Clinica delle Malattie Infettive e Tropicali
Università degli Studi dell'Insubria – ASST-Sette Laghi, Varese
"Second Opinion" Infettivologica Centro Nazionale Trapianti, ISS, Roma

Rete Nazionale Trapianti

Il rischio infettivo e la profilassi delle infezioni opportunistiche nel pre e post-trapianto di organo solido

Paolo Antonio Grossi

SITA Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina
13° CONGRESSO NAZIONALE
PADOVA | 23-24 novembre 2023

Conflict of interest

I have the following conflict(s) of interest to declare:

Consultant for: MSD, BIOTEST, GILEAD, ALLOVIR, TAKEDA, ASTRA-ZENECA

Speaker’s bureau for: MSD, GILEAD, BIOTEST, TAKEDA, ASTRA-ZENECA

GODT
Global Observatory on Donation and Transplantation

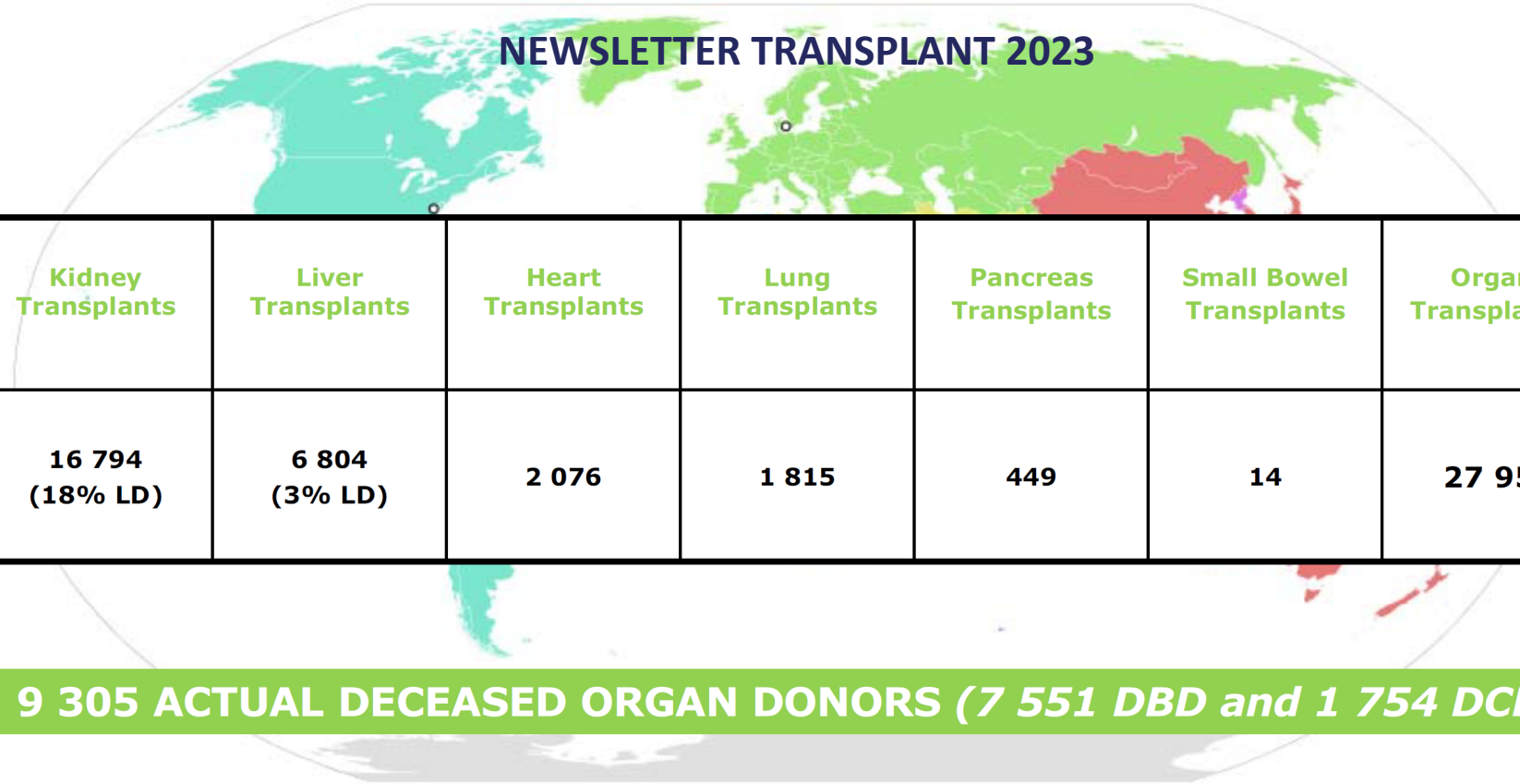
WHO Collaborating Centre on Donation and Transplantation

GOBIERNO DE ESPAÑA MINISTERIO DE SANIDAD

ONT ORGANIZACIÓN NACIONAL DE TRASPLANTES

EUROPEAN UNION DATA

NEWSLETTER TRANSPLANT 2023



Kidney Transplants	Liver Transplants	Heart Transplants	Lung Transplants	Pancreas Transplants	Small Bowel Transplants	Organs Transplanted
16 794 (18% LD)	6 804 (3% LD)	2 076	1 815	449	14	27 952

9 305 ACTUAL DECEASED ORGAN DONORS *(7 551 DBD and 1 754 DCD)*

2022 data

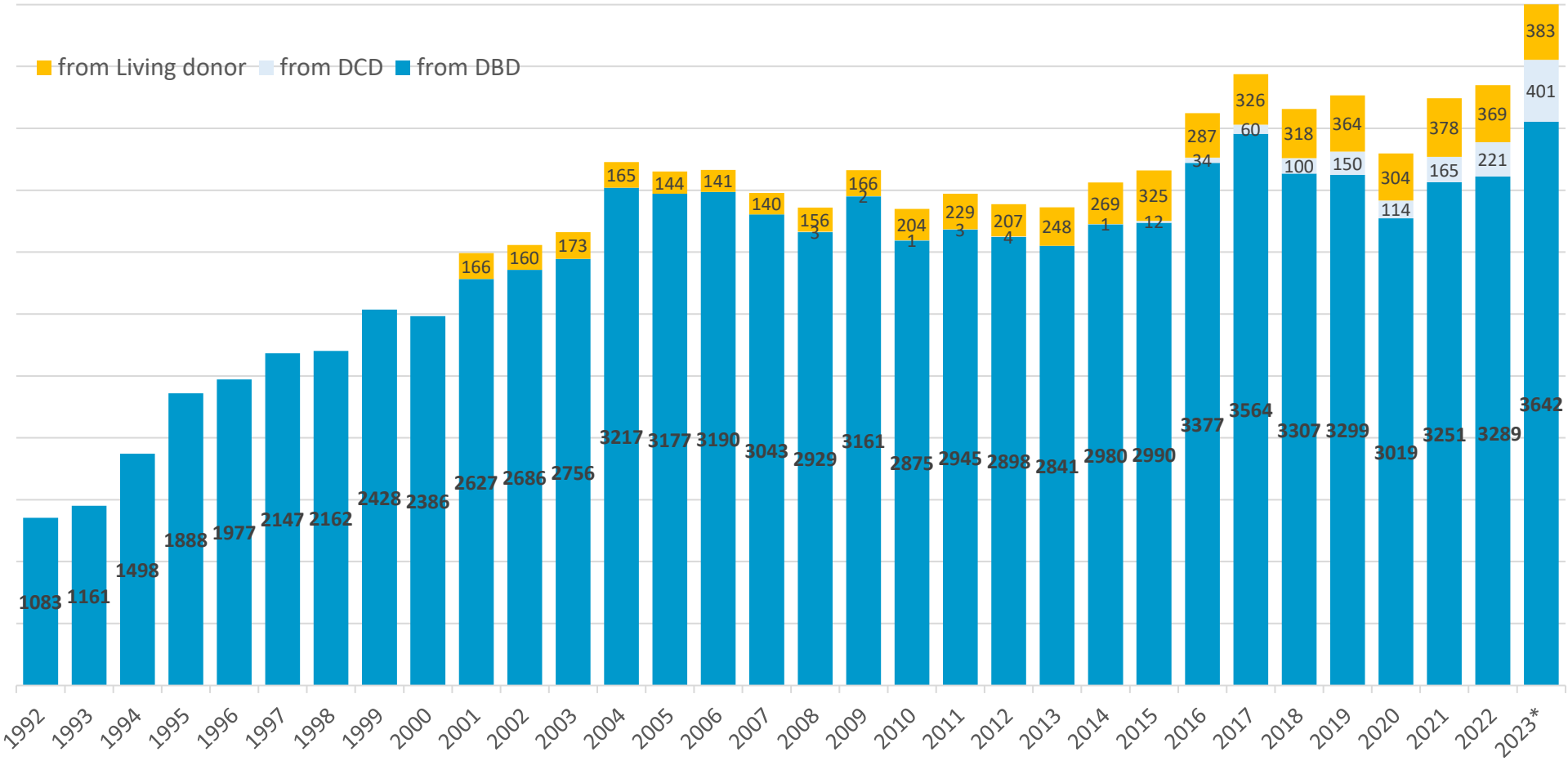
N= 27 COUNTRIES (445.0 million inhabitants)

EUROPE

L'EUROPE

National Transplantation activity 1992– 2023

Centro Nazionale Trapianti
ISTITUTO SUPERIORE DI SANITÀ



Tx from Deceased (DBD & DCD) + Living donor

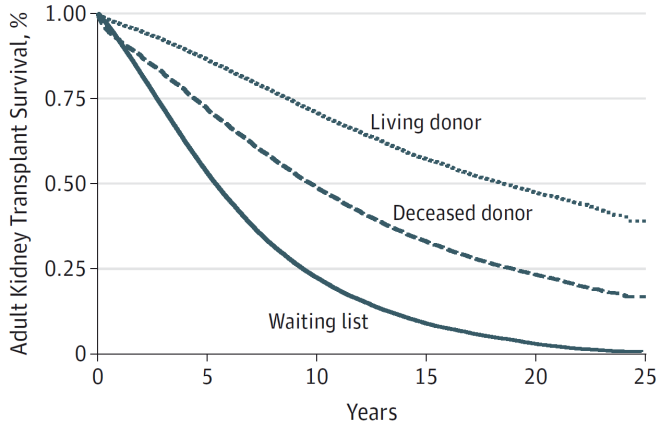
numbers

*Data projections for the year (*updated 30/06/2023*)

