Infectious complications in SOT recipients

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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.

American Journal of Transplantation 2017; 17: 856–879

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

Donor derived infections

Table 8.2. **Basic screening for infections in deceased organ donors**

Before organ recovery or transplant (1-3 h)	**As soon as possible (not necessarily before organ recovery and transplant)**	**Retrospectively after transplant, if indicated at the recipient transplant centre**
anti-HIV-1/2 (incl. HIV-1-p24-Ag) HBsAg and anti-HBc anti-HCV	anti-CMV IgG anti-EBV-VCA-IgG, anti-EBNA1-IgG anti-*Treponema pallidum* ELISA (enzyme-linked immunosorbent assay or VDRL/ RPR) anti-Toxoplasma IgG	Additional tests can be performed according to the recipient profile for targeting specific prophylaxis VDRL: Venereal Disease Research Laboratory RPR: rapid plasma reagin

TABLE 2 Pathogens reported to be transmitted with solid organ transplantation

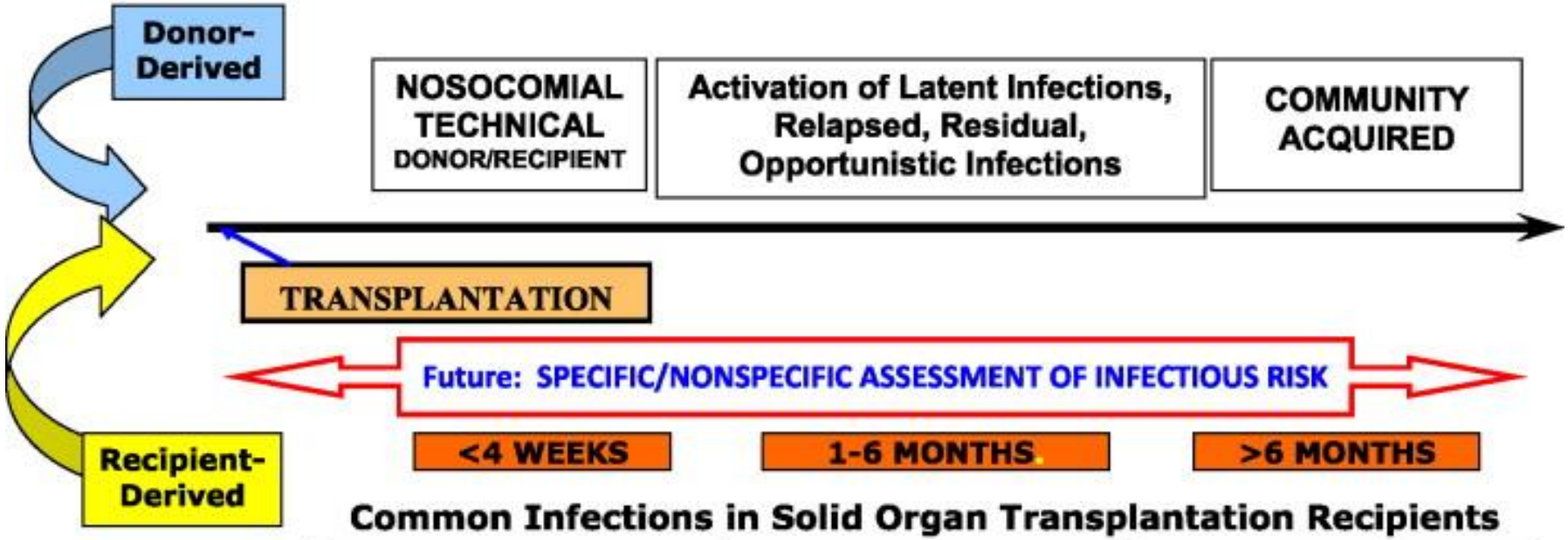
Bacteria	**Mycobacteria**
Staphylococcus aureus	*Mycobacterium tuberculosis*
Klebsiella species	Non-tuberculous mycobacteria
Bacteroides fragilis	
Pseudomonas aeruginosa	**Parasites/Protozoa**
Escherichia coli	*Toxoplasma gondii*
Salmonella species	*Strongyloides stercoralis*
Yersinia enterocolitica	*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

European Directorate for the Quality of Medicines & HealthCare (EDQM)
Council of Europe

Przeszczepy narządowe

Wytyczne europejskie zalecane przez POLTRANSPLANT

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).

Viral infections in SOT

- **Herpes: HSV 1, 2, VZV, CMV, EBV, HHV 6, HHV 7, HHV 8**
- **Hepatitis A, 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)**

Cytomegalovirus

The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

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on behalf of the The Transplantation Society International CMV Consensus Group

Abstract: Despite recent advances, cytomegalovirus (CMV) infections remain one of the most common complications affecting solid organ transplant recipients, conveying higher risks of complications, graft loss, morbidity, and mortality. Research in the field and development of prior consensus guidelines supported by The Transplantation Society has allowed a more standardized approach to CMV management. An international multidisciplinary panel of experts was convened to expand and revise evidence and expert opinion-based consensus guidelines on CMV management including prevention, treatment, diagnostics, immunology, drug resistance, and pediatric issues. Highlights include advances in molecular and immunologic diagnostics, improved understanding of diagnostic thresholds, optimized methods of prevention, advances in the use of novel antiviral therapies and certain immunosuppressive agents, and more savvy approaches to treatment resistant/refractory disease. The following report summarizes the updated recommendations.

(*Transplantation* 2018;102: 900–931)

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 disease

	Proven or definite	Probable
CMV syndrome	Not defined	Detection of CMV in the blood by viral isolation, rapid culture, antigenemia, or QNAT Plus, at least two of the following: 1. Fever ≥38°C for at least 2 d 2. New or increased malaise or fatigue 3. Leukopenia or neutropenia on 2 separate measurements 4. 5% atypical lymphocytes 5. Thrombocytopenia 6. Hepatic aminotransferases increase to two times ULN (except non-liver transplant recipients)
Gastrointestinal CMV disease	Presence of upper and/or lower GI symptoms plus macroscopic mucosal lesions plus CMV documented in tissue by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization techniques	Presence of upper and/or lower GI symptoms and CMV documented in tissue but without macroscopic mucosal lesions CMV documented in blood by NAT or antigenemia alone is not sufficient for diagnosis of CMV GI disease
CMV 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	Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with detection of CMV by viral isolation and rapid culture of BALF, or quantitation of CMV DNA in BALF
CMV hepatitis	Abnormal liver tests plus CMV documented in liver tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques plus the absence of other documented cause of hepatitis	Not defined
CMV retinitis	Typical ophthalmological signs as assessed by an ophthalmologist experienced with the diagnosis of CMV retinitis If the presentation is atypical or an experienced ophthalmologist is not available, the diagnosis should be supported by CMV documented in vitreous fluid by NAT	Not defined
CMV encephalitis	CNS symptoms plus detection of CMV in CNS tissue by virus isolation, rapid culture, immunohistochemical analysis, in situ hybridization, or quantitative NAT	CNS symptoms plus detection of CMV in CSF without visible contamination of blood (“bloody tap”) plus abnormal imaging results

