Mitigating Transplant Infection Risk: Donor/Recipient Screening and Prophylaxis

Camille Nelson Kotton MD, FIDSA, FAST
Clinical Director, Transplant & Immunocompromised Host Infectious Diseases Group,
Infectious Diseases Division, Massachusetts General Hospital
Associate Professor, Harvard Medical School
Past Chair, Infectious Disease Community of Practice,
American Society of Transplantation
Past President, Infectious Disease Section, The Transplantation Society

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Disclosures: Camille Nelson Kotton MD

Company	Role	Details
Merck	Consultant, Adjudication committee member	Transplant infections, CMV antiviral trial
QIAGEN	Consultant	Transplant diagnostics (CMV)
Oxford Immunotec	Consultant, research	Novel diagnostics in transplant patients
Shire-Takeda	Consultant, adjudication committee member	CMV management in transplant patients
Hookipa	Consultant, research	CMV vaccine
Hologic	Consultant	CMV diagnostics
Synklino	Consultant	CMV therapeutics
COGEN Therapeutics, Inc.	Consultant	CMV immunology
GSK	Consultant	CMV vaccines

I will discuss off label use and/or investigational use in my presentation

Mitigating Transplant Infection Risk: Donor/Recipient Screening

Part I

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

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

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

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

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

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 Inf
Community of Practice

Test	Candidate	Deceased donor	Living donor
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	

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Mitigating Transplant Infection Risk: Donor/Recipient Screening

Part I

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Liver Transplant Candidate

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

	12/15/2018 2224	12/16/2018 0541	12/18/2018 0536	1/28/2019 1109	1/28/2019 1110
HEPATITIS					
HAV Ab, IgG		Nonreactive	Nonreactive		
HAV Ab, IgM		Nonreactive	Nonreactive		
HBV Core Ab(s)		Nonreactive			
HBV Surface Ab		<8.00 *			
HBV Surface Ag		Nonreactive			
HCV Ab				Positive * !	
HCV Viral Load (IU...	172,785 *				1,090,000 *

	12/15/2018 2224	12/16/2018 0541	12/18/2018 0536	1/28/2019 1109	1/28/2019 1110
ROUTINE SEROLOGY					
CMV Ab, IgG					Negative
Measles Ab, IgG					Positive
Mumps Ab, IgG					Positive
Rubella Ab, IgG					Positive
INFECTIOUS DISEASE...					
EBV - VCA Ab, IgG					>750.00 *
EBV - VCA Ab, IgM					59.10 *
EBV Ab(s)					Recent *
EBV Nuclear Ab, IgG					>600.00 *
HIV-1/2 Ab/Ag		Nonreactive *		Non-Reactive *	
T SPOT				Positive *	
T SPOT TB TEST					
Varicella Ab, IgG					Positive *
					Positive
Treponemal Ab(s)				Non-Reactive *	

T-SPOT.TB ****POSITIVE** (ELISpot)**
Panel A Spot Count (Corrected for Negative Control) **5**
Panel B Spot Count (Corrected for Negative Control) **18**
Negative Control **Passed**
Positive Control **Passed**

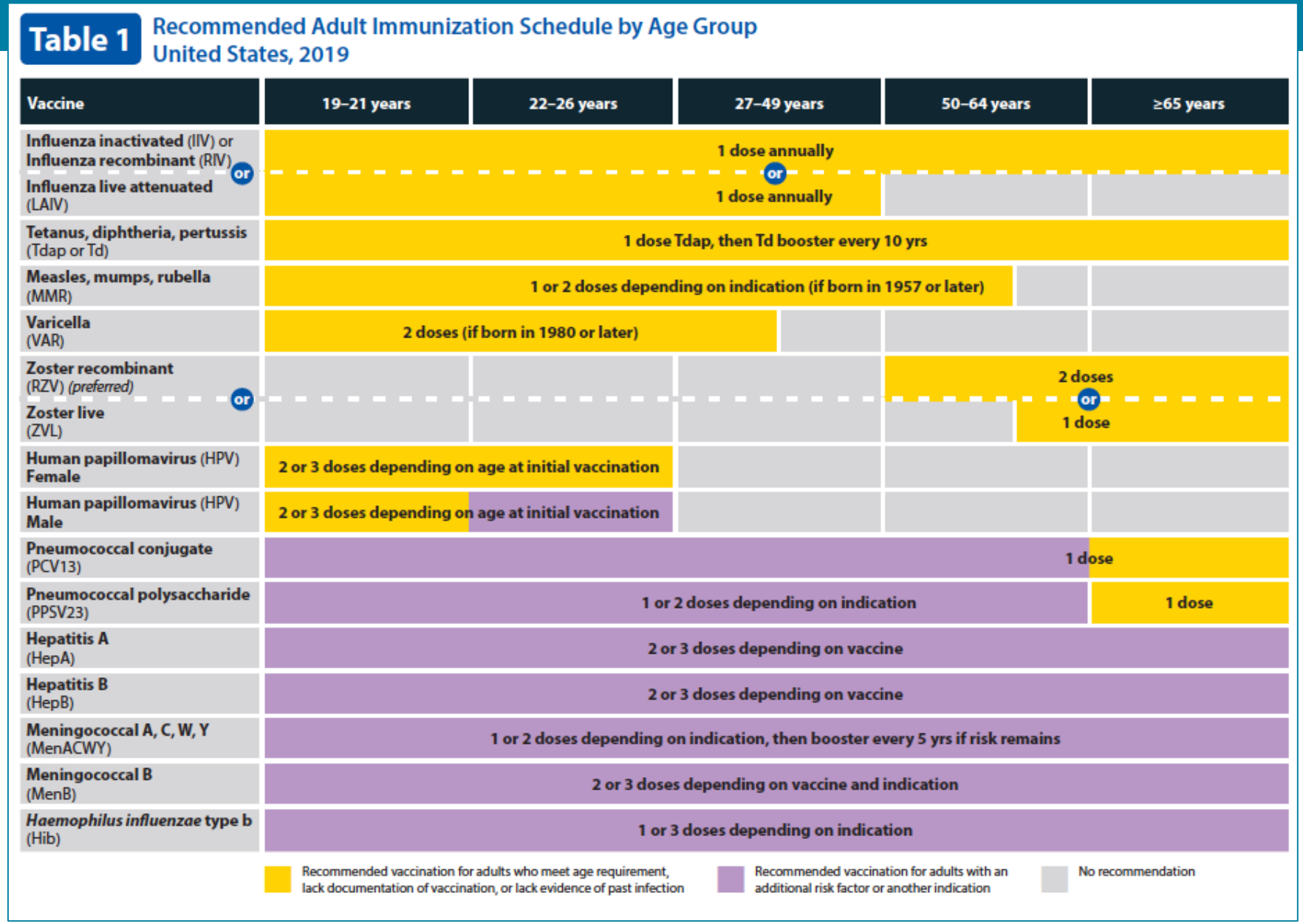


Table 1 Recommended Adult Immunization Schedule by Age Group
United States, 2019

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV)	1 dose annually				
or Influenza live attenuated (LAIV)	1 dose annually				
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap, then Td booster every 10 yrs				
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)				
Varicella (VAR)	2 doses (if born in 1980 or later)				
Zoster recombinant (RZV) *(preferred)*				2 doses	
or Zoster live (ZVL)					1 dose
Human papillomavirus (HPV) Female	2 or 3 doses depending on age at initial vaccination				
Human papillomavirus (HPV) Male	2 or 3 doses depending on age at initial vaccination				
Pneumococcal conjugate (PCV13)	1 dose				
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication				1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine				
Hepatitis B (HepB)	2 or 3 doses depending on vaccine				
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication				
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication				

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

No recommendation

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications United States, 2019

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count <200	HIV infection CD4 count ≥200	Asplenia, complement deficiencies	End-stage renal disease, on hemodialysis	Heart or lung disease, alcoholism[1]	Chronic liver disease	Diabetes	Health care personnel[2]	Men who have sex with men
IIV or RIV	1 dose annually										
or										or	
LAIV	CONTRAINDICATED					PRECAUTION				1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td booster every 10 yrs									
MMR	CONTRAINDICATED			1 or 2 doses depending on indication							
VAR	CONTRAINDICATED			2 doses							
RZV *(preferred)*	DELAY					2 doses at age ≥50 yrs					
or						or					
ZVL	CONTRAINDICATED			1 dose at age ≥60 yrs							
HPV Female	DELAY	3 doses through age 26 yrs				2 or 3 doses through age 26 yrs					
HPV Male		3 doses through age 26 yrs				2 or 3 doses through age 21 yrs					2 or 3 doses through age 26 yrs
PCV13		1 dose									
PPSV23	1, 2, or 3 doses depending on age and indication										
HepA	2 or 3 doses depending on vaccine										
HepB	2 or 3 doses depending on vaccine										
MenACWY	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains										
MenB	PRECAUTION	2 or 3 doses depending on vaccine and indication									
Hib		3 doses HSCT[3] recipients only			1 dose						

- Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
- Recommended vaccination for adults with an additional risk factor or another indication
- Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction
- Delay vaccination until after pregnancy if vaccine is indicated
- Contraindicated—vaccine should not be administered because of risk for serious adverse reaction
- No recommendation

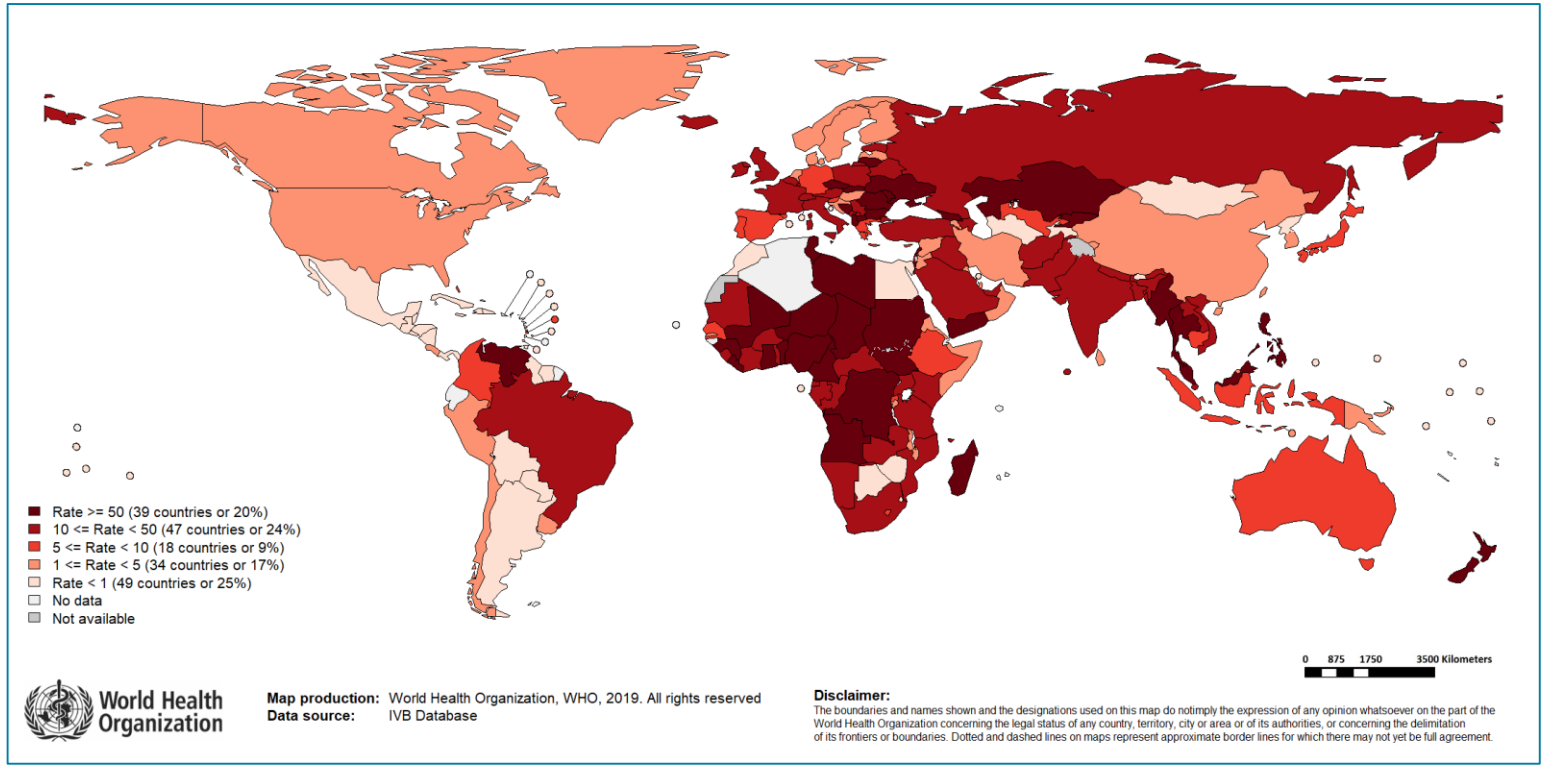
https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

Measles: WHO Data: July 2018 to June 2019

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Top 10**		
Country	**Cases**	**Rate**
Madagascar	150976	6064.62
Ukraine	84394	1899.11
Philippines	45847	443.74
India****	39299	29.68
Nigeria	25814	138.79
Yemen	12001	435.07
Brazil	10241	49.32
Kazakhstan	9430	524.25
DR Congo	9244	117.4
Pakistan	8644	44.74