Data source: SIT and TCs

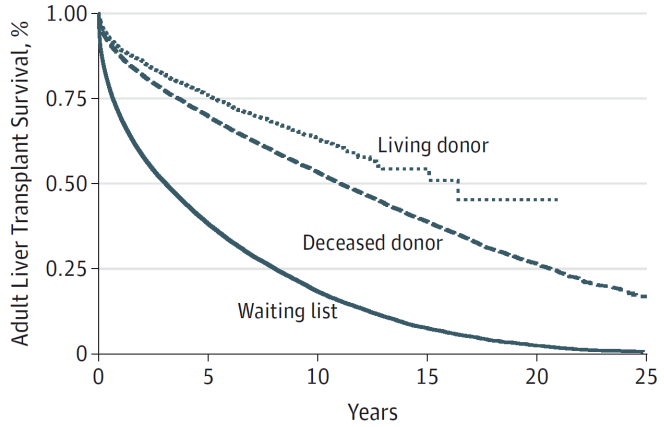
Survival Benefit of Solid-Organ Transplant in the United States

A Adult kidney transplantation



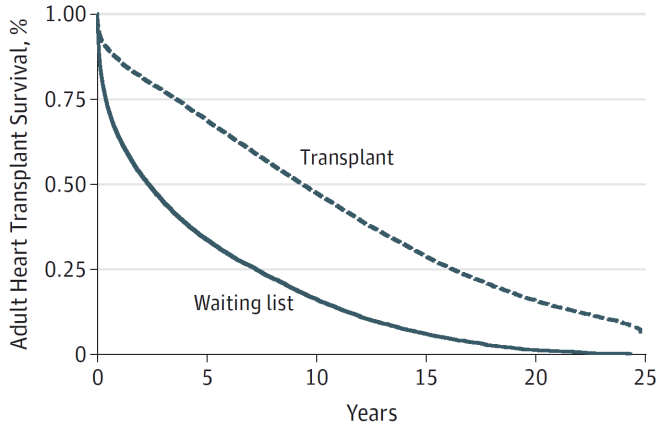
No. at risk						
Waiting list	239 162	43 202	7083	1472	275	32
Deceased donor	148 292	74 561	27 850	8576	1859	16
Living donor	87 387	50 125	19 255	5275	1115	8

B Adult liver transplantation



No. at risk						
Waiting list	69 193	11 764	2705	473	76	16
Deceased donor	72 817	35 986	15 434	5339	1096	13
Living donor	2616	1426	446	16	3	0

C Adult heart transplantation

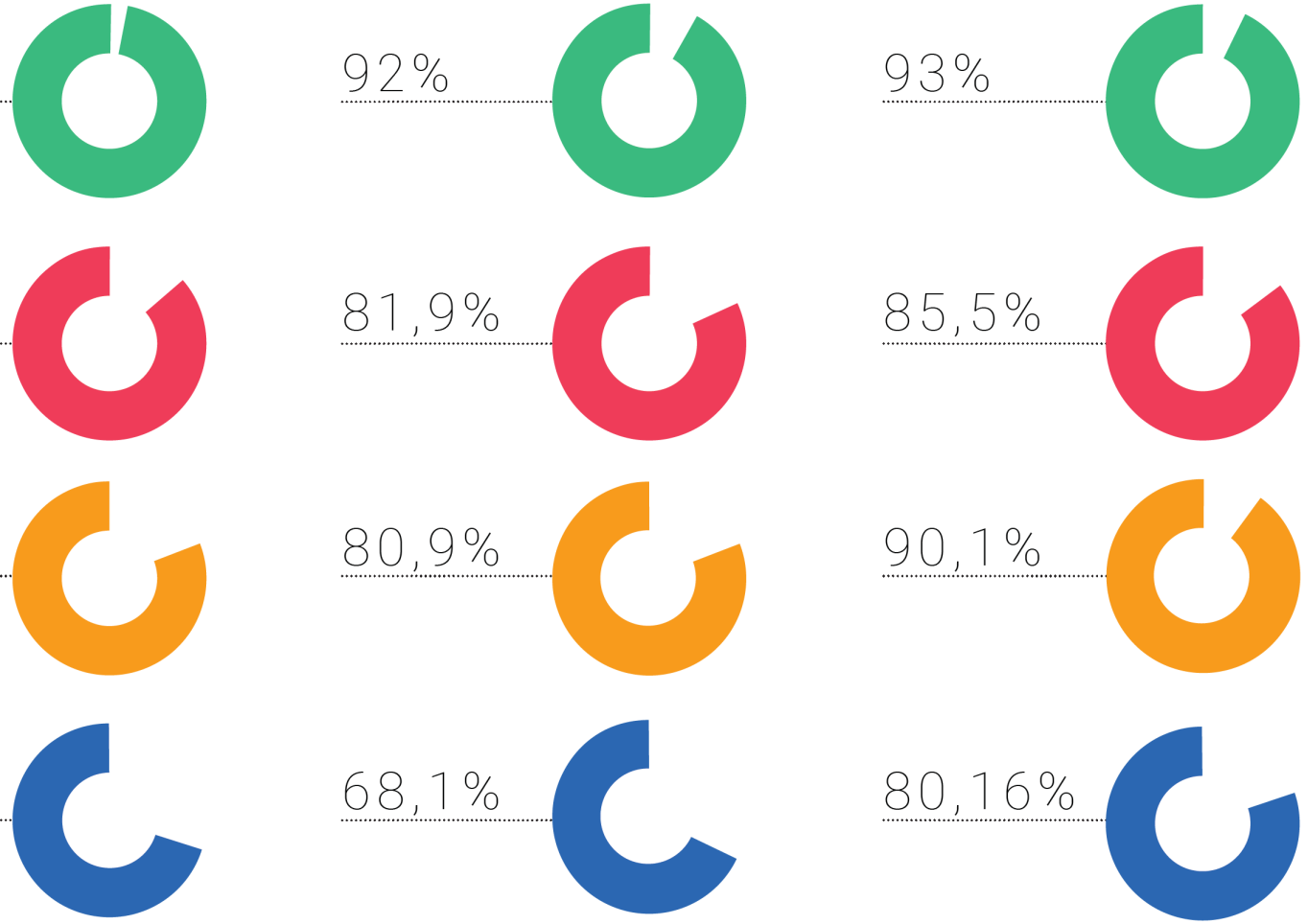


No. at risk						
Waiting list	23 945	3332	1070	265	39	1
Transplant	41 763	23 272	11 378	4080	902	12

Rana A, et al. JAMA Surg. 2015;150(3):252-259.

QUALITÀ DEI **TRAPIANTI**

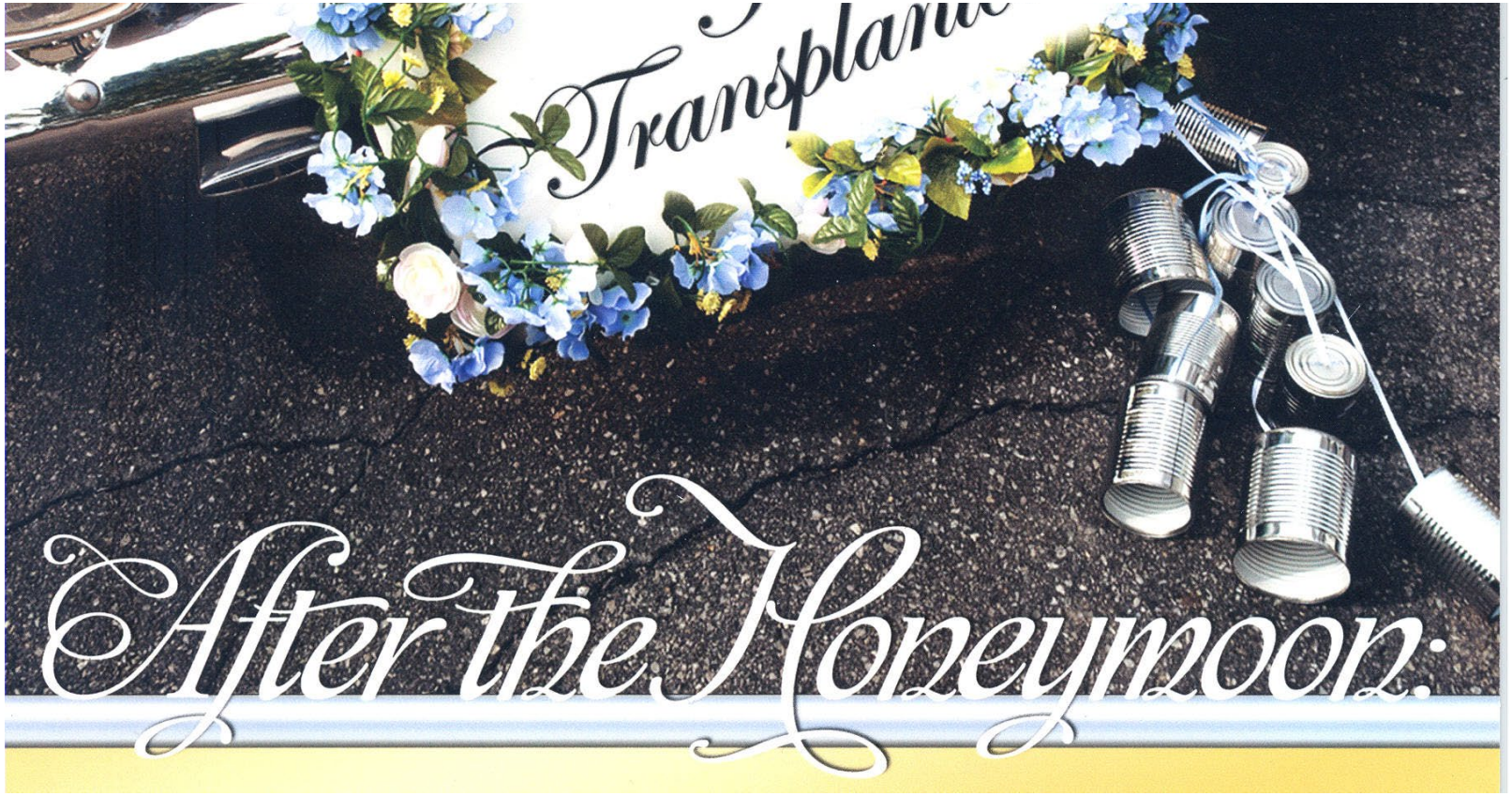
	SOPRAVVIVENZA* del **PAZIENTE** ad un anno dal trapianto	SOPRAVVIVENZA* dell'**ORGANO** ad un anno dal trapianto	**PAZIENTI** CHE LAVORANO** o sono in condizioni di farlo
TRAPIANTI DI RENE Periodo di riferimento 2000-2015	97,3%	92%	93%
TRAPIANTI DI FEGATO Periodo di riferimento 2000-2014	86,5%	81,9%	85,5%
TRAPIANTI DI CUORE Periodo di riferimento 2000-2015	80,9%	80,9%	90,1%
TRAPIANTI DI POLMONE Periodo di riferimento 2002-2015	69,6%	68,1%	80,16%