Direct and indirect CMV effects

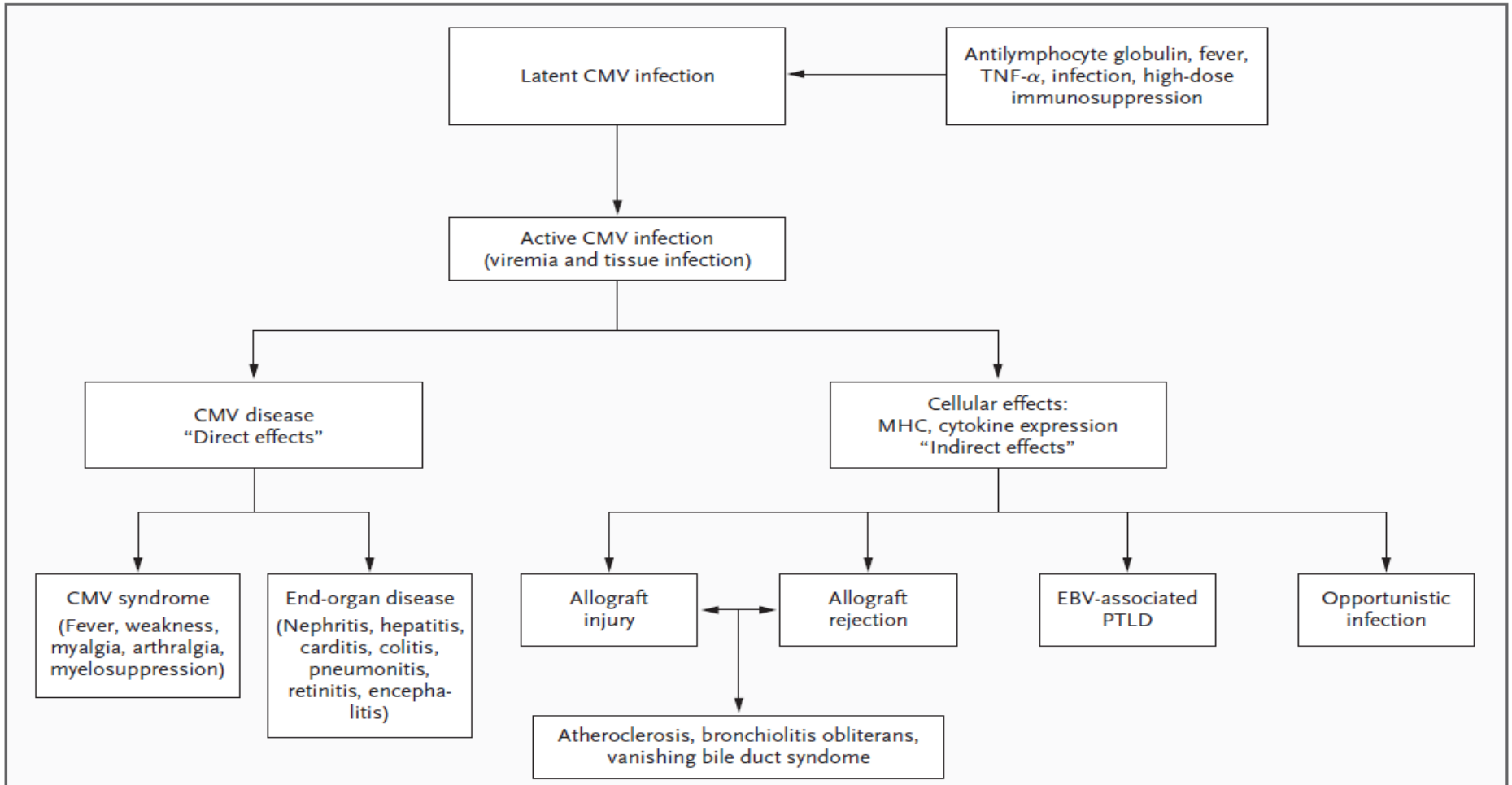


Figure 5. Cytomegalovirus Infection.

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.

