assessment recommended if available. *Haemophilus influenzae* vaccine-induced anticapsular (polyribosylribitol phosphate) antibodies greater than 0.15 mg/L is considered protective in the general population.
[d]Not routinely administered. Recommended for exposures or potential exposures due to vocation.
[e]The indications for BCG administration in the US are limited to instances in which exposure to tuberculosis is unavoidable and where measures to prevent its spread have failed or are not possible.
[f]Transplant recipients who are face-to-face contacts of a patient with smallpox should be vaccinated; vaccinia immune globulin may be administered concurrently if available. Those who have less intimate contact should not be vaccinated.

RSV Vaccines

- 2023 FDA approved 2 RSV vaccines (recombinant based on prefusion F glycoprotein) to prevent RSV-associated LRTD

	RSVPreF3 OA (Arexy®)	RSVPreF (Abrysvo®)
Type	AS01$_E$-adjuvanted, monovalent (A)	Non-adjuvanted, bivalent
Approved in	Adults ≥ 60 y	Adults ≥ 60 y Pregnant individuals, 32-36wk GA
Inclusion of SOT or HCT	No	No
Vaccine efficacy (2 seasons)	74.5 [97.5% CI 60-84.5]	84.4 [95% CI 59.6-95.2]
against RSV LRTD*, S1	82.6 [96.95% CI 57.9-94.1]	88.9 [95% CI 53.6-98.7]
against RSV LRTD, S2	56.1 [95% CI 28.2-74.4]	78.6 [95% CI 23.2-96.1]
Safety: serious AE, RR [95%CI]	1.02 [0.91-1.15]	1.04 [0.94-1.15]
severe AE#, RR [95%CI]	4.10 [1.99-8.45]	1.43 [0.85-2.39]
Recommendations CDC, ACIP, ASTCT	Provide 1 dose to ≥ 65 y; ≥ 60 y at ↑est risk of RSV disease: 1 dose using shared decision making; provide prior to onset of RSV season	

*LRTD case definitions not aligned; #6 severe adverse inflammatory neurologic events (Guillain-Barré syndrome, acute disseminated encephalomyelitis) among 38,247 participants (0.016%) within 42d.

Papi et al, NEJM, 2023; Walsh et al, NEJM, 2023; Melgar et al, MMWR, 2023; Fleming-Dutra, MMWR, 2023; Ison et al, *CID*, 2024

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Shingrix (*szczepionka przeciw herpes zoster, rekombinowana, z adiuwantem*)

Przegląd wiedzy na temat szczepionki Shingrix i uzasadnienie udzielenia pozwolenia na dopuszczenie do obrotu w UE

Czym jest szczepionka Shingrix i w jakim celu się ją stosuje

Shingrix jest szczepionką stosowaną do ochrony osób dorosłych w wieku od 50 lat przed półpaścem (herpes zoster) oraz neuralgią półpaścową (długotrwałym bólem nerwu występującym po przebytym półpaścu). Można ją również stosować u osób dorosłych w wieku od 18 lat, u których występuje zwiększone ryzyko pojawienia się herpes zoster.