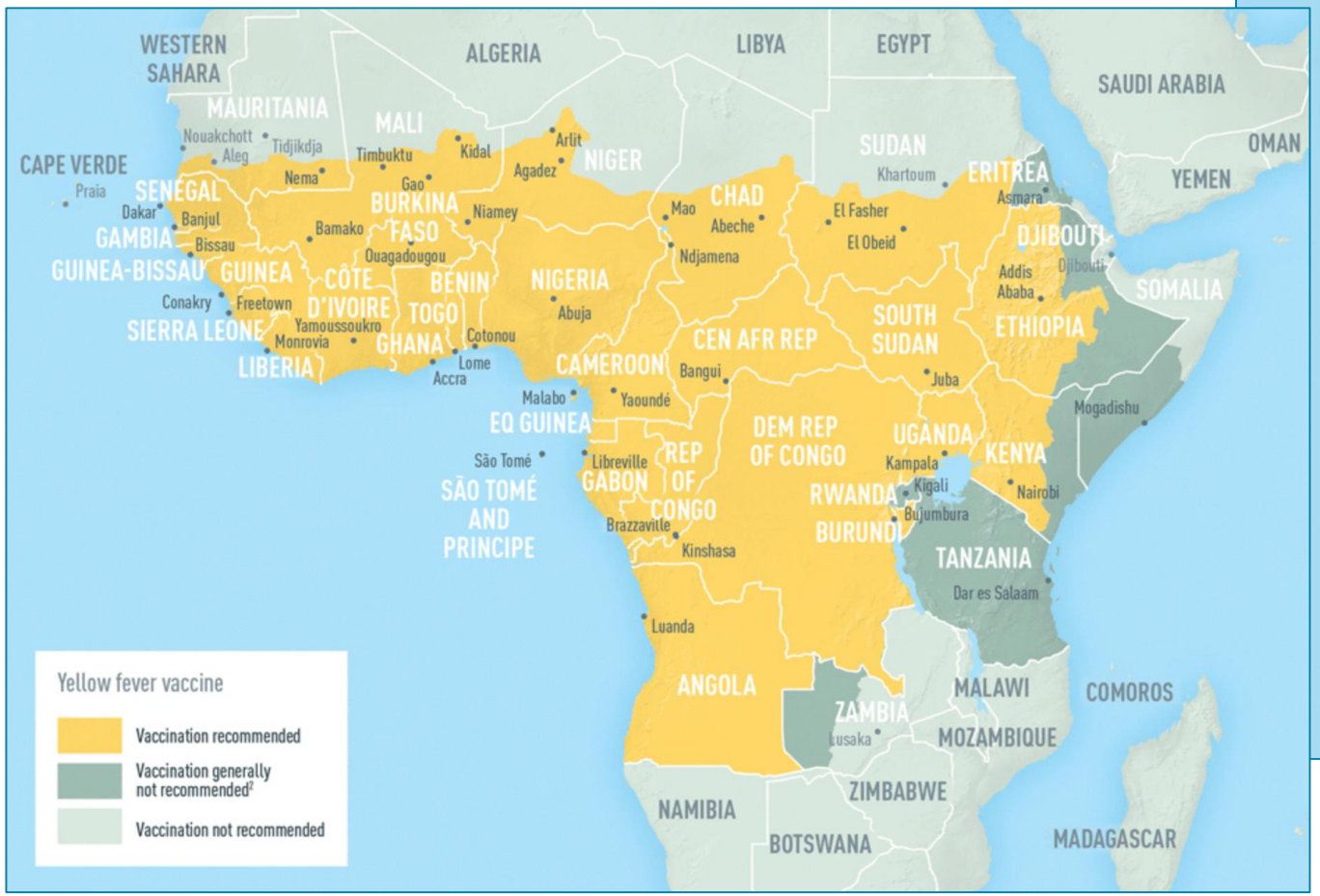
Other countries with high incidence rates***		
Country	**Cases**	**Rate**
Georgia	4950	1261.02
The Republic of North Macedonia	1885	905.72
Kyrgyzstan	2928	491.63
Israel	3982	486.09
Bosnia and Herzegovina	1323	376.19



https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/

Notes: Based on data received 2019-08 and covering the period between 2018-07 and 2019-06 - Incidence: Number of cases / population* * 100,000 - * World population prospects, 2019 revision - ** Countries with the highest number of cases for the period - *** Countries with the highest incidence rates (excluding those already listed in the table above) ****WHO classifies all suspected measles cases reported from India as measles clinically compatible if a specimen was not collected as per the algorithm for classification of suspected measles in the WHO VPD Surveillance Standards. Thus numbers might be different between what WHO reports and what India reports.

Yellow Fever Zones



https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/yellow-fever

Liver Transplant Candidate

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

	12/15/2018 2224	12/16/2018 0541	12/18/2018 0536	1/28/2019 1109	1/28/2019 1110
HEPATITIS					
HAV Ab, IgG		Nonreactive	Nonreactive		
HAV Ab, IgM		Nonreactive	Nonreactive		
HBV Core Ab(s)		Nonreactive			
HBV Surface Ab		<8.00 *			
HBV Surface Ag		Nonreactive			
HCV Ab				Positive * !	
HCV Viral Load (IU...	172,785 *				1,090,000 *

	12/15/2018 2224	12/16/2018 0541	12/18/2018 0536	1/28/2019 1109	1/28/2019 1110
ROUTINE SEROLOGY					
CMV Ab, IgG					Negative
Measles Ab, IgG					Positive
Mumps Ab, IgG					Positive
Rubella Ab, IgG					Positive
INFECTIOUS DISEASE...					
EBV - VCA Ab, IgG					>750.00 *
EBV - VCA Ab, IgM					59.10 *
EBV Ab(s)					Recent *
EBV Nuclear Ab, IgG					>600.00 *
HIV-1/2 Ab/Ag		Nonreactive *		Non-Reactive *	
T SPOT				Positive *	
T SPOT TB TEST					
Varicella Ab, IgG					Positive *
					Positive
Treponemal Ab(s)				Non-Reactive *	

Exclude active disease, then give isoniazid or rifampin (after transplant if needed)

Hepatitis A x 2
Hepatitis B x 3

Prevnar
Pneumovax
Tdap

(no need for MMR)

Shingrix x 2

Family Members & Vaccines

Avoid live influenza, oral polio*, smallpox*

Varicella, "The presence of an immunodeficient … family member does not contraindicate vaccine use in other family members." Red Book, Amer. Academy of Pediatrics

MMR, yellow fever acceptable for family members

balancing risk of disease in home vs vaccine

Rotavirus for infants - caution

ACIP Red Book
British Soc for Rheum "Vaccinations In The Immunocomp. Person"

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

How to Interpret Serology in Patient on IVIG or Heavily Transfused?

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

- Adult male needs lung transplant
- Born in 1960s
- Has diagnosis: common variable immune deficiency (CVID)
- On IVIG every 2 weeks
- Says he's not had any adult vaccines
- How to correctly interpret testing?

	7/24/2019 1028	7/24/2019 1028	
HEPATITIS			
HAV Ab, IgG		Positive *	?
HBV Core Ab(s)		Negative *	
HBV Surface Ab	19.48 *	Positive *	?
HBV Surface Ag		Negative	
HCV Ab		Negative *	
ROUTINE SEROLOGY			
CMV Ab, IgG		Positive	?
Measles Ab, IgG		Positive	?
Mumps Ab, IgG		Positive	?
Rubella Ab, IgG		Positive	?
Toxoplasma Ab, IgG		Negative	
INFECTIOUS DISEASE...			
EBV - VCA Ab, IgG		>750.00 *	▲
EBV - VCA Ab, IgM		<36.00 *	
EBV Ab(s)		Past *	
EBV Nuclear Ab, IgG		42.20 *	▲
HIV-1/2 Ab/Ag		Non-Reactive *	
T SPOT		Negative *	
T SPOT TB TEST			
Varicella Ab, IgG		Positive *	?
Mumps Ab, IgG		Positive	
Treponemal Ab(s)		Non-Reactive *	

Who Should Get Tested for TB

World Health Organization 2018: Patients receiving dialysis, patients preparing for an organ or haematological transplant should be systematically tested and treated for LTBI. ***(Strong recommendation, low–very low-quality evidence. Updated recommendation) (from*** **WHO 2018 Latent tuberculosis infection Updated and consolidated guidelines for programmatic management)**

USA Centers for Disease Control: Certain people should be tested for TB bacteria because they are more likely to get TB disease, including: (www.cdc.gov/tb/topic/testing/)

- People who have spent time with someone who has TB disease
- **People with HIV infection or another medical problem that weakens the immune system**
- People who have symptoms of TB disease (fever, night sweats, cough, and weight loss)
- People from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
- People who live or work somewhere in the US where TB disease is more common (homeless shelters, prison or jails, or some nursing homes)
- People who use illegal drugs

Elements of Latent TB Screening

Medical history

Epidemiologic risk factors

TB skin test (TST)

IGRA blood test

- T-SPOT.®*TB*, QuantiFERON®-TB Gold

Radiographic findings

- Old granulomatous disease, apical scarring

Enumerates effector T-cell response to stimulation with a combination of peptides simulating ESAT-6 and CFP10 (+ TB7.7 for QFN) antigens

Detects prior exposure to:

- *M. tuberculosis* complex organisms (*M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti)*
- *M. kansasii, M. szulgai,* and *M. marinum*

Not + with prior BCG vaccine (bacille Calmette–Guérin) exposure

More sensitive than skin testing in immunocompromised hosts and those on dialysis

Strongyloides

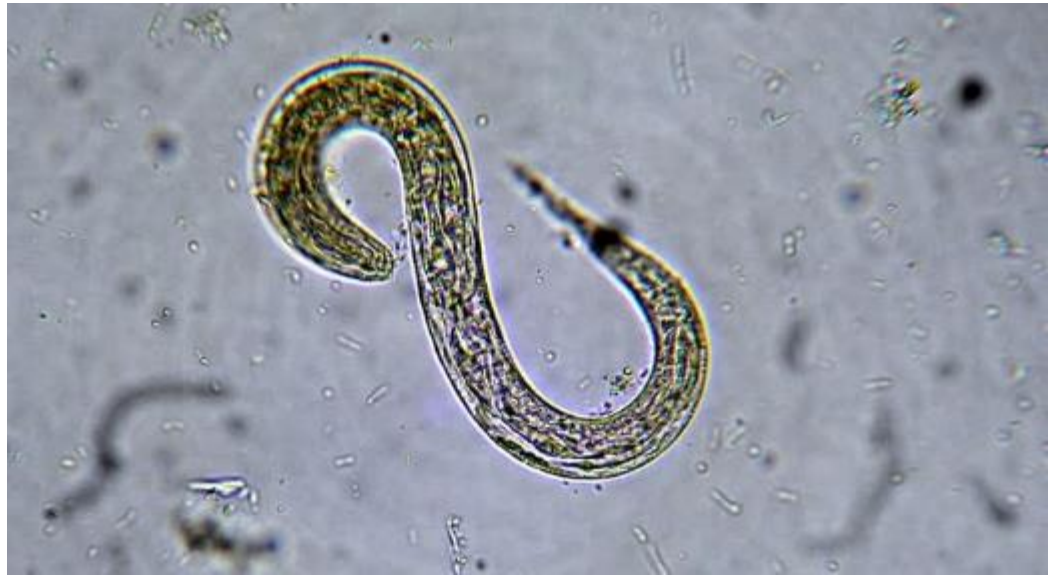
Nematode “roundworm”

100-200 million people worldwide are infected

>50% mortality immunocompromised patients with disseminated disease

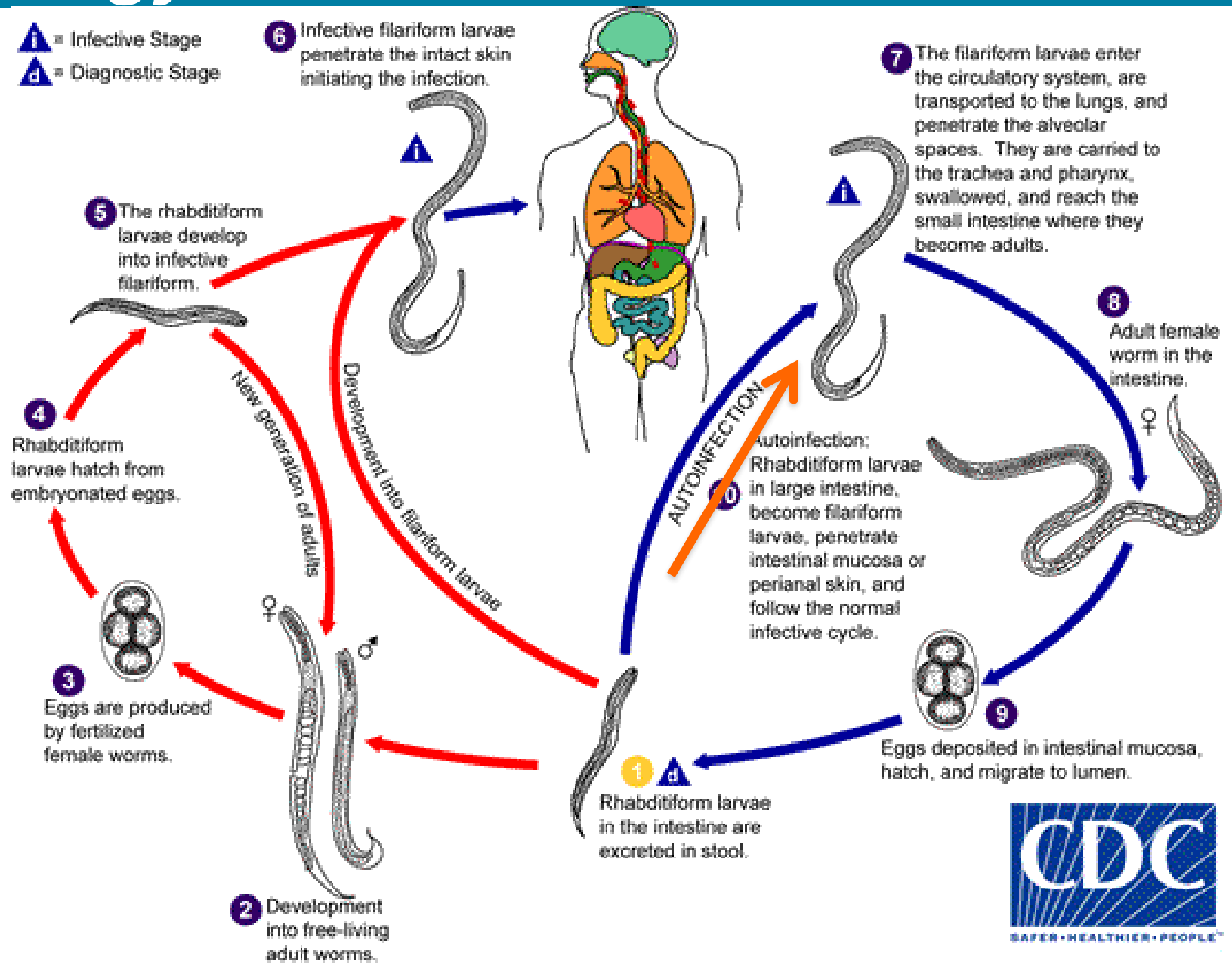
Autoinfection – allows for infection for decades