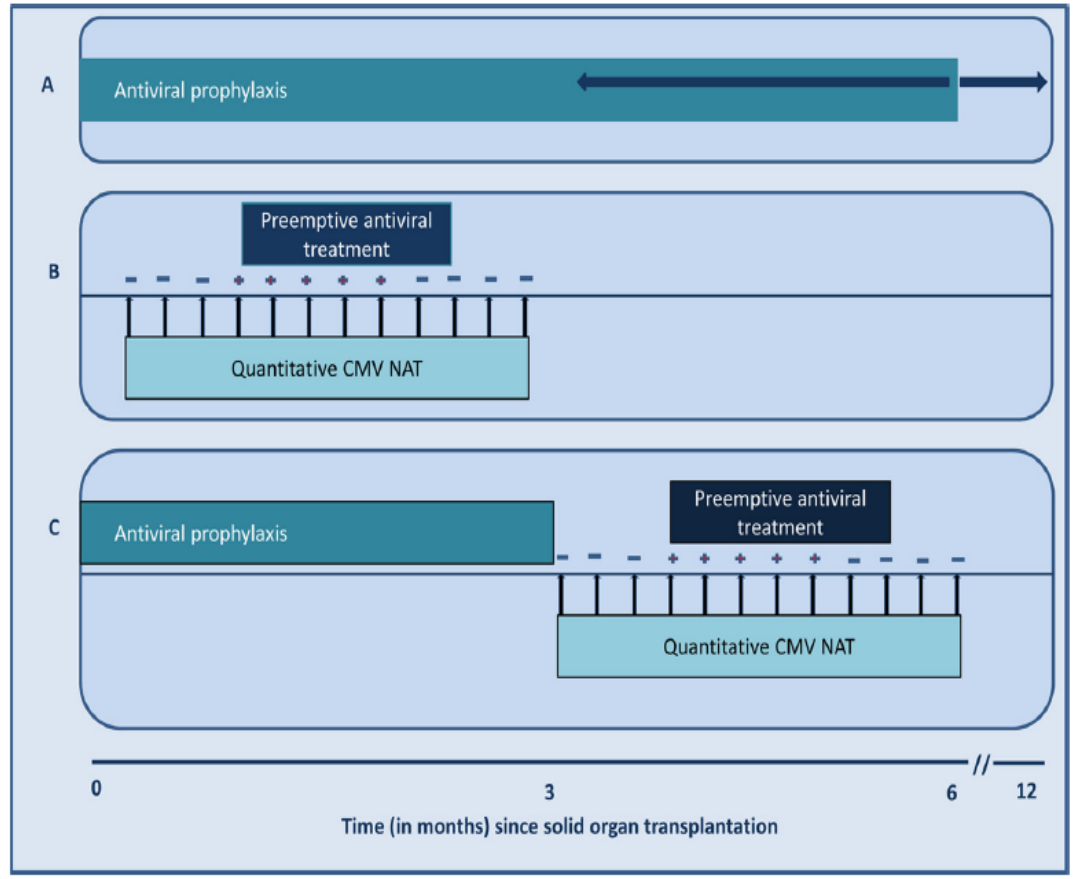
Diagnosis

- **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.**

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

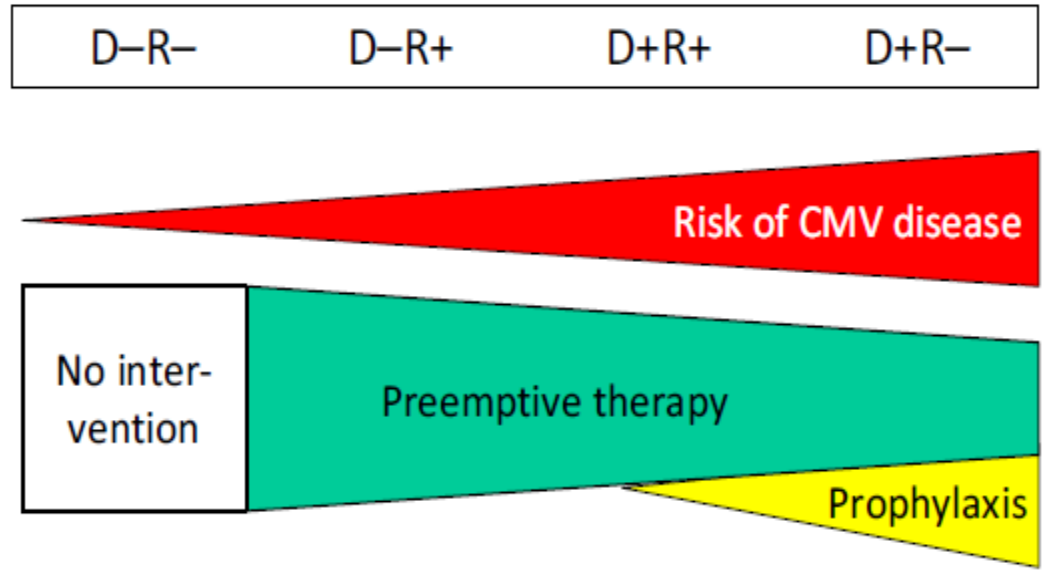


Figure 2 Proposal for use of pre-emptive therapy and anti-CMV prophylaxis. The risk of CMV disease is highly influenced by the serostatus of donor and recipient prior to transplantation. Here, we propose a risk-adapted use of pre-emptive therapy and antiviral prophylaxis with respect to the serostatus.

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

TABLE 6.

Recommended approaches for CMV prevention in different organs for adult SOTR

Organ	Serostatus	Risk level	Recommended	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 months of GCV/VGCV OR Preemptive therapy	
	R+	Intermediate	3 months of VGCV OR Preemptive therapy	
Liver	D+R–	High	3 -6 months of VGCV (VGCV not FDA approved in liver) OR Preemptive therapy	
	R+	Intermediate	3 months of VGCV (VGCV not FDA approved in liver) OR Preemptive therapy	
Pancreas	D+R–	High	3 -6 months of VGCV	Preemptive therapy
	R+	Intermediate	3 months of VGCV OR Preemptive therapy	
Islet	D+R–	Intermediate	3 months of VGCV	Preemptive therapy
	R+	Intermediate	3 months of VGCV OR Preemptive therapy	
Heart	D+/R–	High	3-6 months of GCV/VGCV	-Preemptive therapy -Some experts add CMV Ig to prophylaxis
	R+	Intermediate	3 months of GCV/VGCV OR Preemptive therapy	
Lung	D+/R–	High	6-12 months of GCV/VGCV -Some experts add CMV Ig to prophylaxis	-Preemptive therapy
	R+	Intermediate	Minimum 6 months of GCV/VGCV	
Intestinal, composite tissue	D+/R–	High	Minimum 6 months GCV/VGCV + – surveillance after prophylaxis	-Preemptive therapy -Some experts add CMV Ig
	R+	High	3-6 months GCV/VGCV + – surveillance after 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.

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

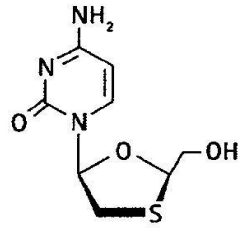
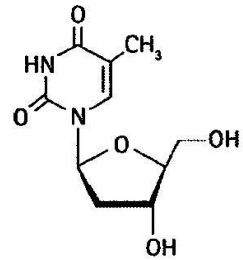
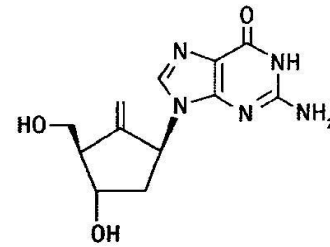
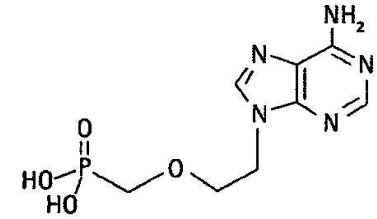
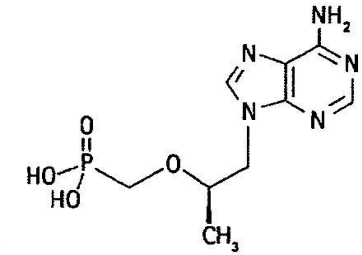
Anemia: severe or persistent • Lack of reticulocyte response • Lack of response to erythropoietin
Lacy skin rash • Not always present because of lack of antigen-antibody complexes[37,42]
Arthropathy • Not always present because of lack of antigen-antibody complexes[37,42]
Pancytopenia • A subset of patients 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 €

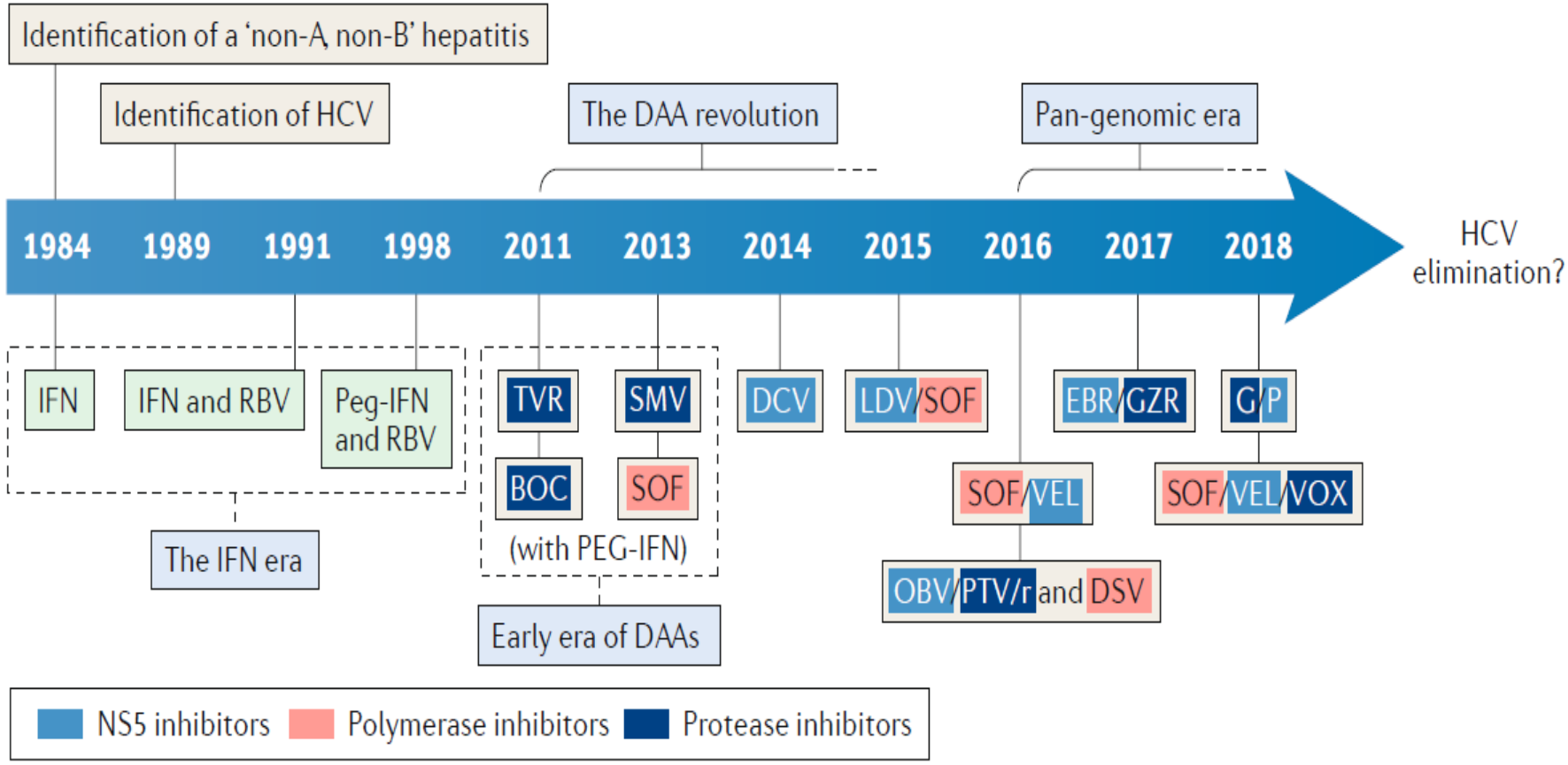
[a]LAM-naive patients; [b]LAM-experienced patients; [c]LAM experienced HBeAg$^+$ patients; [d][15,21–23].