*** I dati si riferiscono ai trapianti da donatore deceduto su pazienti adulti e pediatrici - ** i dati si riferiscono al 70% circa dei trapianti analizzati**

FONTE: REPORT CRT

Organ transplantation has many potential post-transplant complications with infection being a major contributor



Risks of transplantation

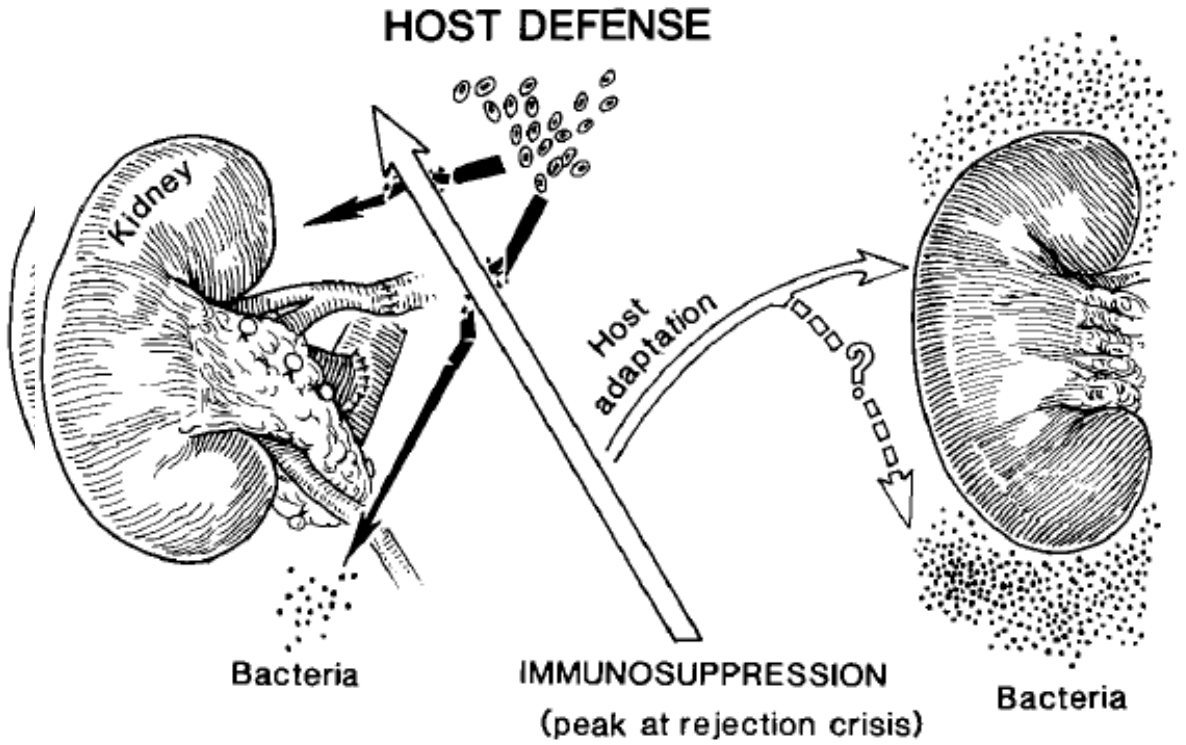
- Transplantation, whether of organs, tissues or cells, **is not without risk**.
- Transplantation carries the risk of the operative procedure itself, the risk of donor-derived disease transmission and the risk of the lifelong immunosuppressive therapy necessary in organ transplantation.
- **However, the most important risk factor in transplantation is not to get an organ in time.**

RISK FOR INFECTION IN SOT RECIPIENTS

The risk of infection for the recipient at any point in time after transplantation is a function of two factors:

1. The **epidemiologic exposures** of the patient and the organ donor including recent, nosocomial and remote exposures.
2. The patient's **“net state of immunosuppression”** including all factors contributing to the risk for infection.

Possible mechanisms of simultaneous loss of host reactivity to specific strains of endogenous bacteria and to the alien renal tissue



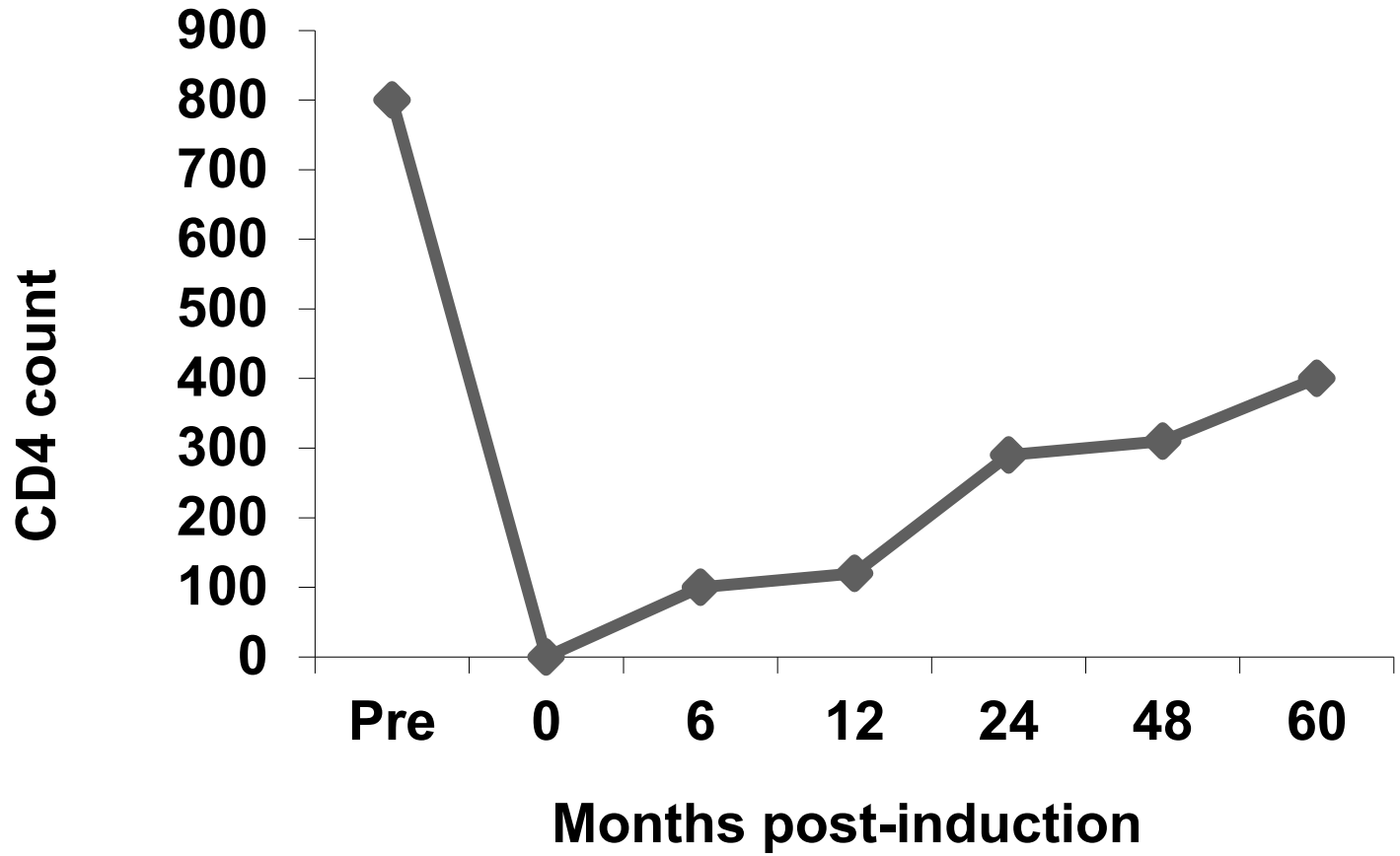
It was feared that chronic drug immunosuppression powerful enough to prevent organ allograft rejection would render the recipient hopelessly vulnerable to indigenous and environmental pathogens.

Starzl, T.E., et al. Surgery 1964;*56:296*

Immunosuppressive agents and their effect on the immune system

Farmaco	Neutrofili	Monociti circolanti	Macrofagi	Linfociti T	Linfociti B	Cellule NK	Risposta infiammatoria
Ciclosporina A				+			
Tacrolimus				+			
Steroidi	+	+	+	+	+	+	+
Acido micofenolico	+			+	+		
Azatioprina	+				+	+	
Sirolimus				+	+	+	
Everolimus				+	+		
ATG/OKT3				+	+		
Basiliximab				+			
Daclizumab				+			
Alemtuzumab		+		+	+	+	

Anti-Thymocyte Globulins and CD4+ T-cell Depletion



- *CD4/CD8 ratio remains persistently inverted*

Muller T, et al. Transplantation 1997;64 - Issue 10 - p 1432-1437

New immunosuppressive strategies and the risk of infection

- New immunosuppressive agents have resulted in a **marked reduction of rejection**
- The improvement gained is jeopardized by a potential **increase in infectious complications**.
- The paradigm example is the recent emergence of BK-virus nephropathy, which has been strongly linked to enhanced immunosuppression.
- While BK-virus nephropathy has been studied very intensely, less is known about the role of newer agents and the risk of infections.