- 2-4% of veterans, *Strongyloidiasis in US veterans of the Vietnam and other wars, Genta et al, JAMA 1987*

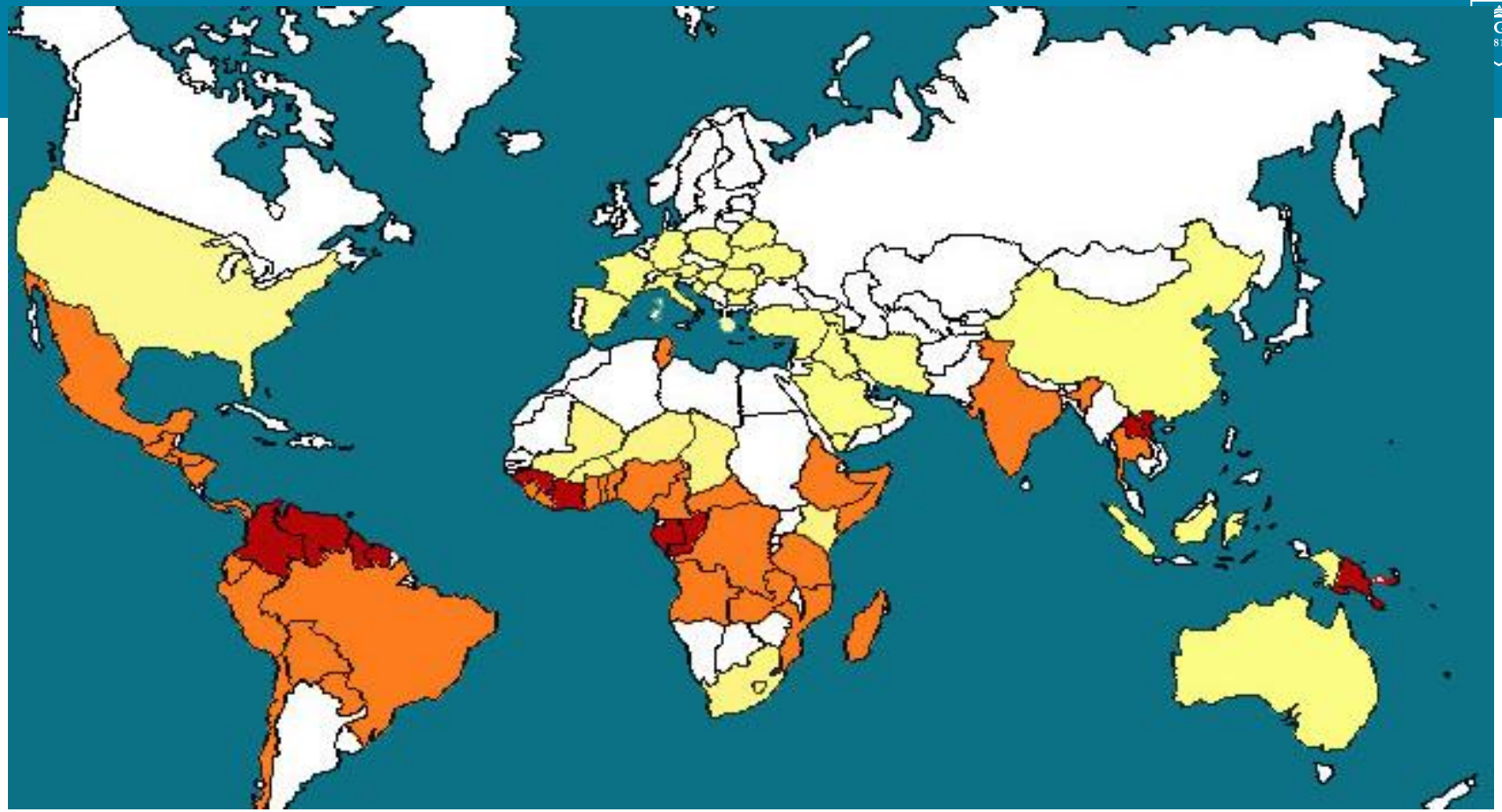


Strongyloides stercoralis

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER



S



The countries highlighted in **yellow** have sporadic endemicity, on the range of 1-3%. Those that are **orange** are endemic, while those that are **red** are generally hyperendemic.

http://web.stanford.edu/group/parasites/ParaSites2006/Strongylodiasis/epidemiology.html

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Strongyloides stercoralis

Most *Strongyloides* infections in organ transplant recipients are due to reactivation of chronic infection after initiation of immunosuppressive therapy.

Donor-derived infection has been reported; the incidence of transmission is unknown

- During 2009–2012, CDC assisted in **seven investigations** of organ donors/recipients with strongyloidiasis determined as donor derived
- Donor-derived infection is difficult to prove, especially if the infected recipient is from a region in which *Strongyloides* is endemic*

UNOS/OPTN: Not an eligible deceased donor if: "active infection with *Trypanosoma cruzi* (Chagas), *Leishmania, Strongyloides*, or malaria (*Plasmodium* sp.)"**

6/58 OPOs in USA currently screen donors for strongyloidiasis***

*Transmission of *Strongyloides stercoralis* MMWR / April 12, 2013 / Vol. 62 / No. 14
**https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf Updated 5/2/2018
***Abanyie et al, TID 2018, Organ donor screening practices for Strongyloides stercoralis infection among US organ procurement organizations

Why multiple doses of ivermectin?

Two oral doses of 200 mg/kg/day is the scheme most frequently used to treat asymptomatic/intestinal, often repeated 2 weeks later

Ivermectin activity is limited to the intestinal stages; effect on extraintestinal stages uncertain

Experimental models of *S. stercoralis* infection:

- ivermectin is effective against adult worms but less effective against eggs and larval stages in tissue

Some evidence that treatment not 100%

Strongyloidiasis Outside Endemic Areas: Long-term Parasitological and Clinical Follow-up after Ivermectin Treatment, Repetto *et al* (Argentina), CID 2018

Mitigating Transplant Infection Risk:
Donor Screening – Living and Deceased

Part I

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

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

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	

Received: 4 March 2019 | Accepted: 18 March 2019
DOI: 10.1111/ctr.13547

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY

Donor-derived infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Cameron R. Wolfe[1] | Michael G. Ison[2] | On behalf of the AST Infectious Diseases Community of Practice

TABLE 1 Potential donor-derived disease transmission as reported to the OPTN: 2005-2017

	Reports (Donors)	Recipients potentially involved[a]	Recipients with proven/ Probable transmission	Donor-derived disease attributable deaths (Recipients)	Liver recipients[a] with proven or Probable transmissions	Heart recipients[a]	Kidney/ Pancreas[a]	Lung or heart/Lung recipients[a]
Malignancy	577	1342	164	43	17	1	26	3
Viruses[b]	463	1463	216	27	26	6	41	14
Bacteria[c]	467	1524	230	21	12	3	39	24
Fungi[d]	299	1043	179	26	10	5	18	15
Mycobacteria[e]	136	468	35	7	0	0	0	3
Parasites[f]	118	385	103	17	8	6	12	5
Other Disease	121	402	68	3	8	0	10	6
Total	1980	5688	908 (15.9%)	135 (14.9%)	81	21	146	70

[a]Organ-specific numbers are only reflective of 2012-2017 data; organ-specific data were not effectively collected prior to this time point.
[b]Viruses: Adenovirus, HBV, HCV, HEV, HHV-8, HIV, HTLV, Eastern Equine Encephalitis, herpes simplex, influenza, LCMV, Parainfluenza (PIV)-3, Parvovirus B19, rabies, West Nile virus.
[c]Bacteria: *Acinetobacter*, Brucella *Enterococcus* (including VRE), *Ehrlichia* spp, *Escherichia coli*, *Enterobacter*, Gram-positive Bacteria, *Klebsiella*, Legionella, Listeria, Lyme Disease, Nocardia, *Pseudomonas*, Rocky Mountain Spotted Fever, *Serratia*, *Staphylococcus aureus* (MRSA), Streptococcus spp, Syphilis, *Ureaplasma urealyticum*, *Veillonella*; bacterial meningitis and bacterial emboli.
[d]Fungi: *Aspergillus* spp, *Candida* spp, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, Scopulariopsis, zygomyces.
[e]Mycobacteria: Tuberculosis, Non-TB Mycobacteria.
[f]Parasites: Babesia, *Balamuthia mandrillaris*, Chagas (*Trypanosoma cruzi*), *Naegleria fowleri*, schistosomiasis, strongyloides, Toxoplasma.

Received: 4 March 2019 | Accepted: 18 March 2019
DOI: 10.1111/ctr.13547

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY

Donor-derived infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Cameron R. Wolfe[1] | Michael G. Ison[2] | On behalf of the AST Infectious Diseases Community of Practice

TABLE 3 Behavioral risk factors for a donor to be at increased risk of transmitting Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV)[109]

- High-risk sexual contacts:
  - Persons who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 mo
  - Men who have had sex with another man (MSM) in the preceding 12 mo
  - Women who have had sex with a man with a history of MSM behavior in the preceding 12 mo
  - Persons who have had sex in exchange for money or drugs in the preceding 12 mo
  - Persons who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for non-medical reasons in the preceding 12 mo.
- Birth to a mother infected with HIV, HBV, or HCV (for infant donors ≤2 y of age)
- Persons who have injected drugs by intravenous, intramuscular, or subcutaneous routes for non-medical reasons in the preceding 12 mo
- Inmates of a correctional facility (eg, jail, prison, or juvenile detention) for >3 d in the preceding 12 mo
- Persons who have or have been treated for syphilis, gonorrhea, chlamydia, or genital ulcers in the preceding 12 mo
- Persons who have been on hemodialysis in the preceding 12 mo (HCV risk only)

5.1 | Key recommendations: Donors with documented infections

- Donors with documented bacteremia should be used with informed consent and involvement of the local Transplant Infectious Diseases team. The donor should be treated with targeted antimicrobial treatment for at least 24-48 hours, optimally with some degree of clinical response. The recipient should receive 7- to 14-day course of antibiotics targeted to the organism isolated from the donor. (Strong, Moderate).
- Bacteremic donors should be assessed for metastatic infections, including embolic infection of the graft or endocarditis. Such metastatic infections may make the risk of infection transmission higher and would warrant longer durations of therapy in recipients (Strong, Low).
- Donors with multi-drug-resistant bacterial infections require careful discussion with the Transplant Infectious Diseases team prior to accepting the organs. Risk-benefit assessment is needed to drive decisions to accept the organ but a clear plan for peri-transplant antibiotics should be outlined prior to use of the organs (Strong, Low).
- Donors with documented bacterial meningitis or *N fowlerii* infection can be used with appropriate treatment of the recipient for the infection (Strong, Moderate).
- Donors with encephalitis of unknown etiology should generally be avoided (Strong, Low)

Received: 4 March 2019 | Accepted: 18 March 2019
DOI: 10.1111/ctr.13547

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY

Donor-derived infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Cameron R. Wolfe[1] | Michael G. Ison[2] | On behalf of the AST Infectious Diseases Community of Practice

Recognize Potential Infection

Consider Donor-Derived Infections in the Following Settings:

- Recipient with atypical post-transplant course: mental status change, encephalitis, unexplained fever, sepsis or hepatitis
- Recipient with early post-transplant bacterial or fungal infection: Should prompt review of donor cultures
- Multiple recipients of organs from the same donor with the same infection (if managed by a single center)
- Atypical infection for the early post-transplant period

Report and Communicate

- Report should be made as soon as any team members considers potential of a donor-derived infection
  - Team should not wait until donor origin is confirmed
  - Report should be made no later than 24 hours after initial concern
- Report of concern should be made to all involved organ procurement organizations (OPO), transplant centers and transplant authorities
  - In the US, reports should be made to UNOS through the Patient Safety Portal
  - In the US, all transplant centers and OPOs are required to have a patient safety contact. There is a list of these contacts in DonorNet
- Inform all key members of the team and hospital, including transplant team, risk management and media relations
- Make direct contact with any involved patients to ensure they are asymptomatic; do not depend on last contact with patient as reflective of current status of the patient
- Provide timely information and updates on your patients and their testing

Collect and Retain Specimens & Data

As soon as you are informed about a potential disease transmission event, collect key specimens and data