HBV

- Administration of ETV, TDF, or TAF, with or without short-term 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

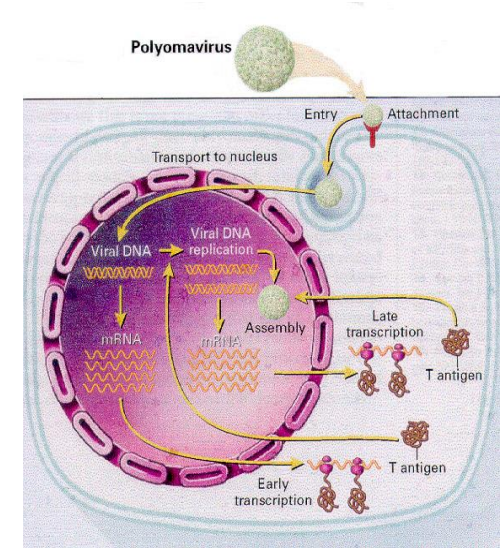
- Primary infection in childhood- >80% seropositivity
- Latent infection- uroepithelium, renal tubular epithelial cells
- Renal transplant recipient- reactivation 60%
- Viruria- 30-40%
- Viremia- 10%-20%
- BKV nephropathy- 1-10%- tublointerstitial nephritis
- Graft loss- 15%-80%

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

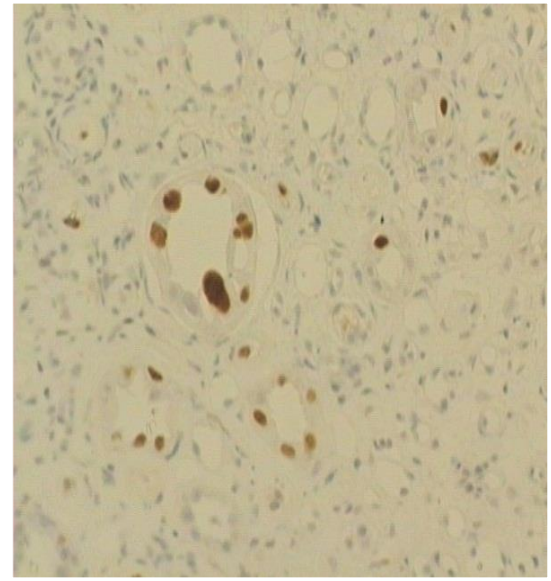
BKV infection evolution

Viruria
↓
Viremia
↓
BKN

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

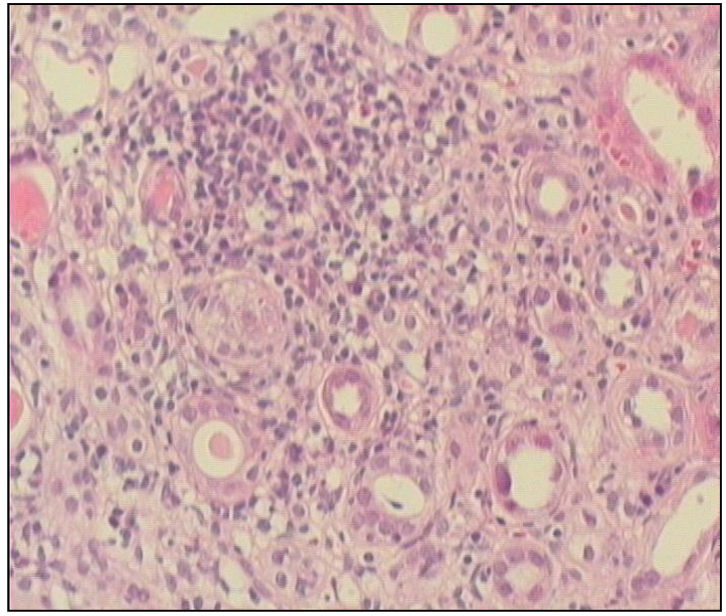


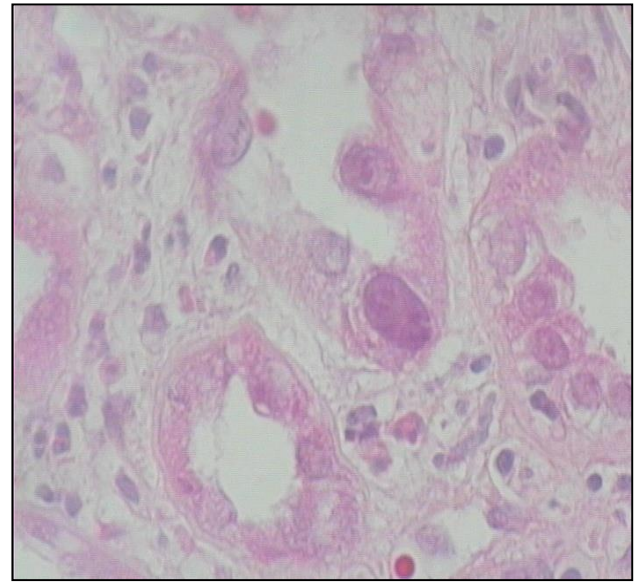
Diagnosis



- 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, or from mycophenolic acid to leflunomide.