Factors determining the risk of infection in solid organ transplant recipients

- **Epidemiological exposure**
  - Donor-derived infections
  - Recipient-derived infections
    - Chronic infections (HIV, HBV, HCV,..)
    - Latent infections
    - Pre-transplant colonization
    - Nosocomial infections
    - Community acquired infections

Received: 5 March 2019 | Accepted: 15 March 2019
DOI: 10.1111/ctr.13548

SPECIAL ISSUE: TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY

Screening of donor and candidate prior to solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Maricar Malinis[1] | Helen W. Boucher[2] | on behalf of the AST Infectious Diseases Community of Practice

REVIEW 10.1111/1469-0691.12557

Recommendations for screening of donor and recipient prior to solid organ transplantation and to minimize transmission of donor–derived infections

O. Len[1,*], C. Garzoni[2,3,*], C. Lumbreras[4], I. Molina[1], Y. Meije[1], A. Pahissa[1], P. Grossi[5] on behalf of the ESCMID Study Group of Infection in Compromised Hosts (ESGICH)

- Pretransplant screening of potential organ donors and recipients is **ESSENTIAL to the success** of SOT
- The goals of pre-Tx infectious disease screening are:
  - to identify conditions which may disqualify either donor or recipient;
  - identify and treat active infection pre-Tx;
  - recognize and (if possible) define the risk of infection and develop strategies for preventing and mitigating post-tx infection;
  - **and implement preventative measures, including immunizations**.

Infectious disease screening for candidates and donors prior to transplantation

Test	Candidate	Deceased donor	Living donor
Viral			
HIV			
Human immunodeficiency virus (HIV) antibody/antigen (fourth Generation HIV screening test)	x	x	x
HIV nucleic acid amplification testing (NAT)		x[b]	x[b]
Cytomegalovirus (CMV) IgG antibody	x	x	x
Hepatitis B virus (HBV)			
HBV surface antigen (HBsAg)	x	x	x
HBV core antibody (HBcAb-IgM and IgG, or total core antibody)	x	x	x
HBV surface antibody (HBsAb)	x		
HBV NAT		x[b]	x[b]
Hepatitis C virus (HCV)			
HCV antibody	x	x	x
HCV NAT	x[c]	x	x
Epstein-Barr virus (EBV) antibody (EBV VCA IgG, IgM)	x	x	x
West Nile virus serology or NAT (seasonal)			x
Parasitic			
Toxoplasma IgG antibody	x	x	x
Strongyloides IgG (if from endemic areas)	x	x	x
Trypanosma cruzi serology (if from endemic areas)	x	x	x
Fungal			
Coccidiodes serology (if from endemic areas)	x	x	x
Bacterial			
Syphilis (any of the following)	x	x	x
Fluorescent treponema antibody absorption (FTA-ABS)			
T. pallidum particle agglutination (TPPA)			
T. pallidum enzyme immunoassay (TP-EIA)			
Rapid plasma reagin (RPR)			
Venereal Disease Research Laboratory (VDRL)			
Tuberculosis (any of the following)	x		x
Purified protein derivative (PPD)			
Interferon gamma release assay (IGRA)			
Urine culture		x	
Blood culture		x	

[a]Donor required screening per the UNOS/OPTN policies.[35]
[b]PHS increased risk donors.
[c]Renal candidates on dialysis.

Malinis M, Boucher HW; Clin Transplant. 2019 Sep;33(9):e13548.

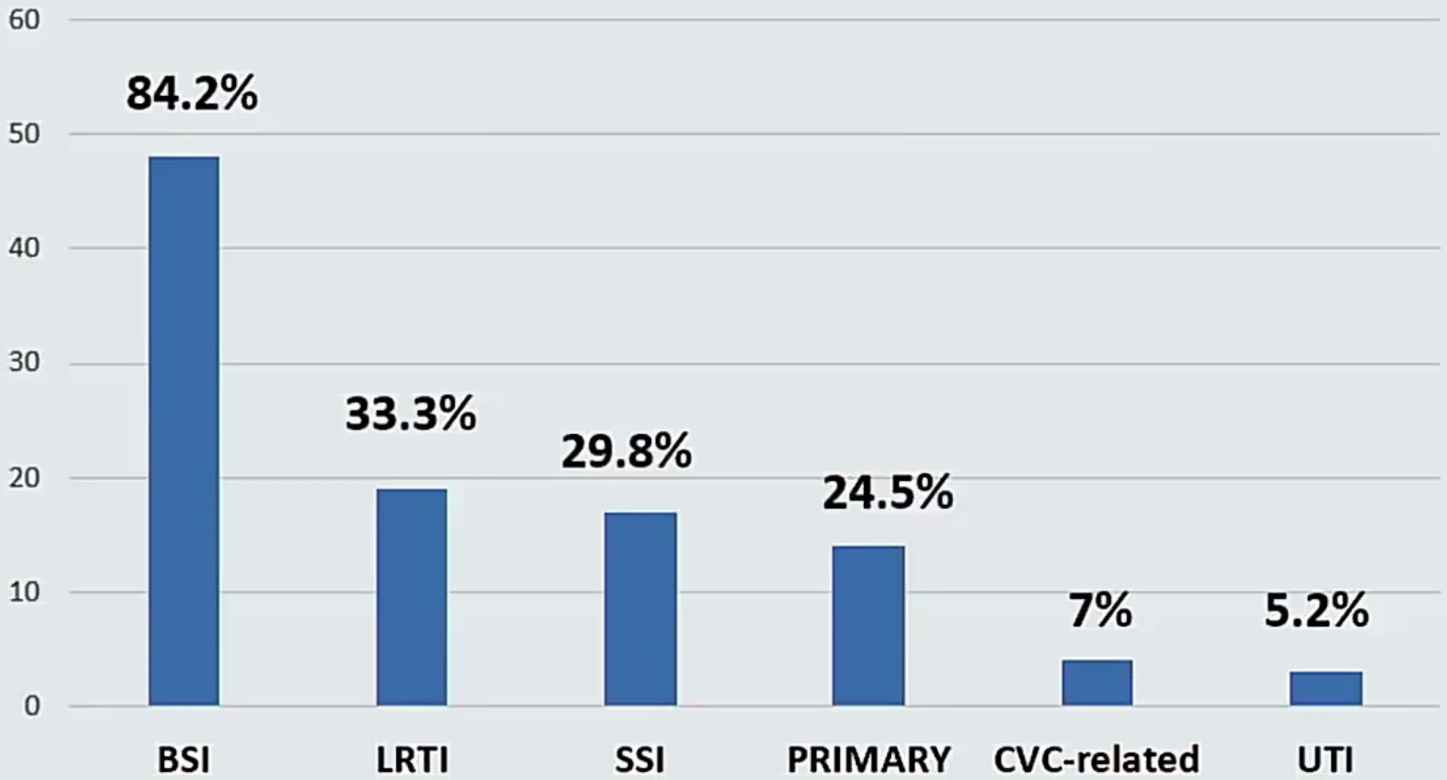
Transplant candidacy

- Given the complexities and complications of infection by MDR Gram-negative pathogens, should patients with evidence of carriage of carbapenem-resistant Gram-negative bacilli be offered transplantation?
- Institutions with active surveillance programs report high attack rates in patients discovered to have rectal carriage of carbapenem-resistant K. pneumoniae, and preliminary data suggest that posttransplant infection with KPC-Kp is associated with poor outcomes after liver transplantation
- Is decolonization feasible?

The impact of carbapenemase-producing Enterobacteriaceae colonization on infection risk after liver transplantation: a prospective observational cohort

CRE infections

Giannella M et al. Clin Microbiol Infect 2019;25:1525-1531



- Severe sepsis and septic shock were present at infection onset in 33.3% and 24.6% of cases, respectively

Oral decontamination with colistin plus neomycin in solid organ transplant recipients colonized by multidrug-resistant Enterobacterales: a multicentre, randomized, controlled, open-label, parallel-group clinical trial

Farinas MC et al. Clin Microbiol Infect 2021;x:1

- Multicenter, open label RCT 1:1
  - ✓ SOT were screened for MDR-E before tx and +7 and +14 days after tx

- 768 tx recipients, 105 colonized pts (ESBL 65, KPC 23)
  - ✓ 53 DT group: colistin sulfate + neomycin sulfate 14 days
  - ✓ 52 NDT group: no treatment

- MDR-E infection 30 days after treatment: 9.4% vs. 13.5%, p=0.52
- Colonization rate 30 days after treatment: 54.7% vs. 73.1%, p=0.05
- Colistin resistance: 6.1% vs. 2%, p=0.62
- Adverse events: 26.4% vs. 3.8%

Table 2
Main recommendation statements for management of gram-negative colonization in solid organ transplant recipients

	GESITRA (2018)[21]	AST (2019)[22]	ESCMID (2022)[23]
ESBL-E/ESCR-E			
Screening	Yes	Controversial outside outbreaks	Yes in LT (conditional, low) GCP in all SOT[a] (expert opinion)
Targeted antibiotic prophylaxis	Yes, but avoid carbapenems	Undefined	Yes in LT (conditional, very low) GCP in all SOT[a] (expert opinion)
Decolonization	No	No	NA[b]
CRE/CPE			
Screening	Yes	Yes	Yes in LT (conditional, low) GCP in all SOT[a] (expert opinion)
Targeted antibiotic prophylaxis	No, but consider if high incidence of CPE SSI	Undefined	Insufficient evidence
Decolonization	No	No	NA[b]
MDR-PA			
Screening	No except in Lu-T recipients	NA	NA
Targeted antibiotic prophylaxis	No in non-Lu-T recipients	NA	NA
Decolonization	Nebulized antibiotics in Lu-T	NA	NA
CR-AB			
Screening	NA	In high-endemic settings or outbreak	Yes in LT[a] (conditional, low) GCP in all SOT[a] (expert opinion)
Targeted antibiotic prophylaxis	No	NA	Insufficient evidence
Decolonization	No	NA	NA

Giannella M, et al. Infect Dis Clin North Am. 2023 May 25:S0891-5520(23)00037-5.