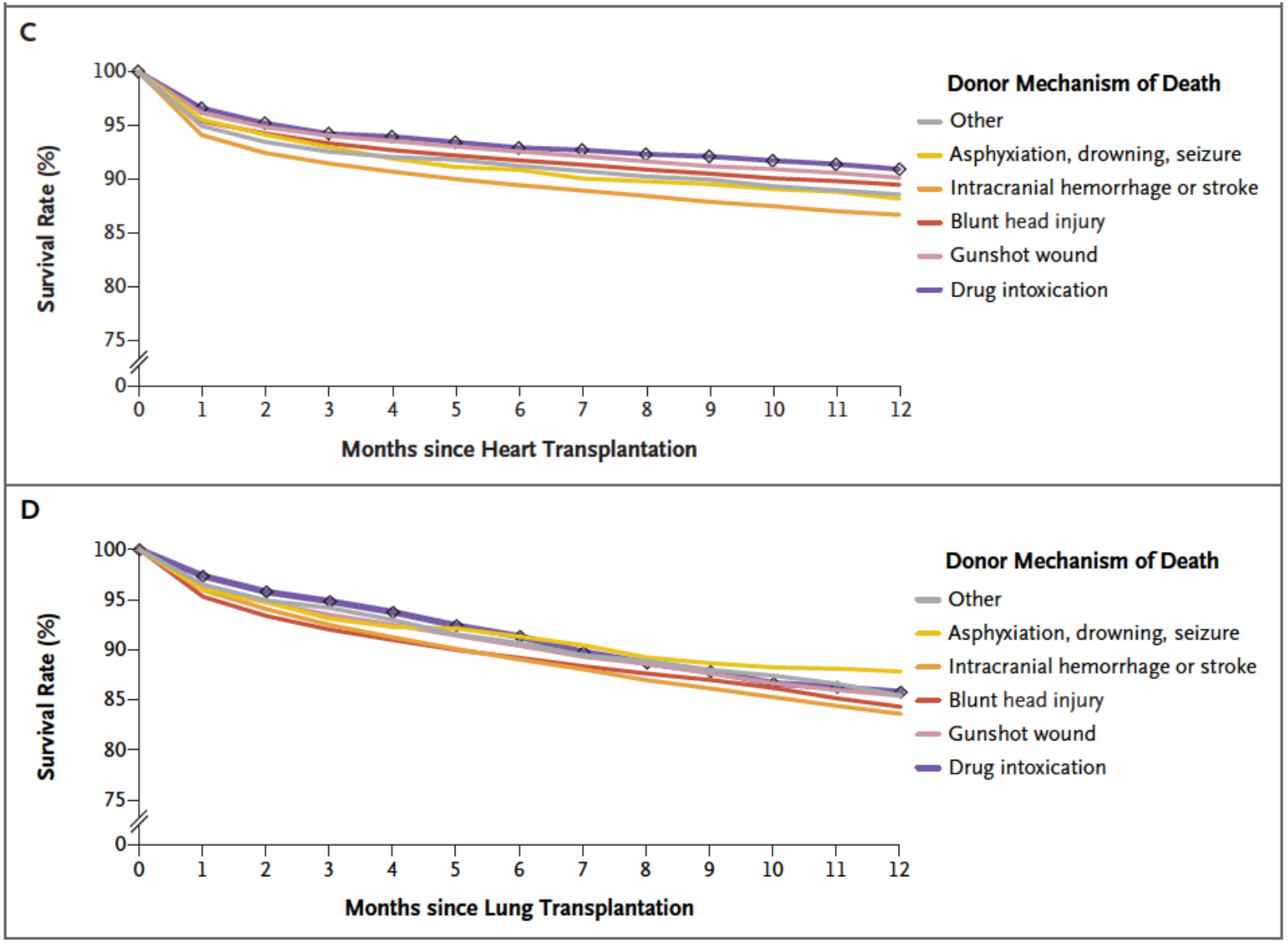
- Contact pathology to retain any fresh residual specimens of biopsies or discarded tissue from donor or recipient
- Contact microbiology to retain any culture or residual specimens that were sent for testing
- Contact molecular diagnostic lab to retain any sequences or specimens sent for PCR or similar testing
- Contact HLA to retain any donor recipient blood, lymph nodes, cells or tissues, particularly pre-transplant specimens

Test and Manage

- Perform appropriate testing of the recipient for potential donor-derived infection
  - For most viral pathogens, you will need to do a direct test for the virus (i.e. PCR/NAT or Antigen detection)
  - Serology may not be reliable in the post-transplant period, particularly if there was significant transfused blood
  - Any routine monitoring for disease transmission (i.e. testing of recipients of organs from PHS Increased Risk Donors) should be done within the first month post-transplant.
- Given the recipient appropriate therapy based on presumed pathogen is one has been identified

FIGURE 2 Approach to a potential donor-derived infection[69]

The Drug-Intoxication Epidemic and Solid-Organ Transplantation, Mehra et al, NEJM 2018



MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

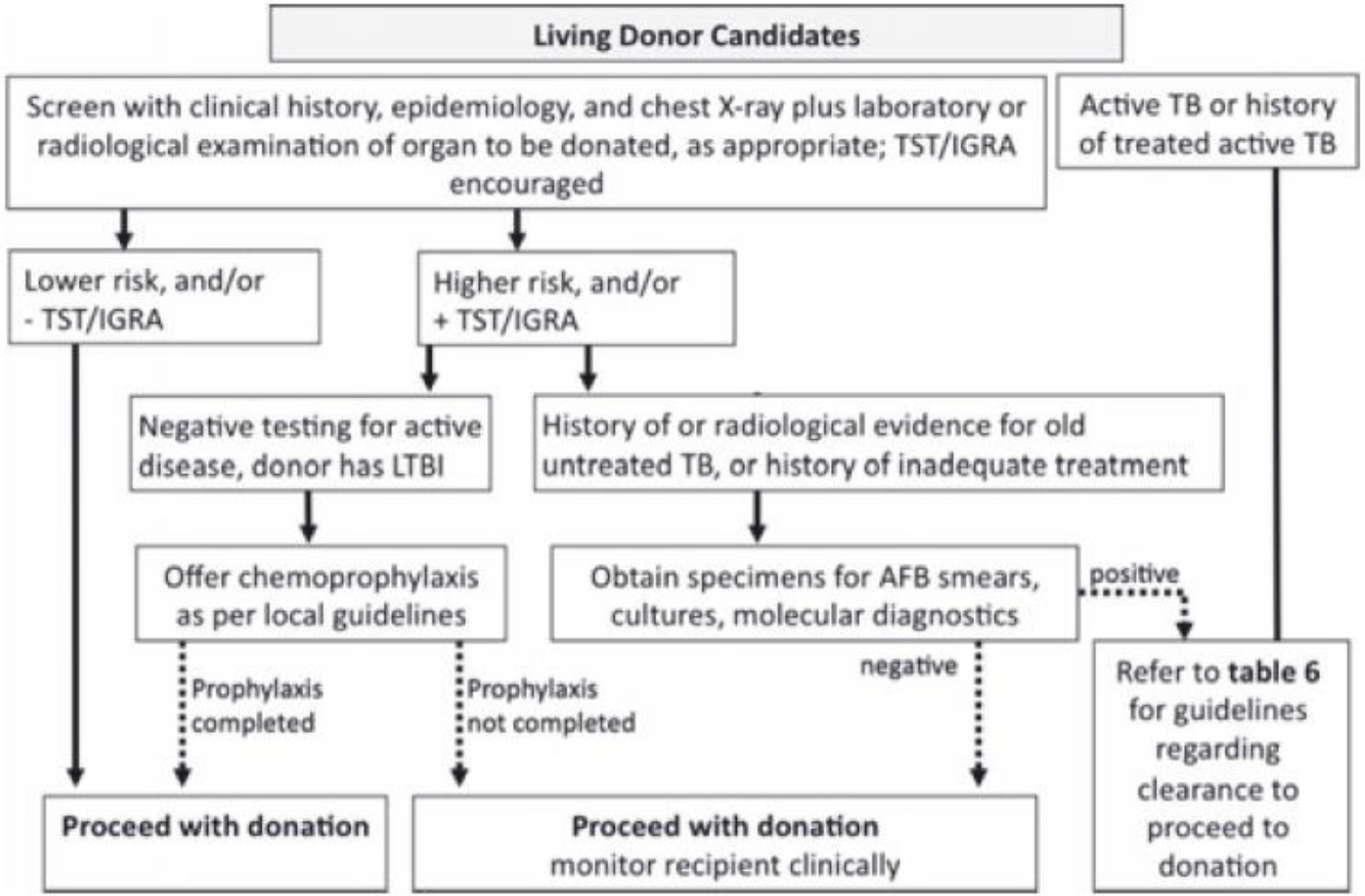
American Journal of Transplantation
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2012.04205.x

Meeting Report

Diagnosis and Management of Tuberculosis in Transplant Donors: A Donor-Derived Infections Consensus Conference Report†

M. I. Morris[a,*], J. S. Daly[b], E. Blumberg[c], D. Kumar[d], M. Sester[e], N. Schluger[f], S.-H. Kim[g], B. S. Schwartz[h], M. G. Ison[i], A. Humar[d], N. Singh[j], M. Michaels[k], J. P. Orlowski[l], F. Delmonico[m], T. Pruett[n], G. T. John[o] and C. N. Kotton[p]



Mitigating Transplant Infection Risk: Perioperative Prophylaxis

Part II

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Organ transplant type	Incidence of SSIs (%)	Predominant pathogens causing SSIs	Secondary pathogens causing SSIs
Renal	3-11	*Staphylococcu aureus*	Gram-negative organisms (Enterobacteriaceae, Pseudomonas)
		CoNS	Yeast
		Enterococci	
Pancreas and pancreas-kidney	9-45	*Staphylococcu aureus*	Gram-negative organisms (Enterobacteriaceae, Pseudomonas)
		CoNS	*Streptococci*
		Enterococci	*Candida spp*
			Mycoplasma hominis
Liver	10-37	Gram-negative organisms	
		(Enterobacteriaceae, *Acinetobacter*, *Pseudomonas*)	
		Enterococci	
		Staphylococcu aureus	
		CoNS	
		Candida spp	
Intestinal/ Multivisceral	14-53	Often polymicrobial	*Staphylococcu aureus*
	Up to 100 if mesh used	Gram-negative organisms (*Pseudomonas*, *Escherichia coli*, *Klebsiella spp*)	CoNS
		Candida spp	
		Anaerobes	
		Enterococci	
Heart	4-19	CoNS	Gram-negative organisms
		MRSA	(Enterobacteriaceae, *Pseudomonas*, *Stenotrophomonas*)
		Enterococci	*Candida species*
Lung	5-19	*Pseudomonas spp*	*Stenotrophomonas*
		Escherichia coli	*Aspergillus*
		Klebsiella spp	
		Candida spp	
		Staphylococcu aureus	
		Enterococci	
		CoNS	
		Burkholderia spp	

Received: 5 May 2019 | Accepted: 6 May 2019
DOI: 10.1111/ctr.13589

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY

Surgical site infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Lilian M. Abbo[1] | Paolo Antonio Grossi[2] | on behalf of the AST ID Community of Practice

TABLE 2 Risk factors for SSI by organ transplant type

Organ transplant type	Risk factor categories			
	Host factors	Surgical factors	Donor/allograft factors	Immunosuppression
Renal	DM	Ureteral leak	DGF	Azathioprine
	Obesity	Hematoma	Contamination of kidney perfusate	ATG
	Chronic GN	Blood transfusion	Acute graft rejection	MMF
	Re-operation			Sirolimus
Pancreas, pancreas-kidney	Re-operation	Prolonged operative time	Donor > 55 y old	
		Prolonged ischemic time	ATN in transplanted kidney	
		Enteric drainage	Graft rejection	
		Post-transplant fistula		
		Hand sewn anastomosis		
		Blood transfusion		
Liver	Prolonged ICU or hospital stay	Prolonged duration of surgery	Donor infection	Muromonab-CD3
	Prior hepato-biliary surgery	Anastomotic leak	Acute rejection	
	Prior liver or renal transplantation	Roux en Y biliary anastomosis		
	Antibiotic use in the prior 3-4 mo	Blood transfusion		
	High pre-transplant MELD score	Entry into GI tract		
	Ascites	Post-transplant RRT		
	Obesity			
	DM			
	Hemochromatosis			

TABLE 3 Recommendations for peri-operative antibiotics by organ transplant type

Organ type		IDSA/ASHP/SIS/SHEA guidelines	An alternative approach	Intra-op re-dosing	Post-op dosing	PCN-allergic	Duration post-op
Renal		Single first-generation cephalosporin (eg, cefazolin)	Cefazolin 2 g IV	Every 4 h	Cefazolin 2 g q8h	Vancomycin[b] or clindamycin 900 mg IV plus gentamicin 5 mg/kg IV	≤24 h
Pancreas, pancreas-kidney		Single first-generation cephalosporin (eg, cefazolin)	Ampicillin-sulbactam 3 g IV plus fluconazole 400 mg IV	Every 2 h (fluconazole not re-dosed)	Ampicillin-sulbactam 1.5 g q6h	Vancomycin[b] or clindamycin 900 mg IV and gentamicin 5 mg/kg IV and fluconazole 400 mg IV	Antibacterial ≤48 h, Antifungal ×1 dose, unless high risk in which case ≤14 d
Liver		Third-generation cephalosporin plus ampicillin or piperacillin-tazobactam alone	Ampicillin-sulbactam 3 g IV ± fluconazole 400 mg IV × 1 or echinocandin or liposomal amphotericin B if high risk for invasive fungal infection (duration depends on the individual risk)	Every 2 h (fluconazole not re-dosed)	Ampicillin-sulbactam 1.5 g q6h	or echinocandin or liposomal amphotericin B if high risk for invasive fungal infection (duration depends on the individual risk)	and antifungal agent and duration depends on the individual risk
Intestinal/multivisceral		None given	Vancomycin[b] plus cefepime 2 g IV plus metronidazole 500 mg IV plus fluconazole 400 mg IV or vancomycin[b] plus piperacillin-tazobactam 4.5 g IV plus fluconazole 400 mg IV	Every 4 h (fluconazole not re-dosed)	Cefepime 2 g q8h, metronidazole 500 mg q8h, fluconazole 400 mg q24h, piperacillin-tazobactam 4.5 g q6h, Vancomycin per weight/GFR[b]	Vancomycin[b] plus levofloxacin 750 mg IV plus metronidazole 500 mg IV	≤72 h; if infected mesh or fistulas, then extend to 7 d
Heart	With prior VAD	Single first-generation cephalosporin (eg, cefazolin)	Vancomycin[b] plus either ceftriaxone 1 g IV or cefepime 2 g IV	Every 4 h	Cefepime 2 g q8h, Vancomycin per weight/GFR[b]	Vancomycin[b] plus levofloxacin 750 mg IV q24h	≤48 h
	Without prior VAD	Single first-generation cephalosporin (eg, cefazolin)	Vancomycin[b] plus cefazolin 2 g IV	Every 4 h	Cefazolin 1 g q8h, Vancomycin per weight/GFR[b]	Vancomycin[b] plus levofloxacin 750 mg IV q24h	≤48 h
Lung		Single first-generation cephalosporin (eg, cefazolin)	Vancomycin[b] plus third-generation cephalosporin or cefepime 2 g IV	Every 4 h	Cefepime 2 g q8h, Vancomycin per weight/GFR[b]	Vancomycin[b] plus levofloxacin 750 mg IV q24h	≤72 h