Additional strategies

Table 1 Anti-Virals for PVN

Anti-Virals			
Name	**Class/Mechanism**	**Dose**	**Comments**
Leflunomide[49–52]	Anti-Inflammatory; Anti-Viral; Immunosuppressive	PO: Loading- 100 mg daily for 3–5 days; maintenance- 20-60 mg qD; Trough Level ~50-100 μg/mL	Can be used following discontinuation of MMF.
Cidofovir[53–55]	Nucleoside analog	IV: 0.25–1.0 mg/Kg at 1–3 weeks	Used in refractory cases; Nephrotoxicity is the most serious adverse effect.
Brincidofovir[56,57]	Investigational Prodrug of Cidofovir; Anti-viral activity	PO: 2 mg/Kg twice weekly	Reasonably well tolerated; Investigational.
Intravenous immunoglobulin (IVIG)[58–61]	Immunoglobulin preparation with high titers of neutralizing antibodies to BK virus	IV: 0.25–2.0 g/Kg	Can be used as an adjunct to other measures in refractory cases.
Levofloxacin[62–64]	Fluoroquinolones; Antiviral, inhibit helicase activity of large T antigen	PO: 500 mg qD (renally adjusted)	Levofloxacin failed to show benefit in randomized controlled trials.
Everolimus[47,48]	Inhibits mammalian target of rapamycin (mTOR) kinase activity, inhibiting T and B lymphocyte activation and proliferation.	PO 0.75 mg twice daily adjusted to trough levels of 3–8 ng/mL.	Can be used following discontinuation of MMF. Limited literature supporting its use.

International Journal of Nephrology and Renovascular Disease 2020:13 187–192

Pnumonia in SOT

Pneumonia in SOT recipients is a complex clinical syndrome with multiple potential etiologies. In patients the most common causes are potentially life-threatening opportunistic infections that are potentially treatable and preventable.

Pneumonia in SOT patients predominantly shows alveolar or interstitial infiltrates of variable extent in the chest X-rays. However, nodular lesions are not uncommon. Differentiating pneumonia from other etiologies of pulmonary infiltrates can be extremely difficult.

Rapid and reliable diagnostic procedures that guide antimicrobial treatment are necessary.

Pneumonia is an infection with the highest related mortality rate in SOT recipients so prompt empirical therapy is highly recommended for patients in critical conditions after obtaining adequate samples .

Respiratory viruses

TABLE 1 Common respiratory virus infections in solid organ transplant recipients

Virus	Isolation recommendations	Prophylactic interventions	Therapeutic alternatives
Influenza	Contact & Droplet	Annual inactivated injectable vaccine Neuraminidase Inhibitor[a]	Neuraminidase inhibitor[a]
RSV	Contact	Palivizumab	Aerosolized or oral ribavirin[b] ± Antibody-based treatment[c] ± Corticosteroids
PIV	Contact	None	Aerosolized or oral ribavirin[b] ± IVIG
hMPV	Contact	None	Aerosolized or oral ribavirin[b] ± IVIG
Rhinovirus	Droplet Contact added if copious secretions or close contact	None	None
Coronavirus	Standard precautions except for MERS-CoV which requires Contact, Droplet, and Airborne precautions	None	None

RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Table 16.2 Diagnostic strategies

Diagnostic procedure	Test types	Clinical examples
Sputum (a) Spontaneous (b) Induced (NaCl 3%)	Gram stain and culture Direct fluorescent antibody PCR	Bacterial pneumonia, Gram-positive or Gram-negative *Legionella* *Nocardia* *Mycobacterium tuberculosis*
Nasopharyngeal swab	PCR (single or multiplex)	Community-acquired respiratory virus
Bronchoscopy: bronchial aspirates	Ziehl-Neelsen stain PCR	*Mycobacterium tuberculosis* Community-acquired respiratory virus
Bronchoscopy: bronchoalveolar lavage	Gram/specific stains and culture Direct fluorescent antibody PCR	*Pneumocystis jirovecii*, bacterial pneumonia, *Aspergillus,* cytomegalovirus, community-acquired respiratory virus
Bronchoscopy: transbronchial biopsy	Culture PCR	Miliary tuberculosis
Blood sample	Culture	*Streptococcus pneumoniae*
Urine	Soluble antigen testing	*Streptococcus pneumoniae* *Legionella pneumophila* serogroup 1
Fungal serum markers	(1-3)-β-D-glucan, galactomannan, cryptococcal antigen	*Aspergillus*, *Cryptococcus*

Yield of (1-3)-β-D-glucan and galactomannan is reduced in SOT recipients compared to other populations, particularly if mold-active antifungal therapy or prophylaxis is being used for the patient

https://doi.org/10.1007/978-3-030-15394-6

Pneumonia- etiology

Viral	Respiratory viruses: Influenza, Parainfluenza, Respiratory Syncytial virus, Human metapneumovirus, Adenovirus, Rhinovirus, Coronavirus,
	Herpesviruses: Herpes simplex virus, Varicella zoster virus, Cytomegalovirus
Bacterial	Community-acquired: *Streptoccocus pneumonia*, *Haemphilus influenzae*, *Moraxella cattarhalis*, *Staphylococcus aureus*
	Healthcare-associated: *Klebsiella* spp, *Enterobacter* spp, *Escherichia coli*, and other Enterobacteriaceae; *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Acinetobacter* spp, others
	Atypical: *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Legionella* spp
	Mycobacterial: *Mycobcaterium. tuberculosis* and Nontuberculous Mycobacteria
	Zoonoses: *Chlamydia psittaci*, *Francisella tularensis*, *Coxiella burnetti*, *Rhodococcus equi*, *Pasteurella multocida*
	Other: *Nocardia* spp and *Actinomyces* spp
Fungal	Endemic/Dimorphic Fungi: *Histoplasma capsulatum* (*var capsulatum* and *var duboisii*); *Blastomyces dermatiditis*; *Coccidioides immitis*; *Penicillium. marneffei*
	Yeasts and Yeast-like Fungi: *Cryptococcus* spp; *Pneumocystis jirovecii*
	Molds: *Aspergillus* spp; Mucormysosis; Fusariosis; *Scedopsporium* spp
Parasitic	Protozoan: *Toxoplasma gondii*
	Helminth: *Strongyloides stercoralis*
	Flatworm: *Echinococcus* spp
Non-infectious	mTORi-induced pneumonitis; Pulmonary embolism; Pulmonary hemorrhage; Lung tumor (primary or metastasis); PTLD; Pulmonary edema; Hepatopulmonary syndrome