AST Recommended vaccinations for adult transplant candidates and recipients

Vaccine	Inactivated/live attenuated (I/LA)	Recommended before transplant	Recommended after transplant	Evaluate for sero-logic 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

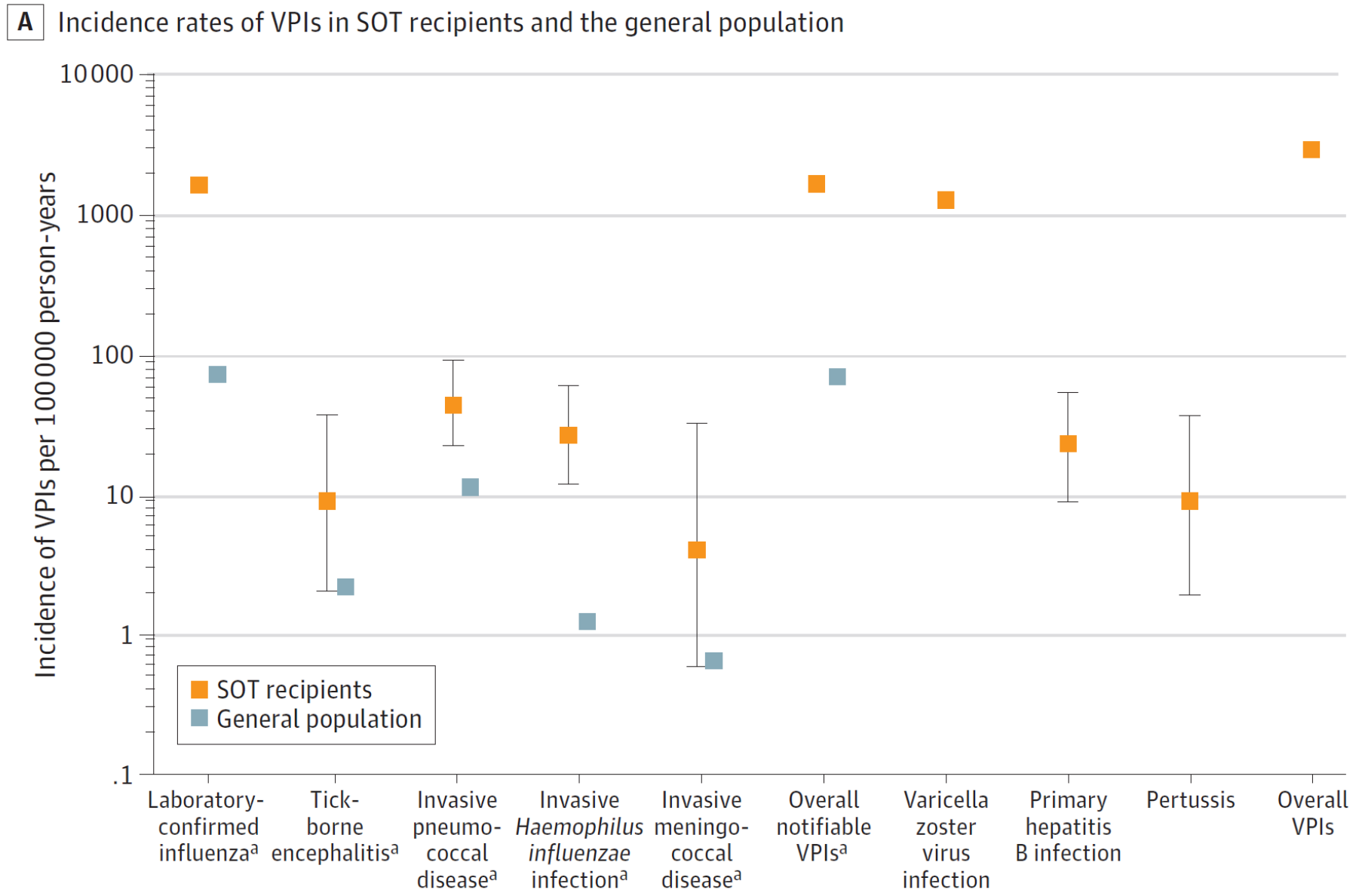
Danziger-Isakov L et al. Clin Transplant. 2019 Sep;33(9):e13563. doi: 10.1111/ctr.13563.

AST Reccommended vaccinations for pediatric transplant candidates and recipients

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	See footnote	Yes	Yes
Pertussis	I	Yes	Yes	No
Diphtheria[59-62]	I	Yes	Yes	No
Tetanus[59-62]	I	Yes	Yes	Yes
Inactivated Polio vaccine[59]	I	Yes	Yes	No
Haemophilus influenza type B[b63]	I	Yes	Yes	Yes
Streptococcus pneumoniae (conjugate vaccine)[25,26,28,29,64,65]	I	Yes	Yes	No
S pneumoniae (polysaccharide vaccine)[25,26,28,29,64,65]	I	Yes	Yes	No
Neisseria meningitides (ACYW)[30,64,66] (MCV4)	I	Yes	Yes	No
N meningitidis B	I	Yes*	Yes*	No
Human papillomavirus (HPV)[64]	I	Yes	Yes	No
Rabies[a,c]	I	Yes	Yes	Yes
Varicella (live attenuated)[67-70]	LA	Yes	No	Yes
Rotavirus	LA	Yes	No	No
Measles/Mumps/Rubella[60,71-74]	LA	Yes	No	Yes
BCG[d]	LA	Yes	No	No
Smallpox[e75]	LA	No	No	No
Anthrax	I	No	No	No

Danziger-Isakov L et al. Clin Transplant. 2019 Sep;33(9):e13563. doi: 10.1111/ctr.13563.

Vaccine-Preventable Infections (VPIs) in Solid Organ Transplant (SOT) Recipients and the General Population



Walti LN, et al. JAMA Netw Open. 2023 Apr 3;6(4):e2310687.

Table 2. Vaccine-Preventable Infection–Associated Morbidity and Mortality in 4967 Solid Organ Transplant Recipients

Disease	Episodes, No.	Patients, No. (%) (N = 4967)	Incidence rate, per 1000 person-years (95% CI)	Episodes, No./total No. (%)		
				Hospitalized for VPI[a]	Graft loss within 90 d after VPI	Death within 30 d after VPI
Overall	668	593 (11.9)	30.57 (28.24-33.10)	198/575 (34.4)	6/668 (0.9)	7/668 (1.0)
Viral VPI						
All	649	578 (11.6)	29.70 (27.41-32.18)	183/558 (32.8)	3/642 (0.5)	7/649 (0.1)
VZV	282	269 (5.4)	12.83 (11.40-14.44)	57/226 (25.2)	3/282 (1.1)	2/282(0.7)
Influenza	360	333 (6.7)	16.55 (14.85-18.46)	124/325 (38.2)	3/360 (0.8)	4/282 (1.4)
HBV infection	5	5 (0.1)	0.23 (0.09-0.54)	0/5	0/5	0/5
TBE	2	2 (<0.1)	0.09 (0.02-0.36)	2/2 (100)	0/2	1/2 (50.0)
Bacterial VPI						
All	19	18 (0.4)	0.87 (0.53-1.39)	15/17 (88.2)	0/19	0/19
IPD	10	9 (0.2)	0.45 (0.23-0.90)	10/10 (100)	0/10	0/10
IHI	6	6 (0.1)	0.27 (0.12-0.61)	4/4 (100)	0/6	0/6
IMD	1	1 (<0.1)	0.04 (0.01-0.32)	1/1 (100)	0/1	0/1
Pertussis	2	2 (<0.1)	0.09 (0.02-0.36)	0/2	0/2	0/2

Abbreviations: HBV, hepatitis B virus; IHI, invasive *Haemophilus influenzae* infection; IMD, invasive meningococcal disease; IPD, invasive pneumococcal disease; TBE, tick-borne encephalitis; VPI, vaccine-preventable infection; VZV, varicella zoster virus.

[a] Data on hospital admission were only available from December 2011 to December 2019 (575 patients).

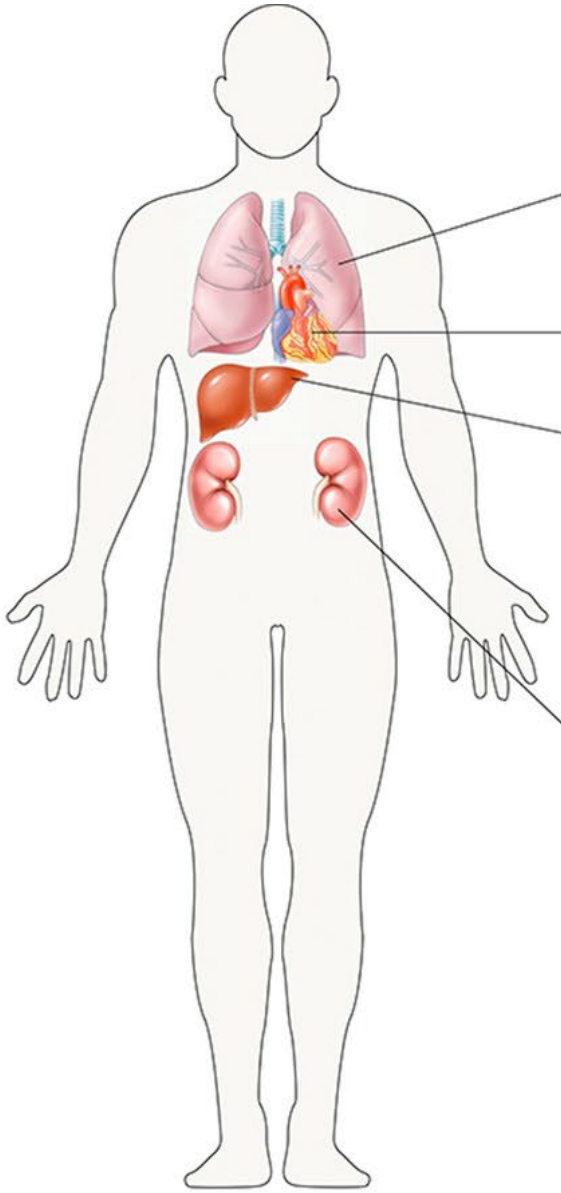
Walti LN, et al. JAMA Netw Open. 2023 Apr 3;6(4):e2310687.