Received: 25 February 2019 | Revised: 26 April 2019 | Accepted: 15 May 2019

DOI: 10.1111/ajt.15488

ORIGINAL ARTICLE

AJT

Risk factors for multidrug-resistant organisms among deceased organ donors

Judith A. Anesi[1,2] | Emily A. Blumberg[1] | Jennifer H. Han[1,2,3] | Dong H. Lee[4] | Heather Clauss[5] | Antonette Climaco[6] | Richard Hasz[7] | Esther Molnar[5] | Darcy Alimenti[1,2] | Sharon West[7] | Warren B. Bilker[2,3] | Pam Tolomeo[2,3] | Ebbing Lautenbach[1,2,3] | for the CDC Prevention Epicenters Program

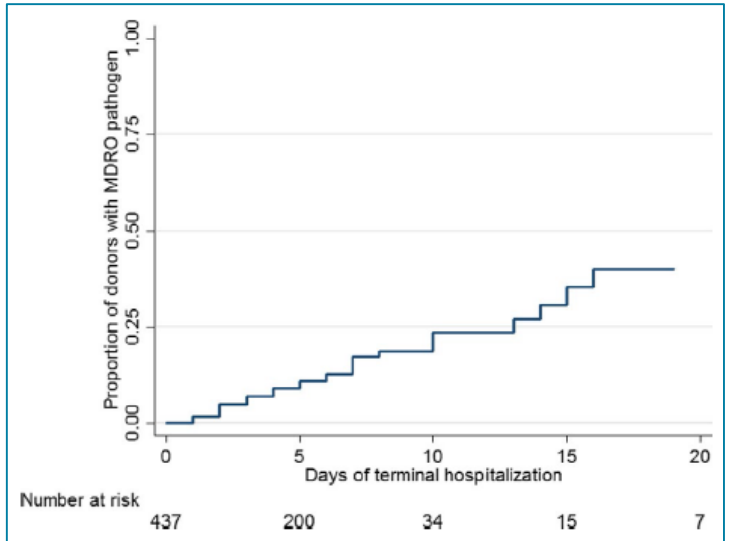


FIGURE 1 Kaplan-Meier failure curve of time to donor MDRO. Time zero is the day of admission to the terminal hospitalization. The failure event is MDRO colonization/infection. Donors were censored at the time of organ procurement. Plotted through 20 days of follow-up

A multicenter retrospective cohort study was conducted at four transplant centers between 2015 and 2016.
Of 440 total donors, 64 (15%) donors grew an MDRO on culture.
Predictors of an MDRO on donor culture included:

- Hepatitis C viremia (hazard ratio [HR] 4.09, 95% confidence interval [CI] 1.71-9.78, P = .002)
- Need for dialysis (HR 4.59, 95% CI 1.09-19.21, P = .037)
- Prior hematopoietic cell transplant (HR 7.57, 95% CI 1.03-55.75, P = .047)
- Exposure to antibiotics with a narrow gram-negative spectrum (HR 1.13, 95% CI 1.00-1.27, P = .045)
    - ceftriaxone, cefotaxime, ampicillin/sulbactam, and amoxicillin/clavulanate

This is the first study to determine risk factors for MDROs among deceased donors and will be important for risk stratifying potential donors and influencing transplant recipient prophylaxis.

Bivariable and multivariable Cox proportional hazard regression model of time…

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

For Donor MDRO+

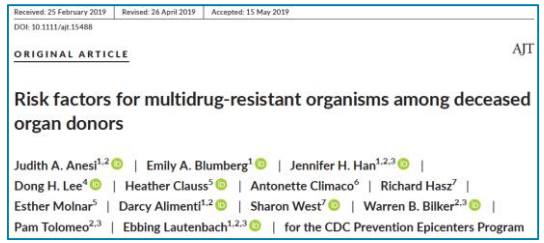
Donor characteristic	Bivariable analysis			Multivariable analysis[b]		
	HR	95% CI	*P* value	aHR	95% CI	*P* value
HCV viremia	3.71	1.56-8.82	.003	4.09	1.71-9.78	.002
Dialysis	3.50	0.85-14.44	.084	4.59	1.09-19.21	.037
Stem cell transplant	5.66	0.78-41.22	.087	7.57	1.03-55.76	.047
THC	1.75	0.90-3.40	.099	1.90	0.97-3.73	.061
Narrow GN antibiotics[a]	—	—	—	1.13	1.003-1.27	.045

aHR, adjusted hazard ratio; GN, Gram-negative; HCV, hepatitis C virus; THC, tetrahydrocannabinol.
[a]Antibiotic exposure incorporated as a time-varying covariate in the multivariable analysis. There is no bivariable HR estimate for time-varying covariates.
[b]Proportional hazards test *P* = .998.

For Donor MRSA+

Donor characteristic	Bivariable analysis			Multivariable analysis[b]		
	HR	95% CI	*P* value	aHR	95% CI	*P* value
HCV viremia	5.04	1.91-13.30	.001	5.39	2.02-14.36	.001
Stem cell transplant	8.97	1.21-66.33	.032	18.95	2.43-147.55	.005
T4 protocol **	3.95	1.17-13.31	.027	5.12	1.49-17.63	.010
THC	2.53	1.18-5.43	.017	2.88	1.33-6.24	.007
Narrow GP antibiotics[a]	—	—	—	0.80	0.66-0.98	.032

GP, Gram-positive; HCV, hepatitis C virus; THC, tetrahydrocannabinol.
[a]Antibiotic exposure incorporated as a time-varying covariate in the multivariable analysis. There is no bivariable HR estimate for time-varying covariates.
[b]Proportional hazards test *P* = .944.


Received: 25 February 2019 | Revised: 26 April 2019 | Accepted: 15 May 2019
DOI: 10.1111/ajt.15488
ORIGINAL ARTICLE
AJT
Risk factors for multidrug-resistant organisms among deceased organ donors
Judith A. Anesi[1,2] | Emily A. Blumberg[1] | Jennifer H. Han[1,2,3] | Dong H. Lee[4] | Heather Clauss[5] | Antonette Climaco[6] | Richard Hasz[7] | Esther Molnar[5] | Darcy Alimenti[1,2] | Sharon West[7] | Warren B. Bilker[2,3] | Pam Tolomeo[2,3] | Ebbing Lautenbach[1,2,3] | for the CDC Prevention Epicenters Program

"The **T4 protocol** is typically employed as one component of "aggressive management of brain-dead donors," which also includes **pulmonary artery catheterization, intravenous fluid resuscitation, and vasopressor infusions**. Such management may increase the risk for bacterial infections, particularly MDROs, due to the **extensive central venous access** required. Further, the administration of **high-dose glucocorticoids** as part of the T4 protocol may result in a degree of immune dysfunction that also increases this risk."

MDROs: Recommendations for Peri-operative Prophylaxis

Be aware of donor risk factors and local epidemiology

Communicate with donor centers and organ procurement organization

Both with screening and if you detect a donor infection

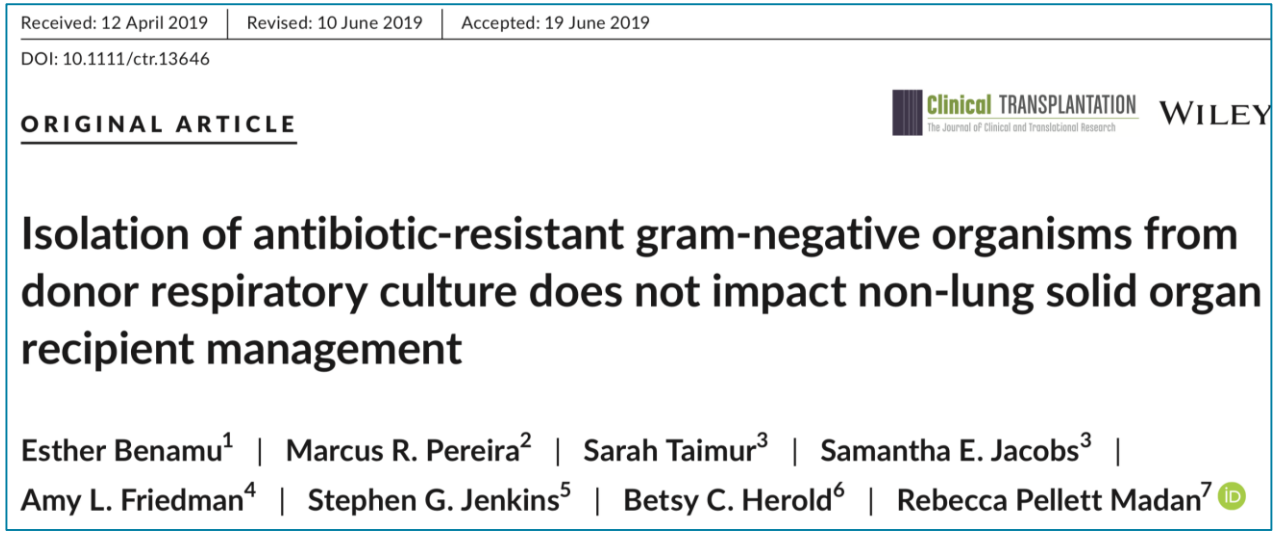
It's not just about using broader antibiotics

(1) increased rates of Clostridium difficile colonization and colitis

(2) Increased rates of antimicrobial resistance

(3) increased adverse drug events

(4) increased financial costs



Received: 12 April 2019 | Revised: 10 June 2019 | Accepted: 19 June 2019

DOI: 10.1111/ctr.13646

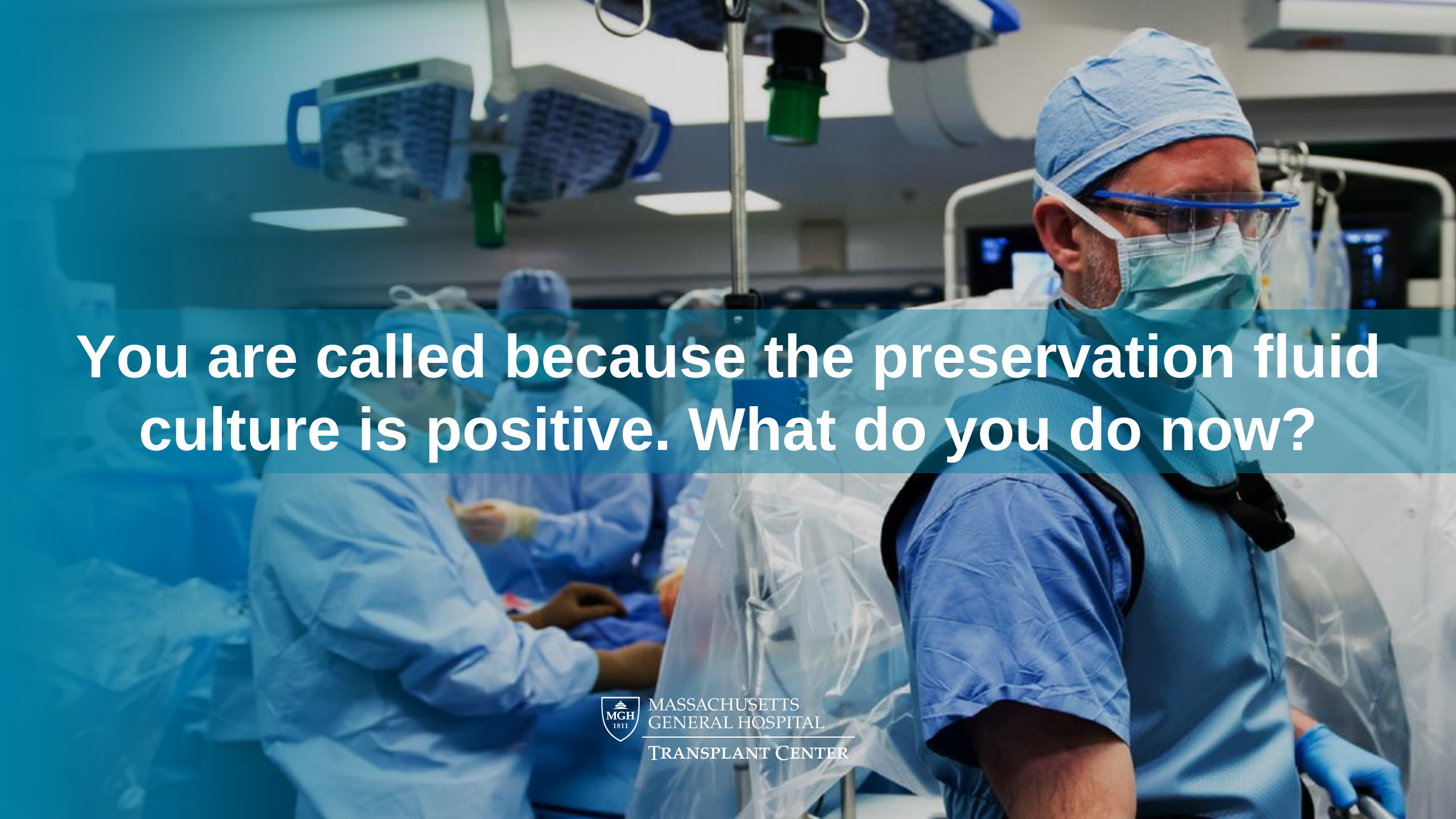
ORIGINAL ARTICLE

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

WILEY

Isolation of antibiotic-resistant gram-negative organisms from donor respiratory culture does not impact non-lung solid organ recipient management

Esther Benamu[1] | Marcus R. Pereira[2] | Sarah Taimur[3] | Samantha E. Jacobs[3] | Amy L. Friedman[4] | Stephen G. Jenkins[5] | Betsy C. Herold[6] | Rebecca Pellett Madan[7]



You are called because the preservation fluid culture is positive. What do you do now?