Received: 26 February 2019 | Accepted: 18 March 2019
DOI: 10.1111/ctr.13545

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
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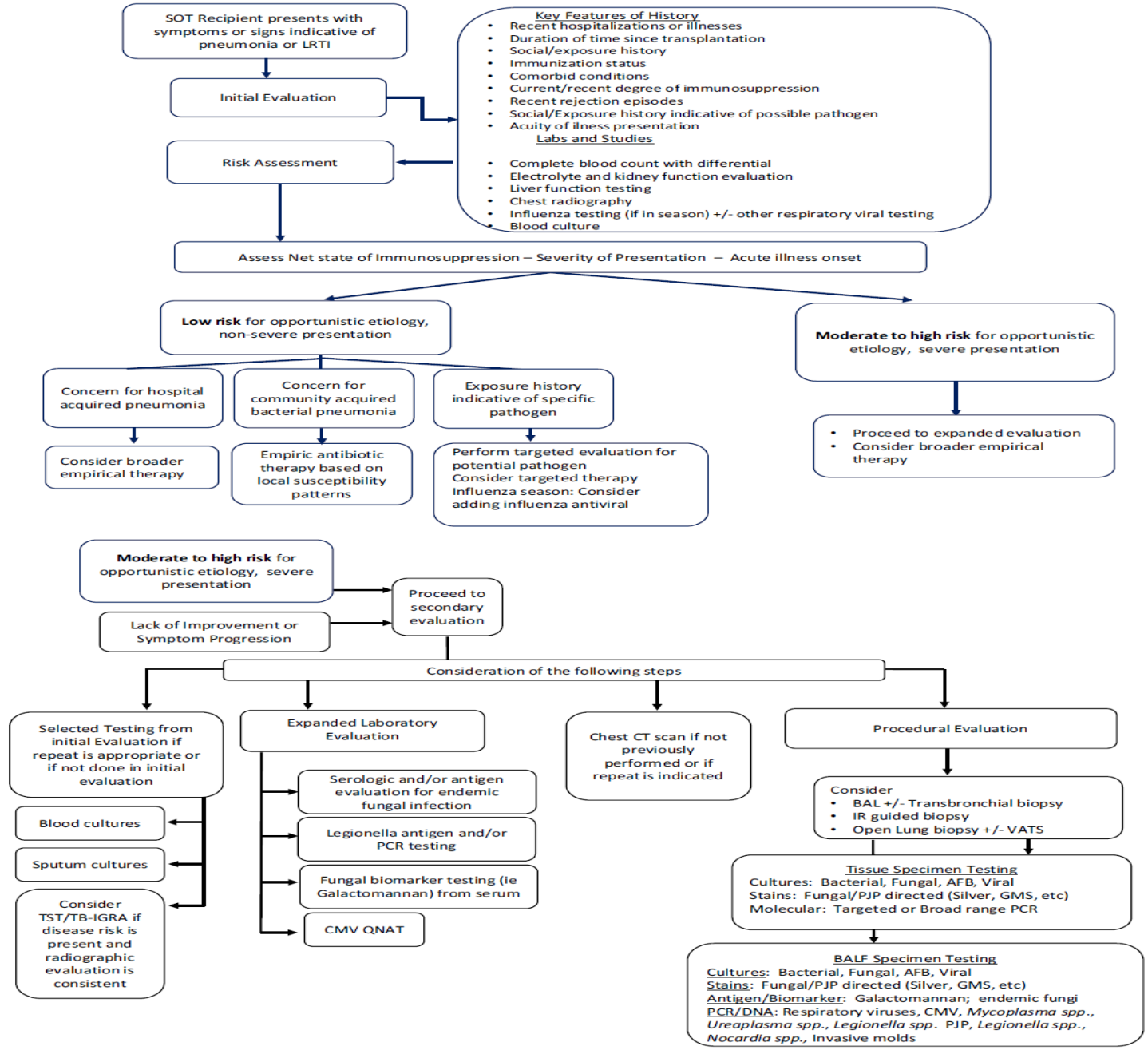


FIGURE 1 Evaluation of the SOT recipient with suspected pneumonia

Fungal infections

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

Fungal infections

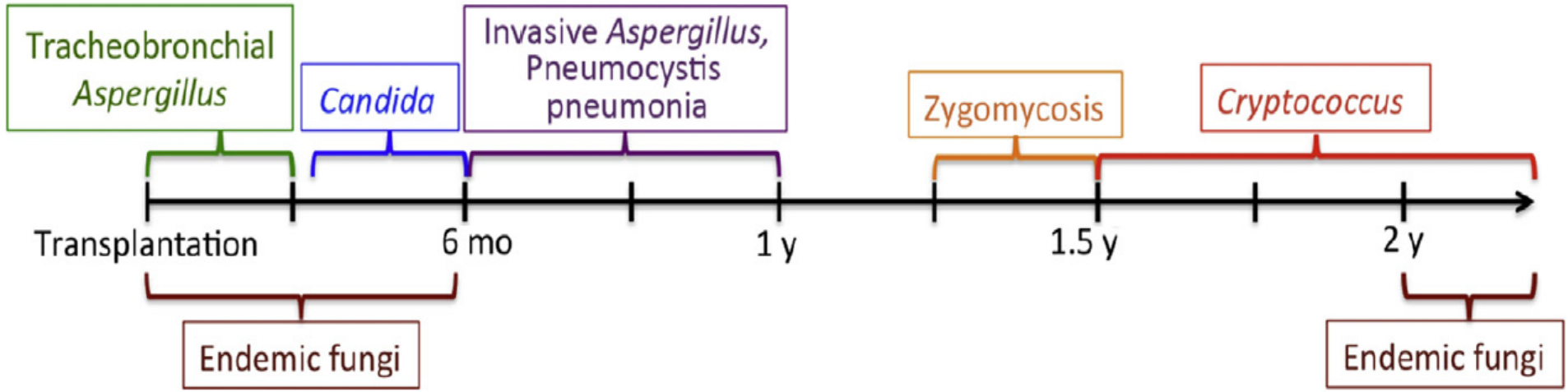
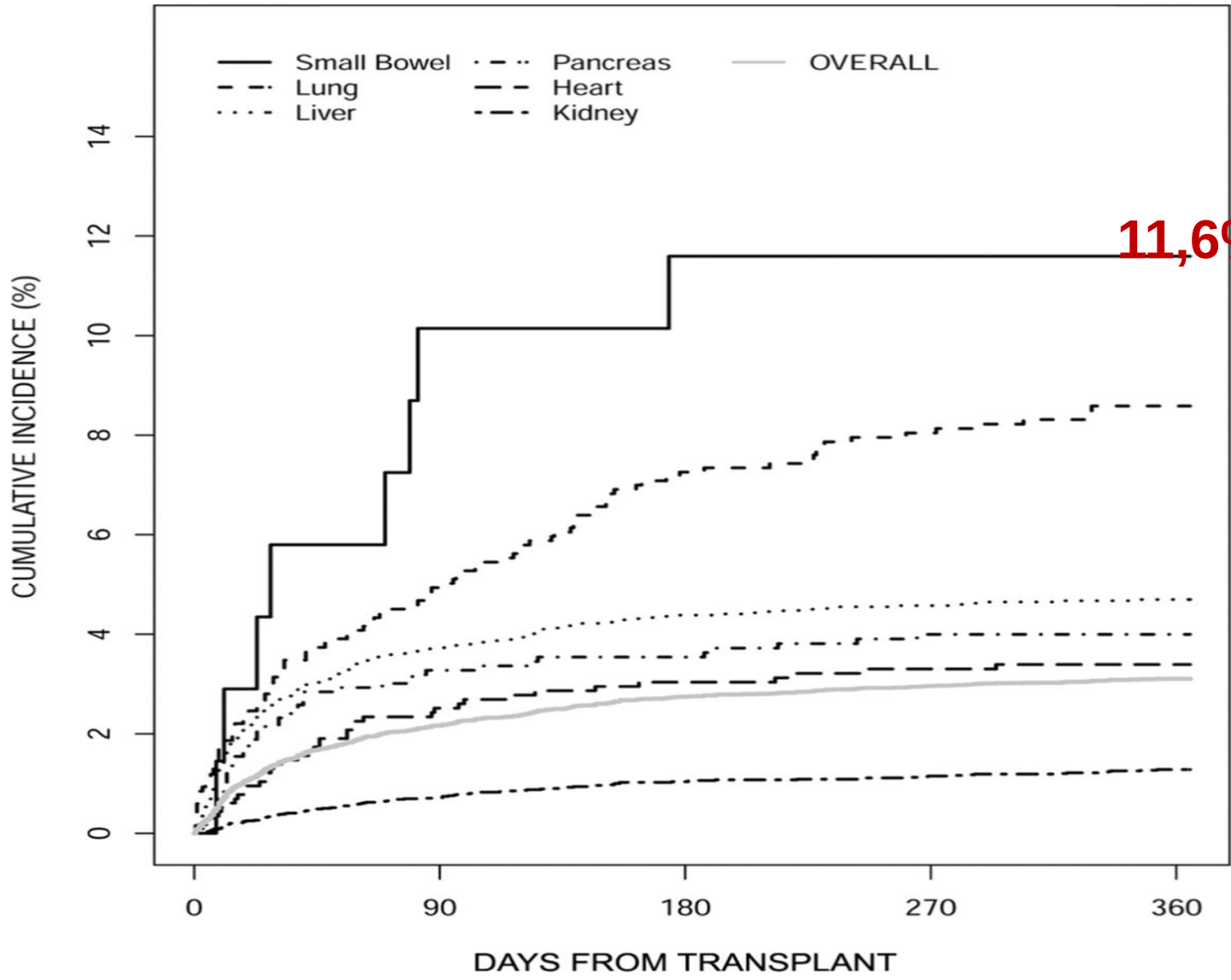