Meta-analysis of the HIR after 3rd vaccine dose in SOT (55.1%)

91 Eligible studies (n=14,011)
- 9 Lung transplant (n=655)
- 12 Heart transplant (n=539)
- 17 Liver transplant (n=1,946)
- 67 Kidney transplant (n=8,746)
- 30 Healthy controls (n=2,125)

Solid organ transplant
Humoral immune response rate
- •1st dose: **9.5%** (95% CI=7%–11.9%)
  RR=0.036 *vs.* Healthy Controls
- •2nd dose: **43.6%** (95% CI=39.3%–47.8%)
  RR=0.382 *vs.* Healthy controls
- •3rd dose: **55.1%** (95% CI=44.7%–65.6%)

Cellular immune response rate
- •1st dose: **12.2%** (95% CI=6.5%–17.8%)
- •2nd dose: **48.3%** (95% CI=34.2%–62.4%)
  RR=0.477 *vs.* Healthy controls
- •3rd dose: **57.6%** (95% CI=-5.4%–120.6%)



Lung transplant
Humoral immune response rate
- •1st dose: **4.4%** (95% CI=0.9%-7.9%)
- •2nd dose: **28.4%** (95% CI=22.3%-34.5%)

Heart transplant
Humoral immune response rate
- •1st dose: **13.2%** (95% CI=8.1%-18.2%)
- •2nd dose: **50.3%** (95% CI=37.6%-63%)

Liver transplant
Humoral immune response rate
- •1st dose: **29.5%** (95% CI=12.2%–46.7%)
- •2nd dose: **64.5%** (95% CI=57.4%–71.6%)
  RR=0.676 *vs.* Healthy controls

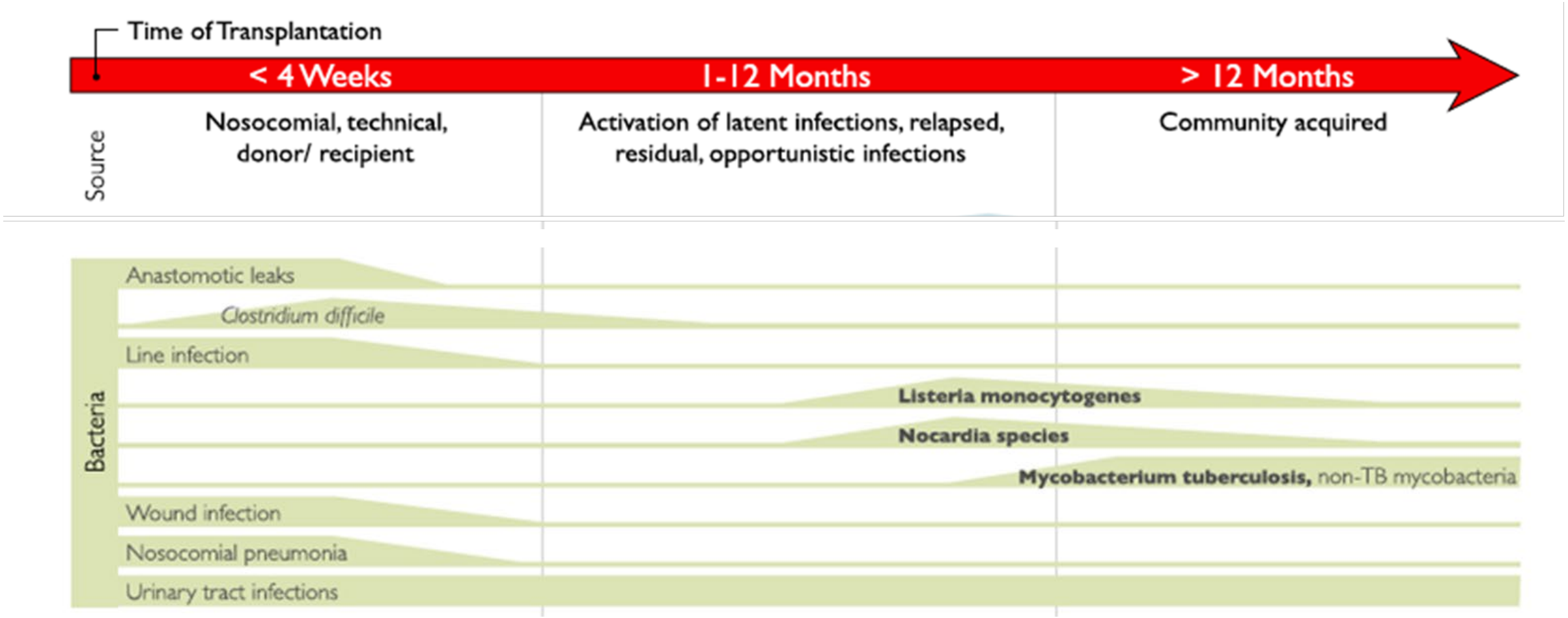
Cellular immune response rate
- •2nd dose:**66.3%** (95% CI=30.1%–102.5%)

Kidney transplant
Humoral immune response rate
- •1st dose: **9.4%** (95% CI=6%–12.7%)
  RR=0.030 vs Healthy Controls
- •2nd dose: **37.6%** (95% CI=33.5%–41.6%)
  RR=0.322 *vs.* Healthy controls
- •3rd dose: **54.4%** (95% CI=40.8%–68.1%)

Cellular immune response rate
- •1st dose: **6.9%** (95% CI=3.1%–10.7%)
- •2nd dose: **42.6%** (95% CI=23.5%–61.7%)
  RR=0.416 *vs.* Healthy controls
- •3rd dose: **57.6%** (95% CI=-5.4%–120.6%)

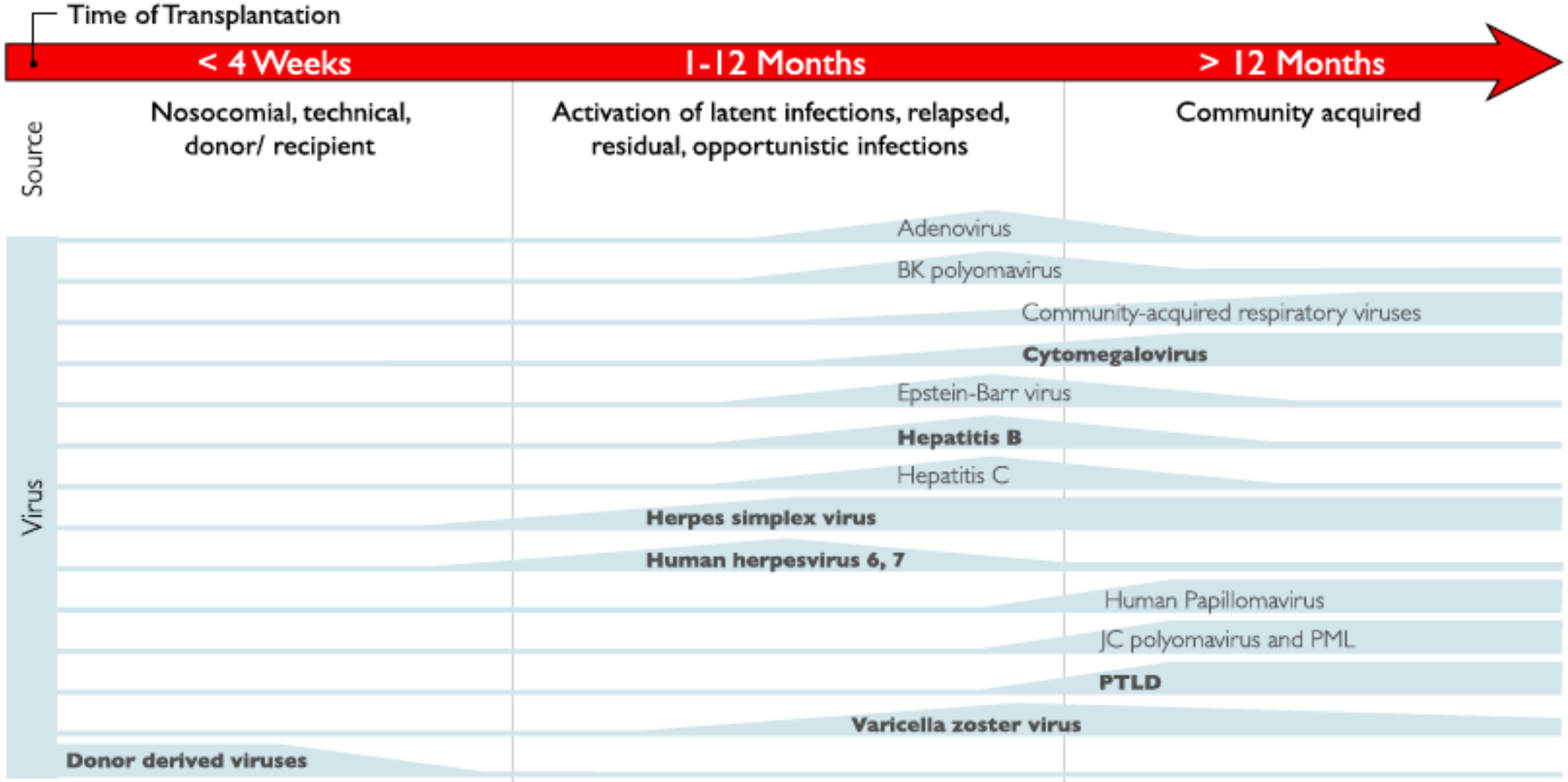
Chen X, et al. Clin Microbiol Infect. 2023 Apr;29(4):441-456.

When do infections occur after solid organ transplantation ?