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Open Forum Infectious Diseases

MAJOR ARTICLE

2019 Apr 26;6(6)

The Impact of Culturing the Organ Preservation Fluid on Solid Organ Transplantation: A Prospective Multicenter Cohort Study

I. Oriol,[1,2,3] N. Sabe,[1,2,3] J. Càmara,[4,5] D. Berbel,[4,5] M. A. Ballesteros,[6] R. Escudero,[7] F. Lopez-Medrano,[8,9] L. Linares,[3,10] O. Len,[11,12] J. T. Silva,[8,9,13] E. Oliver,[14] L. Soldevila,[1] S. Pérez-Recio,[1] L. L. Guillem,[1] D. Camprubí,[1] L. LLadó,[15] A. Manonelles,[16] J. González-Costello,[17] M. A. Domínguez,[2,4,18] M. C. Fariñas,[19] N. Lavid,[20] C. González-Rico,[19] L. Garcia-Cuello,[19] F. Arnaiz de las Revillas,[19] J. Fortun,[7] J. M. Aguado,[8,9] C. Jimenez-Romero,[8,9] M. Bodro,[3,10] M. Almela,[3,10] D. Paredes,[3,10] A. Moreno,[3,10] C. Pérez-Cameo,[12,21] A. Muñoz-Sanz,[13] G. Blanco-Fernández,[22] J. A. Cabo-González,[23] J. L. García-López,[24] E. Nuño,[24] and J. Carratalà[1,2,3]

Background. We analyzed the prevalence, etiology, and risk factors of culture-positive preservation fluid and their impact on the management of solid organ transplant recipients.

Methods: July 2015 to March 2017, 622 episodes of adult SOT, 7 university hospitals in Spain, prospective

Results:

- Prevalence of **culture-positive preservation fluid was 62.5% (389/622**).
- 25.2% (98/389) of the cases were the isolates considered "high risk" for pathogenicity
- Multivariate regression analysis, **advanced donor age** was the main associated risk factor
- **Preemptive antibiotic therapy** given in 19.8% (77/389); significant protective factor for 90-day infection

  Also, lower rate of acute rejection and graft loss

Conclusions. The routine culture of preservation fluid may be considered a tool that provides information about the contamination of the transplanted organ.

Open Forum Infectious Diseases
MAJOR ARTICLE

The Impact of Culturing the Organ Preservation Fluid on Solid Organ Transplantation: A Prospective Multicenter Cohort Study

I. Oriol,[1,2,3] N. Saba,[1,2,3] J. Cámara,[4,5] D. Berbel,[4,5] M. A. Ballesteros,[6] R. Escudero,[7] F. Lopez-Medrano,[8,9] L. Linares,[9,10] O. Len,[11,12] J. T. Silva,[8,9,13] E. Oliver,[14] L. Soldevila,[1] S. Pérez-Recio,[1] L. L. Guillem,[1] D. Camprubí,[1] L. Lladó,[15] A. Manonelles,[16] J. González-Costello,[17] M. A. Domínguez,[4,5,18] M. C. Fariñas,[19] N. Lavid,[20] C. González-Rico,[21] L. García-Cuello,[22] F. Arnaiz de las Revillas,[19] J. Fortun,[7] J. M. Aguado,[8,9] C. Jimenez-Romero,[23] M. Bodro,[2,24] M. Almela,[2,25] D. Paredes,[2,26] A. Moreno,[2,26] C. Pérez-Cameo,[10,27] A. Muñoz-Sanz,[28] G. Blanco-Fernández,[29] J. A. Cabo-González,[29] J. L. García-López,[29] E. Nuño,[29] and J. Carratalà[1,2,3]

Table 2. Microorganisms Isolated in the PF Culture of SOT

Culture-Positive PF (N = 389)		No. (%)
High risk[a]		98 (15.8)
Monomicrobial		71 (11.4)
Gram-positive bacteria	*Staphylococcus aureus*	19 (4.9)
	Enterococcus faecalis	7 (1.8)
	Enterococcus faecium	2 (0.5)
	Streptococcus pneumoniae	1 (0.2)
	Streptococcus agalactiae	1 (0.2)
Gram-negative bacilli	*Escherichia coli*	10 (2.6)
	Enterobacter cloacae	5 (1.3)
	Klebsiella spp.	4 (1.0)
	Pseudomonas spp.	3 (0.8)
	Serratia spp.	2 (0.5)
	Haemophilus influenzae	2 (0.5)
	Other[b]	10 (2.6)
Anaerobes	*Bacteroides* spp.	1 (0.2)
Fungi	*Candida* spp.[c]	4 (1.0)
Polymicrobial (high-risk +/- low-risk isolates)		27 (6.9)
Low risk[d]		291 (46.8)
Monomicrobial		243 (39.1)
Gram-positive bacteria	CNS	225 (57.8)
	Other[e]	15 (3.9)
Anaerobes	Other[f]	3 (0.5)
Polymicrobial (only low-risk microorganisms)		48 (12.3)

Table 3. Univariate and Multivariate Analyses of Factors Associated With High-risk Culture-Positive PF = preservation fluid

Variables	High-risk PF[a] (n = 98, 15.6%)	Low-risk[b] or Culture-Negative PF (n = 524, 84.2%)	*P* Value	Adjusted OR (95% CI)	*P* Value
Sex of donors (male)	53 (54.1)	295 (56.1)	.656		
Type of donation			.141		
Living donors	10 (10.2)	29 (5.5)			
Brain death donors	73 (74.5)	374 (71.4)			
Donation after circulatory death	15 (15.3)	119 (22.7)			
Type of transplant					
KT	47 (48.0)	315 (60.1)	.025	0.51(0.11–2.51)	.411
LT	33 (33.7)	133 (25.4)	.089	0.86 (0.17–4.27)	.852
HT	1 (1.0)	31 (5.9)	.044	0.15 (0.01–1.86)	.140
PT lung transplant	15 (15.3)	36 (6.9)	.005	1.77 (0.34–9.31)	.501
MT	2 (2.0)	9 (1.7)	.824		
Donor infection	12 (12.2)	100 (19.2)	.103		
Mean ischemia time	578 (485–672)	678 (603–753)	.259		
Advanced donor age[c]	81 (82.7)	383 (73.1)	.046	1.88 (1.16–3.05)	.010
ICU days of donor	3.1 (2.3–3.9)	3.6 (3.2–3.9)	.317		

Table 4. Clinical Characteristics of PF-Related Infections

5 = 1.3% of those with positive PF culture

Cases	Type of Transplant	Sex of SOT Recipient	Age of Recipient, y	Days From Transplant to Infection	Microorganism Isolated	Type of Infection	Days of ICU Post-transplant	AGR	Graft Loss	Re-intervention	90-Day Mortality
1	LT	Male	47	5	*E. faecium*	Intra-abdominal infection	6	No	No	Yes	No
2	HT	Male	19	7	*S. epidermidis*	Surgical site infection	14	No	No	Yes	No
3	PT	Female	58	28	*S. aureus*	Respiratory tract infection	11	Yes	No	No	No
4	PT	Male	28	6	*E. cloacae*	Respiratory tract infection	10	Yes	No	No	No
5	PT	Male	64	2	*S. marcescens*	Respiratory tract infection	90	No	No	No	No

Abbreviations: AGR, acute graft rejection; ICU, intensive care unit; HT, heart transplant; LT, liver transplant; PT, lung transplant; SOT, solid organ transplant.

How successful is pre-emptive therapy (PE-T)?

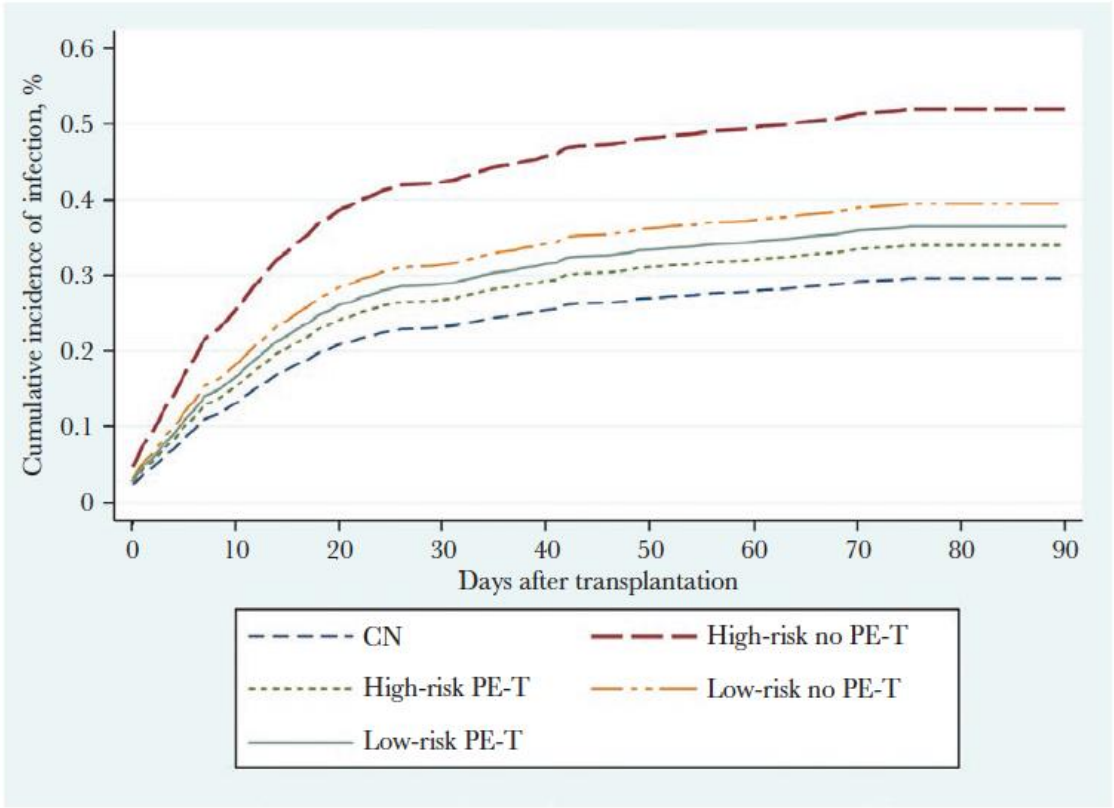


Figure 1. Cumulative incidence of infection on solid organ transplant recipients depending on the result of the preservation fluid culture and the decision to carry out PE-T. Abbreviations: CN, culture-negative preservation fluid; PE-T, preemptive antibiotic therapy.

Open Forum Infectious Diseases
MAJOR ARTICLE

The Impact of Culturing the Organ Preservation Fluid on Solid Organ Transplantation: A Prospective Multicenter Cohort Study

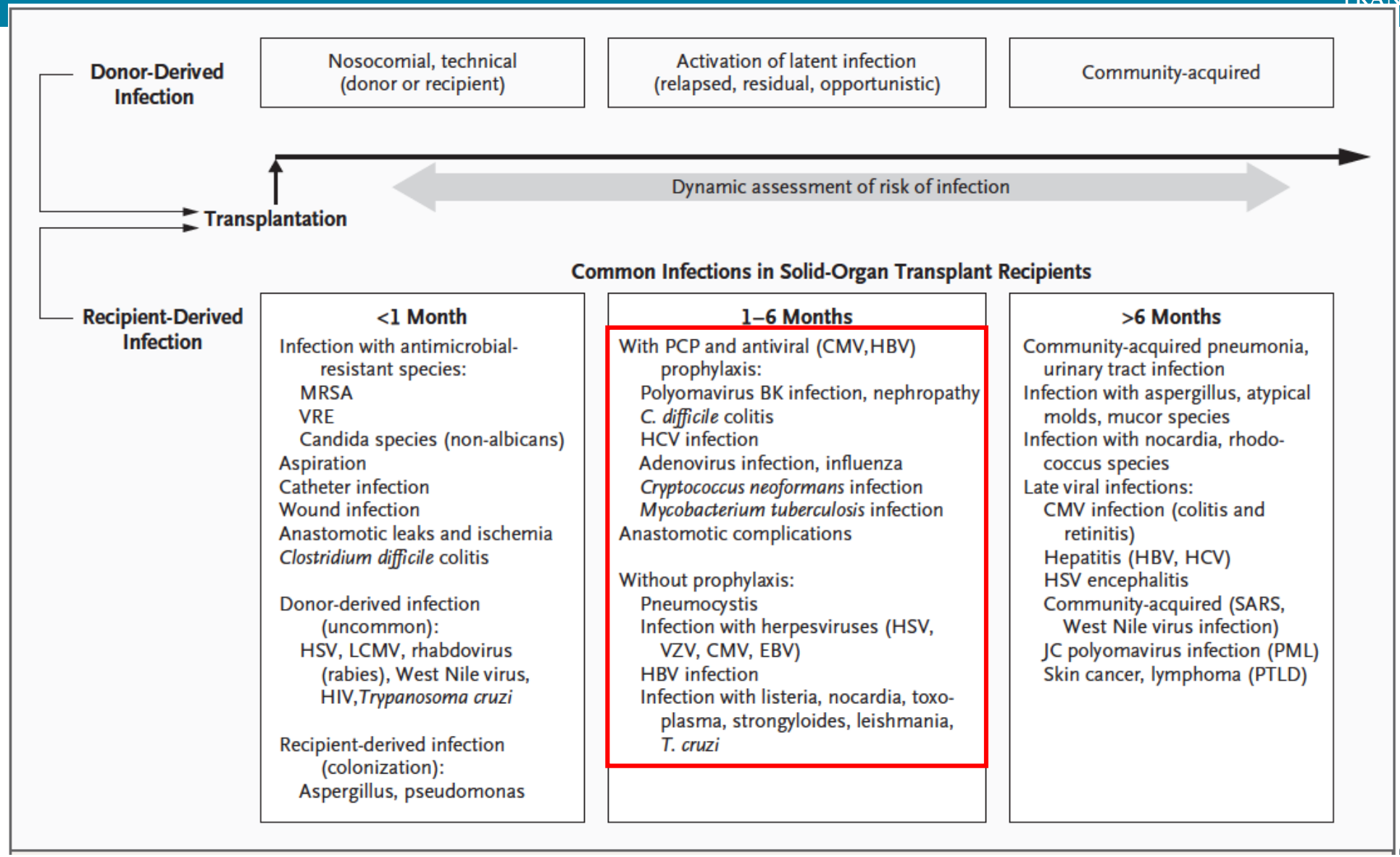
I. Oriol,[1,2,3] N. Sabe,[1,2,3] J. Cámara,[4,5] D. Berbel,[4,5] M. A. Ballesteros,[4] R. Escudero,[7] F. Lopez-Medrano,[8,9] L. Linares,[3,10] O. Len,[11,12] J. T. Silva,[8,9,13] E. Olivez,[14] L. Soldevila,[1] S. Pérez-Recio,[1] L. L. Guillem,[1] D. Camprubí,[1] L. LLadó,[15] A. Manonelles,[16] J. González-Costello,[17] M. A. Domínguez,[2,4,18] M. C. Fariñas,[19] N. Lavid,[20] C. González-Rico,[14] L. García-Cuello,[20] F. Arnaiz de las Revillas,[19] J. Fortún,[7] J. M. Aguado,[8,9] C. Jiménez-Romero,[8,9] M. Bodro,[3,10] M. Almela,[3,10] D. Paredes,[3,10] A. Moreno,[3,10] C. Pérez-Cameo,[10,21] A. Muñoz-Sanz,[15] G. Blanco-Fernández,[22] J. A. Cabo-González,[23] J. L. García-López,[24] E. Nuño,[25] and J. Carratalà[1,2,3]