Fig. 1. Timing of IFIs following SOT.

Invasive fungal infections

Transplanted organ	(%)	Pathogen
Heart	3-21	Aspergillus 70-90%
Liver	4-42	Candida 35-91% Aspergillus 9-34%
Lung	10-44	Candida 43-72% Aspergillus 20-50%
Pancreas	6-38	Candida 97-100%
Kidney	1-14	Candida 50-80% Aspergillus 7-19%
Small bowel	40-59	Candida 90%

Cumulative incidence curve of first invasive fungal infection (IFI) according to transplant type.



11,6%

8,6%

4,7% LTx

4,0% HTx

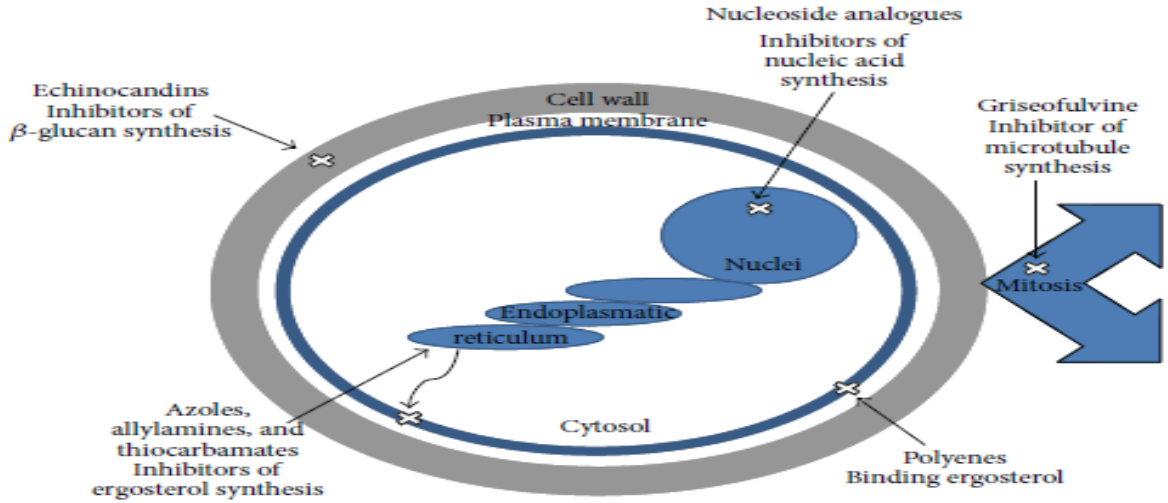
3,4% PTx

1,3% KTx

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.**

Neofytos et al. BMC Infectious Diseases (2021) 21:296
https://doi.org/10.1186/s12879-021-05958-3

BMC Infectious Diseases

GUIDELINES Open Access

Invasive aspergillosis in solid organ transplant patients: diagnosis, prophylaxis, treatment, and assessment of response

Dionysios Neofytos[1*], Carolina Garcia-Vidal[2], Frédéric Lamoth[3,4], Christoph Lichtenstern[5], Alessandro Perrella[6,7] and Jörg Janne Vehreschild[8,9,10]

Population	Incidence (%)	Overall mortality (%)
Heart	3.5–26.7	36–66.7
Kidney	1.2–4	4–25
Liver	1–4.7	83–88
Lung	8.3–23.3	4.2

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*

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

Accepted: 12 February 2019

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

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.

Pnumonia

Viral	Respiratory viruses: Influenza, Parainfluenza, Respiratory Syncytial virus, Human metapneumovirus, Adenovirus, Rhinovirus, Coronavirus,
	Herpesviruses: Herpes simplex virus, Varicella zoster virus, Cytomegalovirus
Bacterial	Community-acquired: *Streptoccocus pneumonia*, *Haemphilus influenzae*, *Moraxella cattarhalis*, *Staphylococcus aureus*
	Healthcare-associated: *Klebsiella* spp, *Enterobacter* spp, *Escherichia coli*, and other Enterobacteriaceae; *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila*, *Acinetobacter* spp, others
	Atypical: *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Legionella* spp
	Mycobacterial: *Mycobcaterium. tuberculosis* and Nontuberculous Mycobacteria
	Zoonoses: *Chlamydia psittaci*, *Francisella tularensis*, *Coxiella burnetti*, *Rhodococcus equi*, *Pasteurella multocida*
	Other: *Nocardia* spp and *Actinomyces* spp
Fungal	Endemic/Dimorphic Fungi: *Histoplasma capsulatum* (*var capsulatum* and *var duboisii*); *Blastomyces dermatiditis*; *Coccidioides immitis*; *Penicillium. marneffei*
	Yeasts and Yeast-like Fungi: *Cryptococcus* spp; *Pneumocystis jirovecii*
	Molds: *Aspergillus* spp; Mucormysosis; Fusariosis; *Scedopsporium* spp
Parasitic	Protozoan: *Toxoplasma gondii*
	Helminth: *Strongyloides stercoralis*
	Flatworm: *Echinococcus* spp
Non-infectious	mTORi-induced pneumonitis; Pulmonary embolism; Pulmonary hemorrhage; Lung tumor (primary or metastasis); PTLD; Pulmonary edema; Hepatopulmonary syndrome

Received: 26 February 2019 | Accepted: 18 March 2019
DOI: 10.1111/ctr.13545

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY

Received: 6 May 2019 | Accepted: 11 May 2019

DOI: 10.1111/ctr.13594

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

WILEY

Multidrug-resistant Gram-negative bacterial infections in solid organ transplant recipients—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Treatment recommendations MDR bacteria