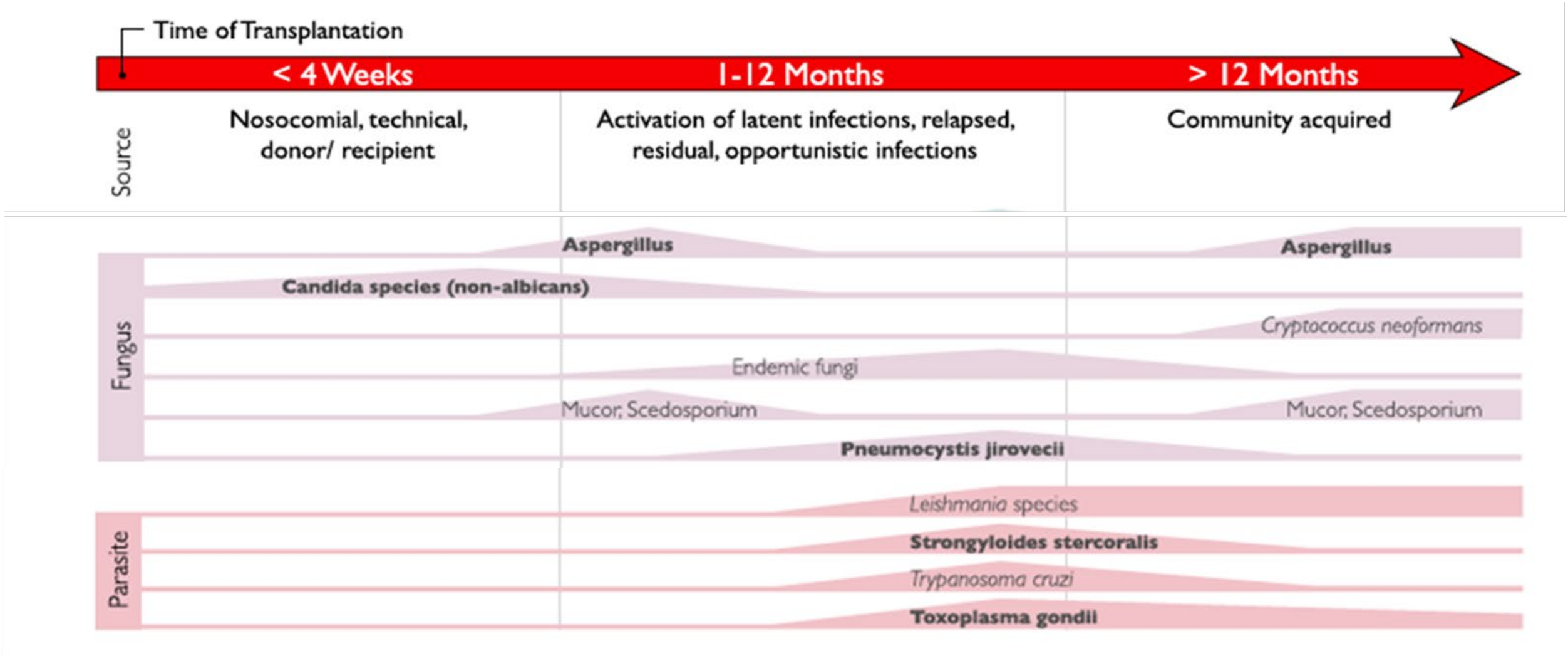
Fishman J. AJT **2017**;17:856

When do infections occur after solid organ transplantation ?



Fishman J. AJT **2017**;17:856

When do infections occur after solid organ transplantation ?



Fishman J. AJT **2017**;17:856

Antimicrobial Prophylaxis in Solid Organ Transplant Recipients

Infection	Drug	Duration	Note
SSI	Antibiotics according to the transplanted organ	24-48 hours	
CMV	Valganciclovir Letermovir	3-6 or 12 months 6 months	Duration varies according to the D/R match and the transplanted organ
Invasive fungal infections	Fluconazole or Itraconazole or Voriconazole or Isavuconazole Echinocandins Amphotericin B	According to the risk factors and the transplanted organ	
Pneumocystis jiroveci	TMP-SMX or Pentamidine, Dapsone, Atovaquone, Clindamycin+Pyrimethamine	6-12 months	TMP-SMX remains the drug of choice for PJP Prophylaxis
Toxoplasma gondii	TMP-SMX ± pyrimethamine, Dapsone + pyrimethamine in allergic patients	6 weeks to lifelong	If D+/R- TMP-SMX ± pyrimethamine remains the drug of choice

Other prophylaxis according to specific risk factors

- HSV prophylaxis if D+/R- or no ganciclovir prophylaxis
- Ivermectin 200ug/kg orally for 2 days with repeat 2 weeks later
  - if donor positive (serology or stools for ova and parasites) or
  - universal prophylaxis in highly endemic areas for *Strongyloides stercoralis*
- Early targeted antimicrobial treatment if unexpected donor's cultures or other tests positivity (blood, urine or BAL; malaria, Leishmania, etc.)

Risk factors for Invasive Aspergillosis

Liver transplant recipients	
Early (0-3 mo)	• Re-transplantation • Renal failure, particularly requiring renal replacement therapy • Fulminant hepatic failure • MELD > 30 • Reoperation involving thoracic or intra-abdominal cavity
Late (>3 mo)	• Cytomegalovirus infection • Creatinine > 3.3 g/dL

Kidney transplant recipients
• Pre-transplant diagnosis of COPD • Acute rejection episode in last 3 mo • Graft failure • High and prolonged duration of corticosteroids

Husain S., Camargo J.F. *Clinical Transplantation.* 2019;33:e13544. https://doi.org/10.1111/ctr.13544

Risk factors for Invasive Aspergillosis

Lung transplant recipients

- Single-lung transplant
- Early airway ischemia
- Cytomegalovirus infection
- Rejection and augmented immunosuppression within last 3 mo, particularly in CF patients
- Pre-transplant *Aspergillus* colonization
- Post-transplant *Aspergillus* colonization within a year of transplant
- Positive intraoperative *Aspergillus* culture in CF patients
- Acquired hypogammaglobulinemia (IgG <400 mg/dL)

Heart transplant recipients

- *Aspergillus* colonization
- Airborne *Aspergillus* spores in ICU
- Reoperation (thoracic)
- CMV disease
- Post-transplant hemodialysis
- Existence of an episode of IA in the program 2 mo before or after heart transplant

Husain S., Camargo J.F. *Clinical Transplantation.* 2019;33:e13544. https://doi.org/10.1111/ctr.13544

Recommendations for peri-operative antibiotics prophylaxis in Liver Transplantation

- We recommend a third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone for up to 24 hours for peri-operative antibiotic prophylaxis in liver transplantation; antifungals may be considered based on individual patient risk (strong, low).
- Another alternative would be ampicillin-sulbactam or in countries were available intravenously amoxicillin-clavulanate for ≤48 hours; antifungals may be considered based on individual patient risk (strong, high).
- The use of selective bowel decontamination prior to liver transplantation is not recommended (strong, low).
- The use of pro-biotics is not recommended (strong, low).
- We recommend that if the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).

Abbo LM & Grossi PA on behalf of the AST ID Community of Practice. Clin Transplant 2019 DOI: 10.1111/ctr.13589

SSI: Risk factors and preventive strategies

- Reducing SSIs requires a multi-faceted approach; **antimicrobials alone are insufficient to prevent this complication.**
- Overall, minimizing surgical operative time and optimizing sterile technique, surgical technique, and peri-operative management of patient comorbidities as well as glucose and temperature regulation are imperative to limit SSIs.
- The 2017 Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection provides evidence based graded recommendations for the general population that are applicable to solid organ transplantation

Abbo LM & Grossi PA on behalf of the AST ID Community of Practice. Clin Transplant 2019 DOI: 10.1111/ctr.13589

CMV Prevention

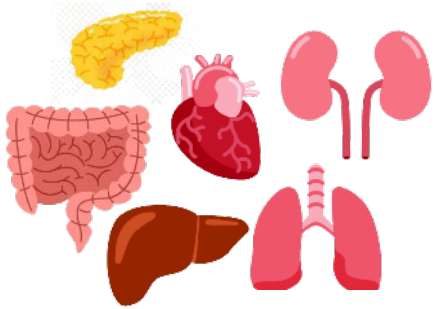
- The optimal approach to the prevention and treatment of infection due to CMV remains uncertain despite years of experience with antiviral therapies.
- Two approaches to the prevention of CMV disease have emerged:
  - **“universal prophylaxis”** and
  - **“preemptive therapy”**
- Although both can prevent tissue-invasive CMV disease, they are, in fact, quite distinct.

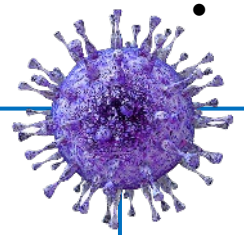
Cytomegalovirus management in solid organ transplant recipients:
A pre-COVID-19 survey from the Working Group of the European Society for Organ Transplantation

METHODS

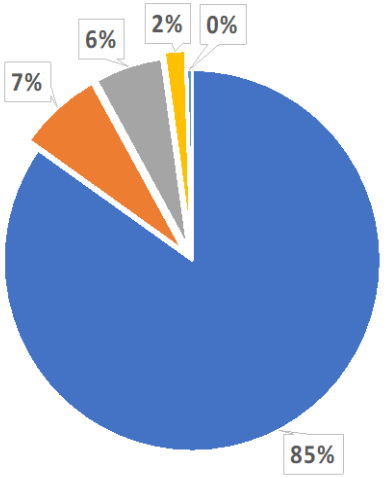
Online Survey
30–40-minute
From 19th Jul to 31stOct 2019

Promoted via
- ESOT congress app
- ESOT social media posting
- European national transplant societies





RESULTS



224
Responses
160 Centers
41 Countries

Heterogenous approach to CMV Diagnosis and Management in SOT

FUTURE PERSPECTIVE

Harmonize management approaches

- Optimizing immunosuppressive protocols'
- Long term impact of CMV on graft dysfunction and comorbidities
- Personalized anti-CMV strategies based on monitoring of CMV-specific T cell response
- Vaccination
- New drug discovery

ESOT
Leading the way in transplantation

PAOLO A. GROSSI, et al. *Transpl Int. 2022 Jun 22;35:10332. doi: 10.3389/ti.2022.10332*

Transplant International

According to donor/recipient CMV serostatus, what is your preventive approach for prevention of CMV disease?

	D+R-	D+R+	D-R+	D-R-
Prophylaxis	173 (77.2%)	99 (44.1%)	87 (38.8%)	32 (14.2%)
PET	21(9.3%)	71(31.6%)	64 (28.5%)	47 (20.9%)
PET after Prophylaxis	28 (12.5%)	12 (5.3%)	14 (6.2%)	5 (2.2%)
none	2 (0.89%)	42 (18.7%)	59 (26.3%)	140 (62.5%)

P.A. Grossi, et al. Transpl Int. 2022 Jun 22;35:10332. doi: 10.3389/ti.2022.10332

Myelotoxicity is main condition impacting patients given VGCV

- ESOT survey conducted July 19th to October 31st 2019
- 224 responses, representing 160 hospitals and 197 SOT programs (41 countries; 167[83%] European programs

- *Despite its widespread use, myelotoxicity was considered to have substantial negative impact on valganciclovir administration (leading to drug discontinuation in 10%–20% of SOT recipients)*

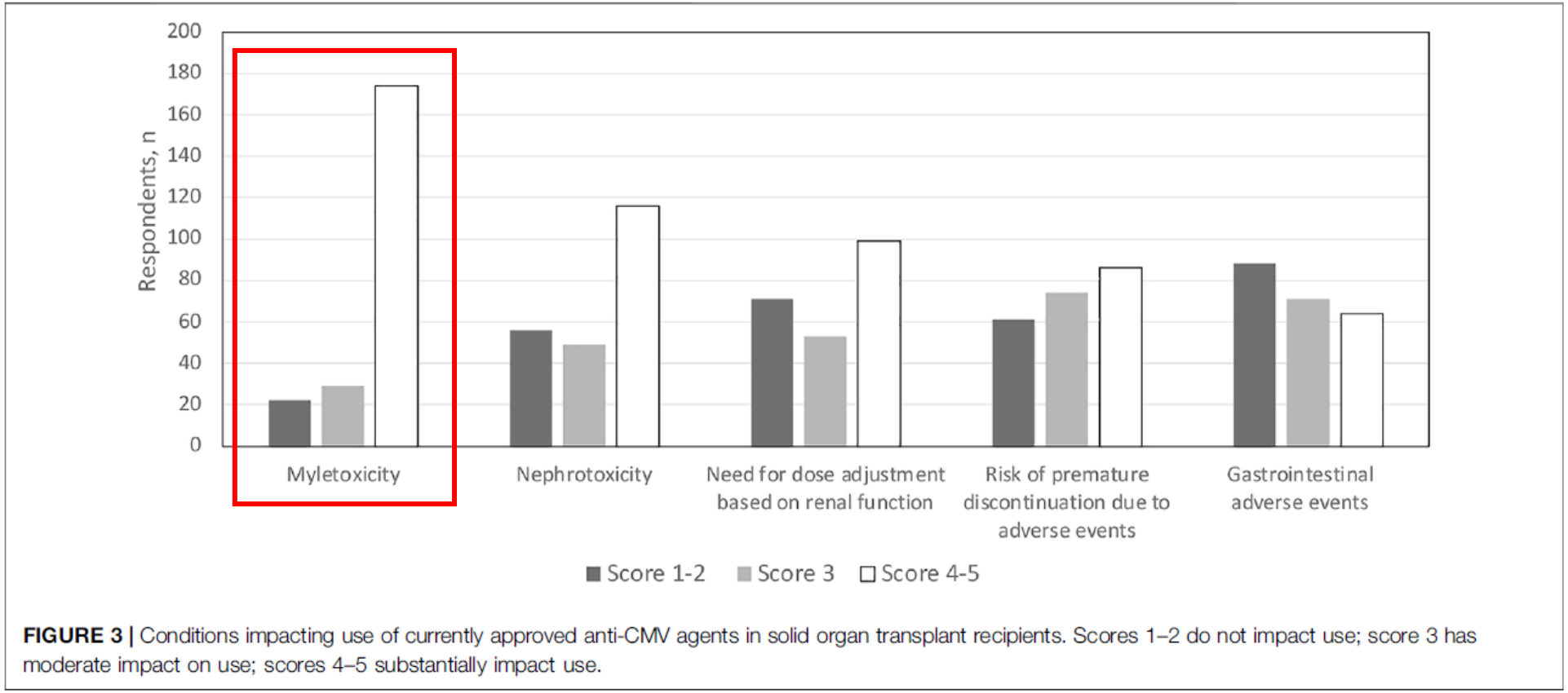


FIGURE 3 | Conditions impacting use of currently approved anti-CMV agents in solid organ transplant recipients. Scores 1–2 do not impact use; score 3 has moderate impact on use; scores 4–5 substantially impact use.

Grossi P.A. et al. Transpl Int June 2022; 35:10332. doi: 10.3389/ti.2022.10332

JAMA

QUESTION Is letermovir noninferior to valganciclovir prophylaxis for cytomegalovirus (CMV) disease prevention in high-risk adult CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor?

CONCLUSION Letermovir was noninferior to valganciclovir for prophylaxis of CMV disease over 52 weeks among adult CMV-seronegative recipients who received an organ from a CMV-seropositive donor.

POPULATION

422 Men
167 Women

Adult CMV-seronegative kidney transplant recipients receiving an organ from a CMV-seropositive donor

Mean age: 50 years

LOCATIONS

94
Hospitals worldwide

INTERVENTION

301
Letermovir
480 mg of letermovir orally daily, 400 mg of acyclovir twice daily, and a valganciclovir placebo

300
Valganciclovir
900 mg of valganciclovir orally daily with letermovir and acyclovir placebos

PRIMARY OUTCOME

CMV disease through 52 weeks after transplant

FINDINGS

Patients with committee-confirmed CMV through week 52

Letermovir
10.4% (30 of 289 patients)

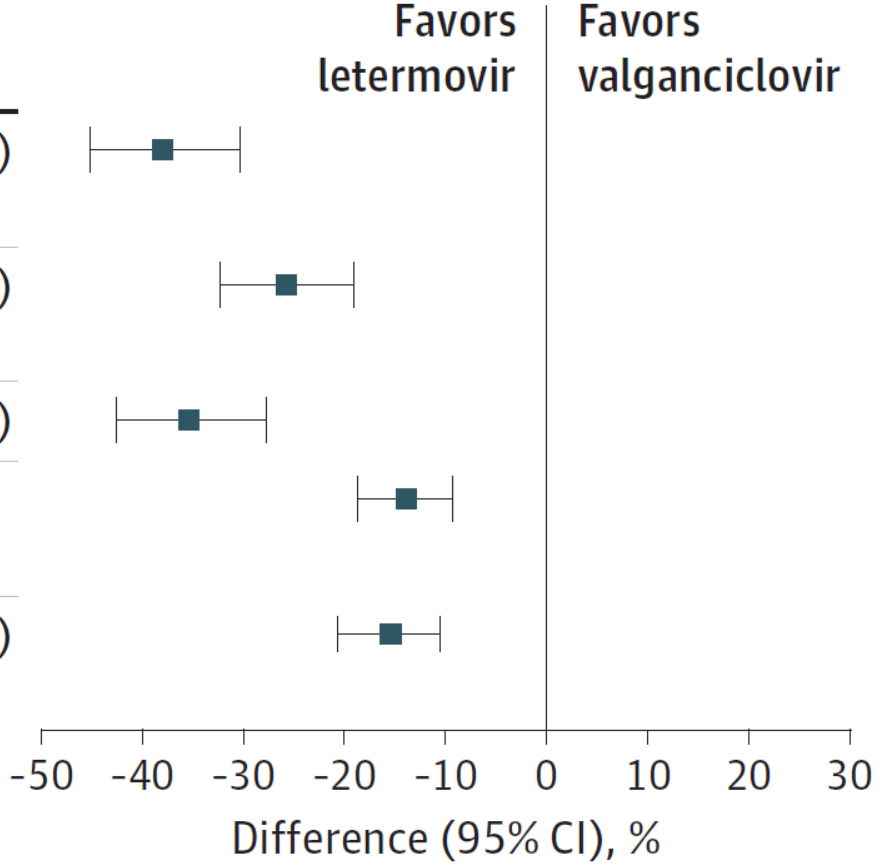
Valganciclovir
11.8% (35 of 297 patients)

Letermovir was noninferior to valganciclovir:
Stratum-adjusted difference, −1.4%
(95% CI, −6.5% to 3.8%)

Limaye AP, et al. JAMA. 2023 Jul 3;330(1):33-42.

Leukopenia or Neutropenia Events and Time to Onset Through Week 28 in the Safety Population

Events	No./total No. (%) Letermovir (n = 292)[a]	Valganciclovir (n = 297)	Difference (95% CI), %
≥1 leukopenia or neutropenia event[b]	76 (26.0)	190 (64.0)	-37.9 (-45.1 to -30.3)
Leukopenia reported as an AE	33 (11.3)	110 (37.0)	-25.7 (-32.3 to -19.1)
WBC count <3500 cells/μL	66 (22.6)	172 (57.9)	-35.3 (-42.5 to -27.7)
Neutropenia reported as an AE	8 (2.7)	49 (16.5)	-13.8 (-18.7 to -9.3)
ANC <1000 cells/μL	12 (4.1)	58 (19.5)	-15.4 (-20.7 to -10.5)



Limaye AP, et al. JAMA. 2023 Jul 3;330(1):33-42.

Conclusions

- Infections continue to be a major challenge in solid organ transplant recipients.
- Pre-transplant screening and vaccination together with peri- and post-transplant antimicrobial prophylaxis is essential to prevent infections.
- CMV prophylaxis is widely used despite some toxicity with the current drugs.
- The use of a preemptive strategy for prevention of CMV and invasive fungal infection is an alternative to universal prophylaxis.
- Letermovir might become the new standard for CMV prophylaxis in kidney transplant recipients.