Mitigating Transplant Infection Risk: Post-transplant Prophylaxis

Part II

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Timeline of Infection after Organ Transplantation



Fishman, Infection in Solid-Organ Transplant Recipients, NEJM 2007

MGH SOT Prophylaxis: ABCs after Transplant

Antivirals

Bactrim (TMP/SMX)

- Covers PCP, toxoplasmosis, bacteria (urinary, Nocardia, respiratory)
- Allergy: atovaquone 1500mg/day or dapsone 100mg/day

Candida/fungal

- Clotrimazole or Nystatin for short time after SOT
  - Lung transplant = itraconazole or voriconazole

Treatment of rejection: resets/prolongs the clock to day 0

Original Clinical Science—General

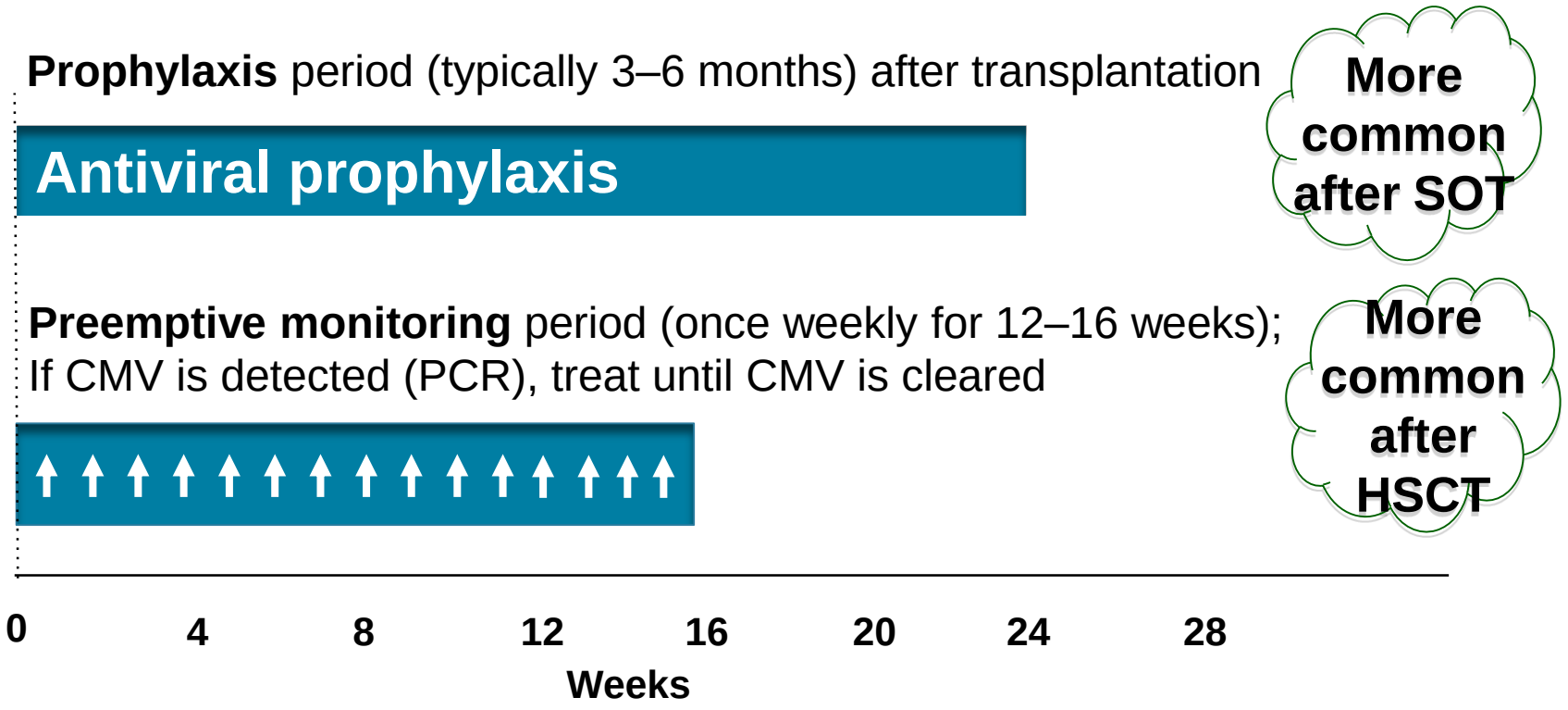
Transplantation ■ June 2018 ■ Volume 102 ■ Number 6

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

Camille N. Kotton, MD,[1] Deepali Kumar, MD,[2] Angela M. Caliendo, MD, PhD,[3] Shirish Huprikar, MD,[4] Sunwen Chou, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] and Atul Humar, MD[7]
on behalf of the The Transplantation Society International CMV Consensus Group

SACHUSETTS
ERAL HOSPITAL
NSPLANT CENTER

CMV: Prophylaxis vs. Preemptive Therapy



"surveillance after prophylaxis" combines both to prevent late CMV

Modified from Humar A, Snydman D; AST Infectious Diseases Community of Practice. *Am J Transplant*. 2009;9 (Suppl 4):S78-S86.

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

MGH Protocol: CMV/Herpes/Varicella Prophylaxis after Renal, Liver, Heart, or Pancreas Transplant

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Induction Agent	Donor CMV Antibody	Recipient CMV Antibody	Prophylaxis	Monitoring with CMV viral load
Thymoglobulin	Positive	Positive	Valganciclovir x 3 months	Monitoring while on prophylaxis only if clinically indicated by symptoms; consider weekly monitoring **after end of prophylaxis** x 8-12 weeks in higher risk patients (CMV D+R-)
	Negative	Positive		
	Positive	Negative	Valganciclovir x **6 months** (plus consider weekly monitoring afterwards x 8-12 weeks in higher risk D+R- on more potent IS)	
	Negative	Negative	Acyclovir, famciclovir, or valacyclovir x 3 months	
Basiliximab OR None	Positive	Positive	Valganciclovir x 3 months	
	Negative	Positive		
	Positive	Negative		
	Negative	Negative	Acyclovir, famciclovir, or valacyclovir x 3 months	

45

CMV Prevention: Approaches & Duration

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

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	

Transplantation ■ June 2018 ■ Volume 102 ■ Number 6

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

TMP-SMX has Broad Coverage

<table>
<tr><th>Gram positive</th><th>Gram negative</th><th>Parasites</th><th>Fungi</th></tr>
<tr><td>MRSA/Staphlyococcus</td><td>E. coli</td><td>Toxoplasma</td><td rowspan="5">PJP</td></tr>
<tr><td>Listeria</td><td>Klebsiella</td><td>Blastocystis hominis</td></tr>
<tr><td>Nocardia</td><td rowspan="4">Moraxella catarrhalis, Shigella, Neisseria gonorrhoeae*, Haemophilus influenzae*, Haemophilus parainfluenzae, Haemophilus ducreyi*, Citrobacter spp., Citrobacter freundii, Klebsiella oxytoca, Enterobacter cloacae, Enterobacter aerogenes, Hafnia alvei, Serratia arcescens, Serratia liquefaciens, other Serratia spp., Proteus mirabilis*, Proteus vulgaris, Morganella morganii*, Providencia rettgeri*, Salmonella typhi, enteritis-inducing salmo- nellae, Shigella spp., Yersinia enterocolitica, other Yersinia spp., Vibrio cholerae, Acinetobacter iwoffi*, Acinetobacter anitratus*, Aeromonas hydrophila, Alcaligenes faecalis.</td><td>Cyclospora</td></tr>
<tr><td>Enterococcus</td><td rowspan="2">I. belli</td></tr>
<tr><td>Strep spp.</td></tr>
</table>

47

The Use of Donor and Recipient Screening for *Toxoplasma* in the Era of Universal Trimethoprim Sulfamethoxazole Prophylaxis

Sita Gourishankar,[1,4] Karen Doucette,[2] Jayne Fenton,[3] Dale Purych,[3] Kinga Kowalewska-Grochowska,[3] and Jutta Preiksaitis[2,3]

Edmonton, Canada

Background. Toxoplasmosis is a serious complication of solid organ transplantation. The highest risk of infection and disease occurs in heart recipients with primary infection transmitted by a seropositive donor to a seronegative recipient (donor-recipient mismatch). Toxoplasmosis has been reported to occur in noncardiac transplant recipients; however, no large studies examining the frequency of such events or the need for serologic screening exist.

Methods. A retrospective cohort study of 1,006 solid organ transplant recipients transplanted in our center between 1984 and 1997 was performed to examine the incidence of *Toxoplasma* seroconversion, reactivation, and clinical toxoplasmosis and to evaluate the impact of trimethoprim sulfamethoxazole (TMP/SMX) prophylaxis on these outcomes.

Results. Pretransplant *Toxoplasma* seroprevalence was 13.4% in donors and 17.8% in recipients. The incidence of *Toxoplasma* donor-recipient mismatch was 9.5% during the 14-year study period, and only 39.1% of mismatched recipients received TMP/SMX prophylaxis. Only four patients seroconverted, of whom two had received prophylaxis. There were no cases of clinical disease; either primary or reactivation.

Conclusions. We therefore conclude that in transplant centers with low *Toxoplasma* seroprevalence, routine screening for *Toxoplasma* in solid organ donors and recipients is not necessary, particularly in the era of routine TMP/SMX prophylaxis.

Keywords: Solid organ transplantation, Toxoplasmosis, Prophylaxis.

(*Transplantation* 2008;85: 980–985)

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

MGH Toxoplasmosis Protocol-Duration for Transplant Recipients

Duration of therapy based on serologic combinations: HEART transplant		
Serologic combination	Risk group	Duration of therapy
D+R-	Highest risk	Lifetime, if possible (otherwise discuss with infectious disease)
R+ (D+ or D-)	Moderate risk	Can stop at one year, or when on low-dose immunosuppression (i.e. prednisone 5 mg a day), whichever is later/longer. Restart during intensification of immunosuppression (i.e. pulse dose steroids, ATG, or Rx of AMR) for same period as after transplant.
D-R-	Lowest risk	

Kidney: 6 months
Liver: 1 year
Lung, pancreas, composite tissue: lifetime

EBV: Whom to Monitor after Transplant? (Guidelines)

- Monitoring of EBV DNAemia should be useful for **EBV D+/R-** SOT recipients (A-II) and should be considered in EBV seropositive recipients of lung and intestinal transplants (BIII).

- Universal monitoring of EBV DNAemia is not recommended in SOT recipients (C-III).

- In chronic/persistent high EBV load patients, rise in EBV load could be more informative for PTLD risk (C-III).

- For SOT patients with significantly increasing EBV loads (usually more than 10-fold or >1 log10 cp/mL), regardless of the EBV-serostatus, a careful clinical and radiological examination using computer tomography and/or PET-CT should be performed to search for lymphadenopathy, mass lesions and other signs of PTLD (B-III).

San Juan et al, CMI, Sept 2014 (European guidelines)

- We recommend EBV viral load surveillance and preemptive interventions in patients who are **EBV-seronegative** pre-transplant (weak/low).
- In patients who receive seropositive donor organs, **monitoring should occur weekly to biweekly, when possible over the first post-transplant year** until EBV DNAemia is detected.
- When this occurs, monitoring should occur weekly during initial acute phase of infection, then less frequently by increasing increments until “set point” is achieved (weak/very low).
- Less frequent initial monitoring (monthly) for community- acquired infection should be considered in seronegative patients who receive seronegative donor organs.

Allen and Preiksaitis(2019) PTLD, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

MGH EBV Protocol

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Screening Population:

Any EBV seronegative recipients

Any mismatched transplant settings (D+/R- or D-/R+)

Recommend:

EBV PCR every 2-3 months for months 6-12 post transplant (longer if trending positive test results).