TABLE 2 Treatment recommendations

Organism	Recommendation	Grade
All	Source control should be aggressively pursued	Strong, moderate
	Early Transplant Infectious Disease consultation	Strong, moderate
ESBL-producing Enterobacteriaceae	Carbapenems	Strong, high
Carbapenem-resistant Enterobacteriaceae	Systemic infections:	
	Preferred regimens:	Strong, moderate
	• Ceftazidime/avibactam	Strong, low
	• Meropenem/vaborbactam	Strong, low
	• Ceftazidime/avibactam plus aztreonam for metallo-β-lactamase-producing CRE	
	Alternative regimens:	Strong, moderate
	• Individualized combination regimen with two or more of the following:	Strong, low
	o High-dose, continuous, or extended-infusion carbapenem	
	o Colistin or polymyxin B	
	o Tigecycline	
	• Dual-carbapenem therapy (ertapenem plus doripenem or meropenem)	
	Uncomplicated UTI:	
	• Oral fosfomycin (if susceptible and with follow-up)	Strong, moderate
	• Intravenous aminoglycosides including plazomicin (if susceptible)	Strong, low

MDR and XDR *Pseudomonas aeruginosa*	Preferred regimens:	
	• High-dose continuous or extended-infusion antipseudomonal β-lactam	Strong, moderate
	• Ceftolozane/tazobactam	Strong, moderate
	• Ceftazidime/avibactam	Strong, moderate
	Alternative regimens:	Strong, moderate
	• Individualized combination regimen with two of the following: o High-dose continuous or extended-infusion antipseudomonal β-lactam o Aminoglycoside o Colistin or polymyxin B o Ciprofloxacin or levofloxacin	
	• Adjunctive aerosolized colistin or tobramycin for pneumonia	Weak, low
PDR *Pseudomonas aeruginosa*	Individualized combination regimen with three of the following:	
	• High-dose continuous or extended-infusion antipseudomonal β-lactam	Strong, moderate
	• Colistin or polymyxin B	
	• Aminoglycosides	
	• Adjunctive aerosolized colistin or tobramycin for pneumonia	Weak, low

Carbapenem-resistant *Acinetobacter baumannii*	Preferred regimen:	
	• Combination therapy with a carbapenem plus colistin or polymyxin B	Strong, moderate
	Alternate regimens:	
	Monotherapy with:	Strong, moderate
	• Ampicillin/sulbactam if susceptible[a] (sulbactam dose ≥9 g daily, dose adjusted for creatinine clearance)	Weak, low
	• Minocycline	
MDR *Stenotrophomonas maltophilia*	Preferred regimen:	
	• High-dose SXT (15 mg/kg/d trimethoprim, dose adjusted for creatinine clearance)	Strong, moderate
	Alternatives (combination therapy if SXT-resistant recommended):	
	• Ceftazidime	Strong, low
	• Minocycline	Strong, low
	• Levofloxacin	Strong, low
	• Ceftazidime/avibactam plus aztreonam	Weak, low

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.**

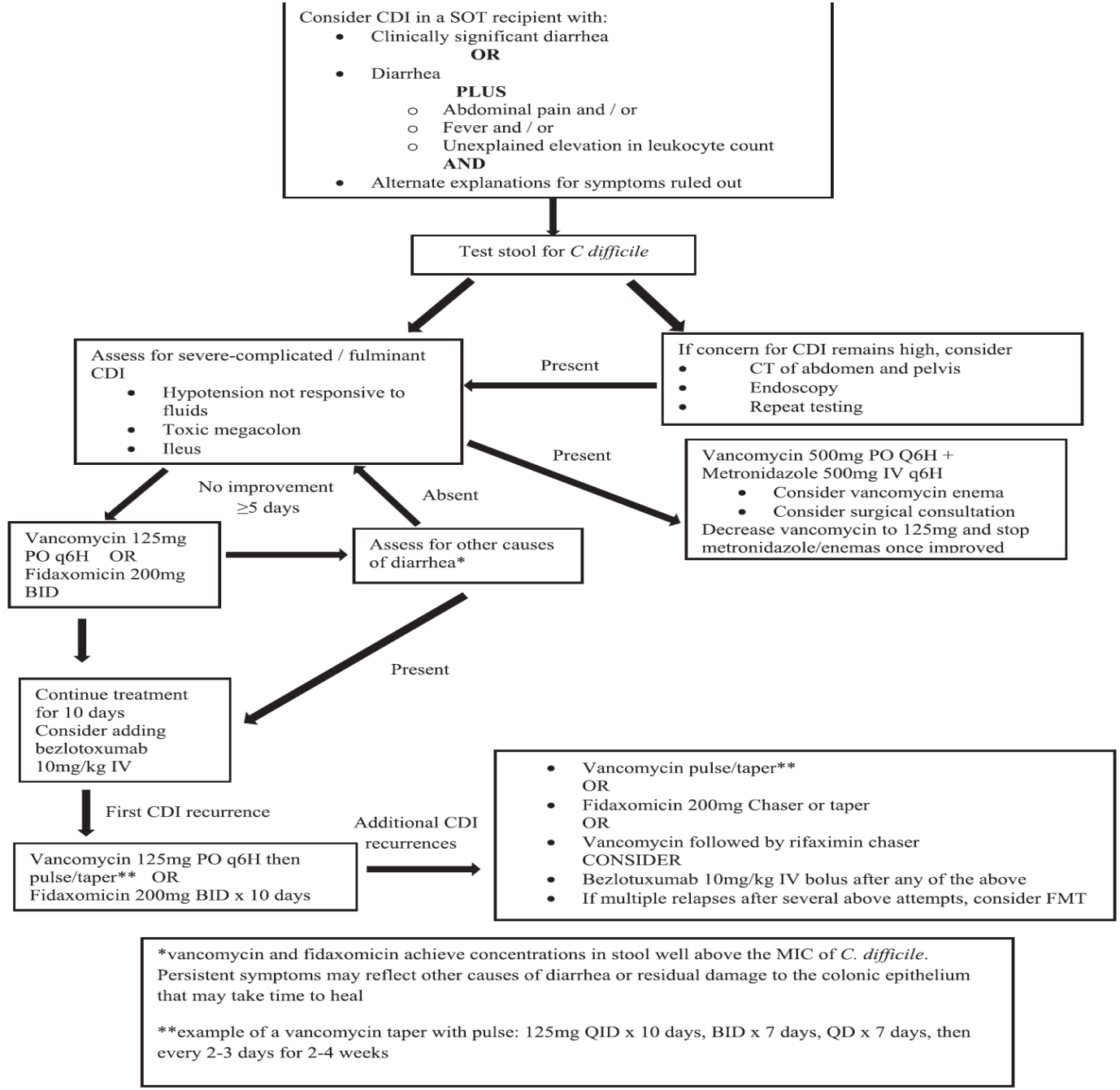

FIGURE 1 Recommended approach to the diagnosis and treatment of *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) presenting with diarrhea in adult solid organ transplant (SOT) recipients

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.

Received: 6 June 2019 | Accepted: 10 June 2019

DOI: 10.1111/ctr.13642

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

WILEY

Foreword: 4th edition of the American Society of Transplantation Infectious Diseases Guidelines

Clinical Transplantation. 2019;00:e13642.
https://doi.org/10.1111/ctr.13642