If positive, consider reducing immunosuppression (especially if viral load is high and/or steadily rising) vs switch to mTor.

Very high EBV DNA titers and/or rapidly increasing levels should prompt CT imaging to assess for adenopathy and mass lesions, including those involving the allograft.

In certain situations, pre-emptive rituximab may be considered in consultation with hematology/oncology

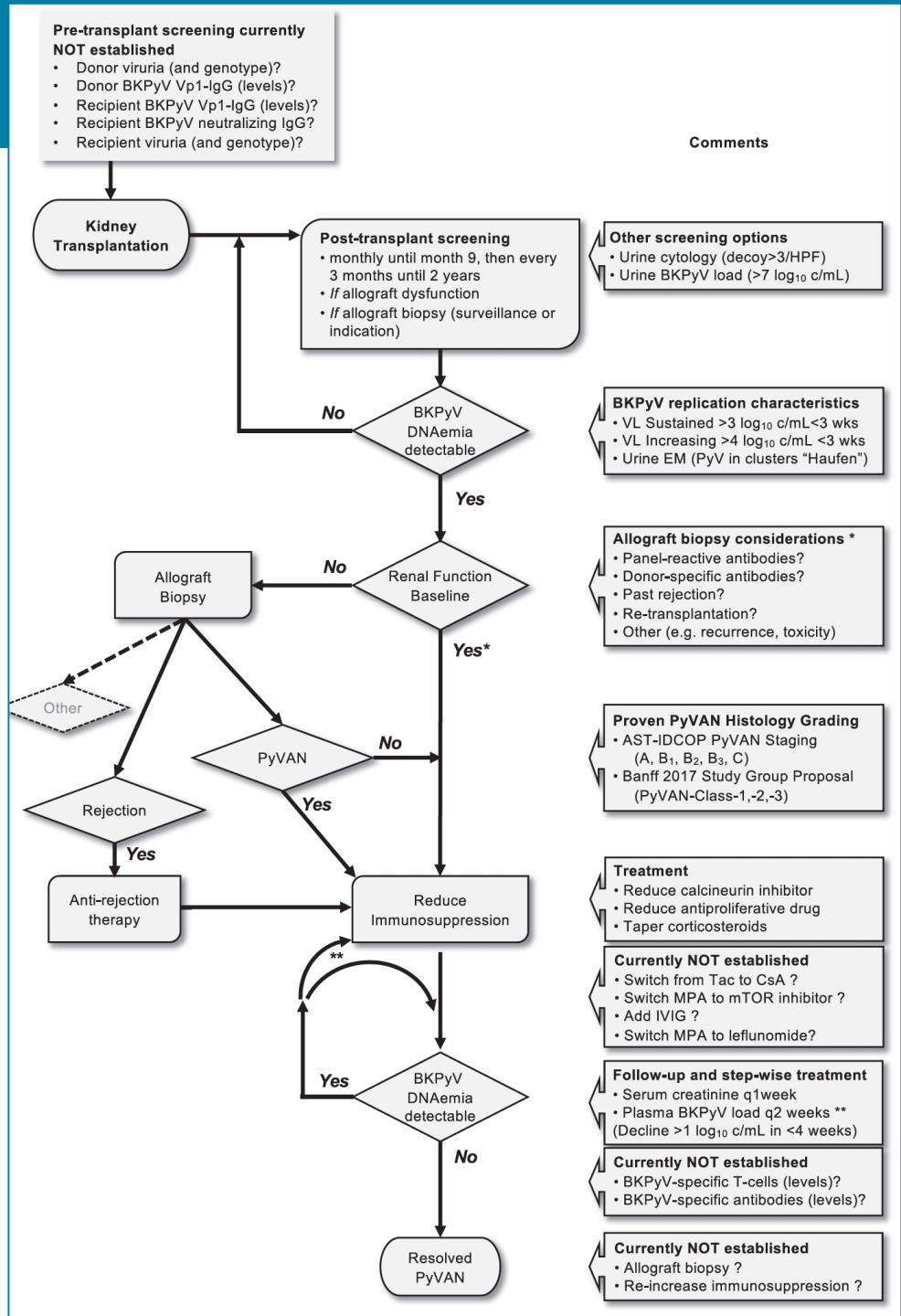
Received: 11 February 2019 | Accepted: 26 February 2019
DOI: 10.1111/ctr.13528

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION

BK polyomavirus in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Hans H. Hirsch[1,2] | Parmjeet S. Randhawa[3,4] | on behalf of AST Infectious Diseases Community of Practice



MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

MGH: HBV Prophylaxis in Transplant Recipients

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Liver

Donor	Recipient	Situation	Post-Transplant Management
Any	DNA (+) HBsAg (+) Anti-HBs (+/-) Anti-HBc total (+)	High risk HBV recipient	1) NRTI indefinitely 2) HBIG 10,000 IU IV during the anhepatic phase and daily for 5-7 days 3) Monthly IM HBIG 4) Surveillance: HBV DNA and HBsAg every 3 months x1 year then every 6 months indefinitely
Any	DNA (-) HBsAg (+) Anti-HBs (+/-) Anti-HBc (+)	Low risk HBV recipient	1) NRTI indefinitely 2) HBIG 10,000 IU IV during anhepatic phase 4) Surveillance: HBV DNA and HBsAg every 3 months x1 year then every 6 months indefinitely
DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (-)	DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (+)	Core positive recipient	Surveillance: HBV DNA every 3 months x1 year
DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (+)	DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (+/-)	Core positive donor	1) NRTI indefinitely 2) Surveillance: HBV DNA every 3 months x1 year then every 6 months indefinitely
DNA (+) or HBsAg (+) Anti-HBs (+/-) Anti-HBc (+/-)	DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (+/-)	HBsAg positive or DNA positive donor (not currently accepted)	1) NRTI indefinitely 2) HBIG if recipient anti-HBs < 100 IU/L: 10,000 IU IV during anhepatic phase and consider daily for 5-7 days 3) Surveillance: HBV DNA every 3 months x1 year then every 6 months indefinitely

Non-Liver SOT

Donor	Recipient	Situation	Post-Transplant Management
DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (-)	DNA (+/-) HBsAg (+) Anti-HBs (+/-) Anti-HBc (+)	HBV infected recipient	1) NRTI indefinitely 2) Surveillance: HBV DNA every 3 months x1 year then every 6 months indefinitely
DNA (-) HBsAg (-) Anti-HBs (+/-) Anit-HBc (-)	DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (+)	Core positive recipient	Surveillance: HBV DNA every 3 months x1 year
DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (+)	HBV DNA (-) HBsAg (-) Anti-HBs (+) Anti-HBc (+/-)	Core positive donor; immune recipient	Surveillance: HBV DNA every 3 months x1 year
DNA (-) HBsAg (-) Anti-HBs (+/-) Anti-HBc (+)	HBV DNA (-) HBsAg (-) Anti-HBs (-) Anti-HBc (+/-)	Core positive donor; non-immune recipient	Surveillance: HBV DNA every 3 months x1 year (Optional: NRTI x1 year)
DNA (+) or HBsAg (+) Anti-HBs (+/-) Anti-HBc (+/-)	Any	HBsAg positive or DNA positive donor (not currently accepted)	1) NRTI indefinitely 2) HBIG if recipient anti-HBs < 100 IU/L: 10,000 IU IV intra-op and daily for 5-7 days 3) Surveillance: HBV DNA and HBsAg every 3 months x1 year then every 6 months indefinitely

MGH: HBV Prophylaxis in Transplant Recipients

Selection of Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI)

- Entecavir (Baraclude) is the preferred therapy due to risk of renal insufficiency with tenofovir – either tenofovir disoproxil fumarate (TDF, Viread) or tenofovir alafenamide (TAF, Vemlidy).
- If the recipient is lamivudine-experienced, tenofovir should be used due to the high rate of entecavir resistance in lamivudine-experienced patients.
- If the patient is on tenofovir or entecavir prior to transplantation and has experienced effective HBV suppression, the pre-transplant antiviral agent should be continued after transplantation
- TAF is preferred over TDF due to a decreased risk of renal and bone toxicity with TAF.
- Lamivudine has a high rate of viral resistance and should generally be avoided. However, it can be considered in select low-risk cases (e.g. core positive non-liver donor to non-immune recipient) due to its lower cost.

The measles exposure phone call: what to do

Most of our transplant recipients have measles IgG result from their pretransplant evaluation. If +, they are protected.

- Alternative: document receipt of two vaccines
- Most born pre-1957 are positive (natural disease)

They should not receive the live viral measles or MMR vaccine after transplant

- Could potentially cause disease (i.e. encephalitis)

Family members can & should get vaccine

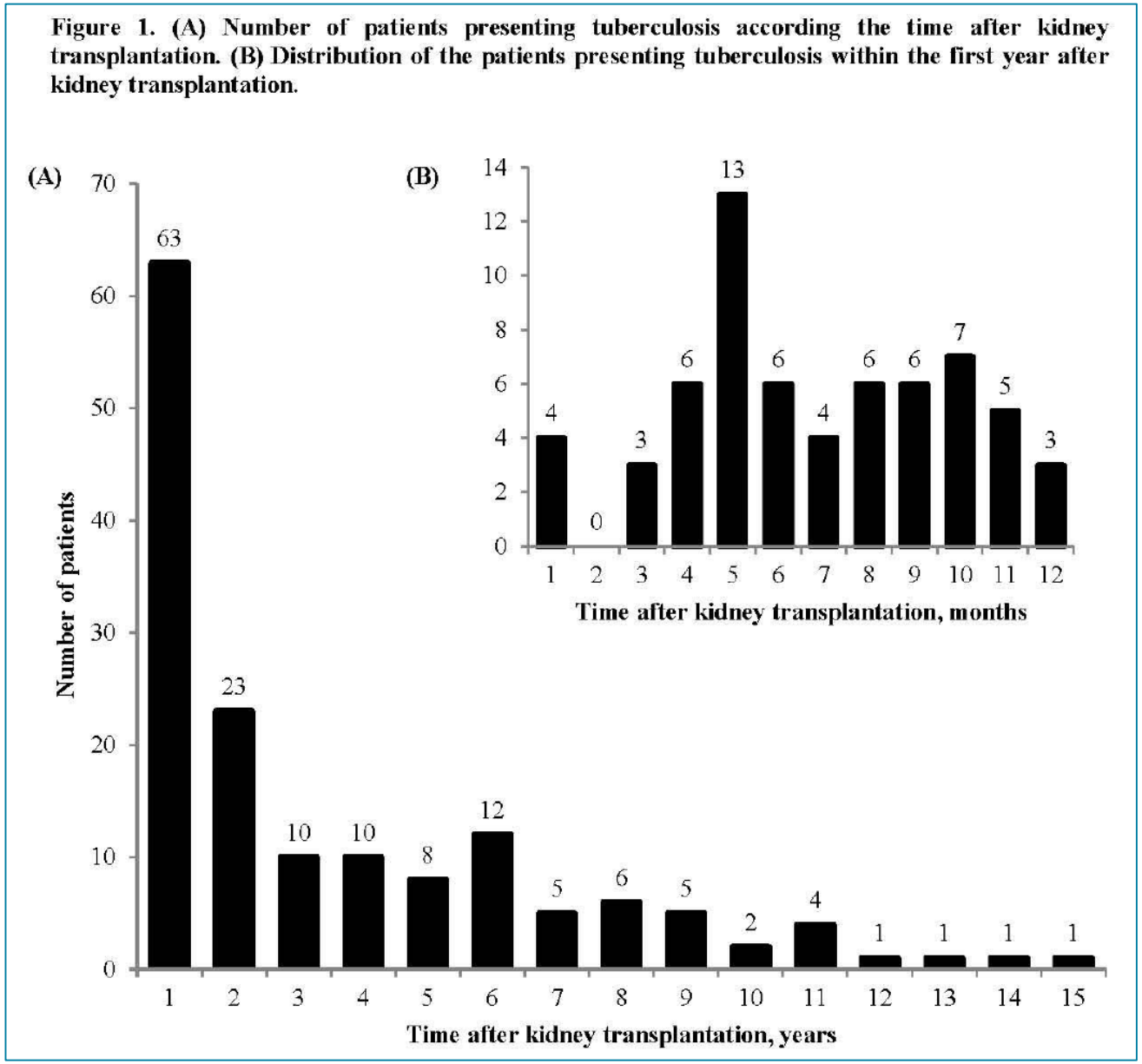
For non-immune transplant recipients (or those with unknown status) with true potential exposure, consider prophylaxis:

- Gammaglobulin (~8 IM injections, 0.5 mL/kg (maximum 15 mL)
- IVIG
- No antiviral therapy available

Infection control!! No clinic visits. Inpatient precautions.

Tuberculosis

Influence of epidemiology, immunosuppressive regimens, clinical presentation, and treatment on kidney transplant outcomes of patients diagnosed with TB: A retrospective cohort analysis (Brazil) Viana et al AJT 2019



- "KT was performed on 11,453 patients, and followed for 1989 (IQR 932-3632) days.
- Among these, 152 patients were diagnosed with TB (1.32%).
- Median time from KT to TB was 18.8 (IQR 7.2-60) months, with 59% of patients diagnosed after the first year."

Received: 10 February 2019 | Accepted: 26 February 2019
DOI: 10.1111/ctr.13519

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION

Strategies for safe living following solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Robin K. Avery[1] | Marian G. Michaels[2] | on behalf of the AST Infectious Diseases Community of Practice

Highlights:

- Infections from water and food sources
- Prevention of respiratory viruses, other community infections
- Animal exposures
- Cannabis use
- Sexual exposures
- Travel medicine

Summary

- Good screening of donor and recipient results in better transplant outcomes
  - General screening for all, plus additional tailored to the individual
- Pre-transplant vaccination is a valuable opportunity
- Prophylaxis during/after transplant is imperative to mitigate infection risk
- All screening and prophylaxis needed to be tailored to local transplant center and individuals

Thank You

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER