Brigham and Women's Hospital
Founding Member, Mass General Brigham

Infections in Transplant Recipients

Barbra M. Blair, MD
Division of Infectious Diseases
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School

bblair@mgb.org

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Barbra M. Blair, MD

- MD: University of Chicago, Pritzker School of Medicine
- Medicine Residency: Beth Israel Deaconess Medical Center (BIDMC)
- Infectious Diseases Fellowship: BIDMC
- Assistant Professor of Medicine, HMS
- Co-Director, MGH COPAT Program
- Clinical Interests: Infections in ICH, Vaccine preventable infections, Orthopedic infections; Complex outpatient antimicrobial therapy

DISCLOSURES

None

OBJECTIVES

- Review Common infections & timeframes after kidney transplant (KT) including Donor derived infections
- Explore prevention & treatment of CMV infections
- Review UTI and recurrent UTI in KT

Risk of Infection & Timeline

- Epidemiologic Risk Factors
  - Starts with pre-transplant evaluation
  - Latent infections
  - Vaccination status
  - Previous infection/colonization with bacteria, fungus

- “Net State of immunosuppression”
  - Pretransplant IS
  - Induction IS
  - Medical Comorbidities

Fishman JA. *N Engl J Med*. 2007;357:2601-14.

Risk of Infection – Pre-transplant Evaluation

- Medical & Travel History
  - Recurrent infections (eg UTI)
  - Tuberculosis
  - Strongyloides
  - Chagas
- Household Contacts
- Occupational Exposures
  - Opportunity for counselling
- Hobbies
  - Opportunity for counselling
- Pre-transplant Serologies
  - Latent viruses; MMR; TB; Varicella; HIV; HBV; HCV; STIs
- Vaccination status (+ HPV, Meningitis)
- Drug allergies (Beta-lactams, Sulfa)

Fishman JA. *N Engl J Med*. 2007;357:2601-14.

Case Presentation #1

- 62yo female with DM, HTN c/b ESRD who underwent DDKT with uncomplicated postoperative course
- Taking trimethoprim/sulfamethoxazole, valganciclovir and triple immunosuppression
- Contacts transplant team 2 weeks post transplant with fever, tenderness over graft surgical site

Case Presentation #1

Which is the most likely source of her fever?

A. C. diff colitis
B. Acute diverticulitis
C. Infected perinephric hematoma
D. BK nephropathy

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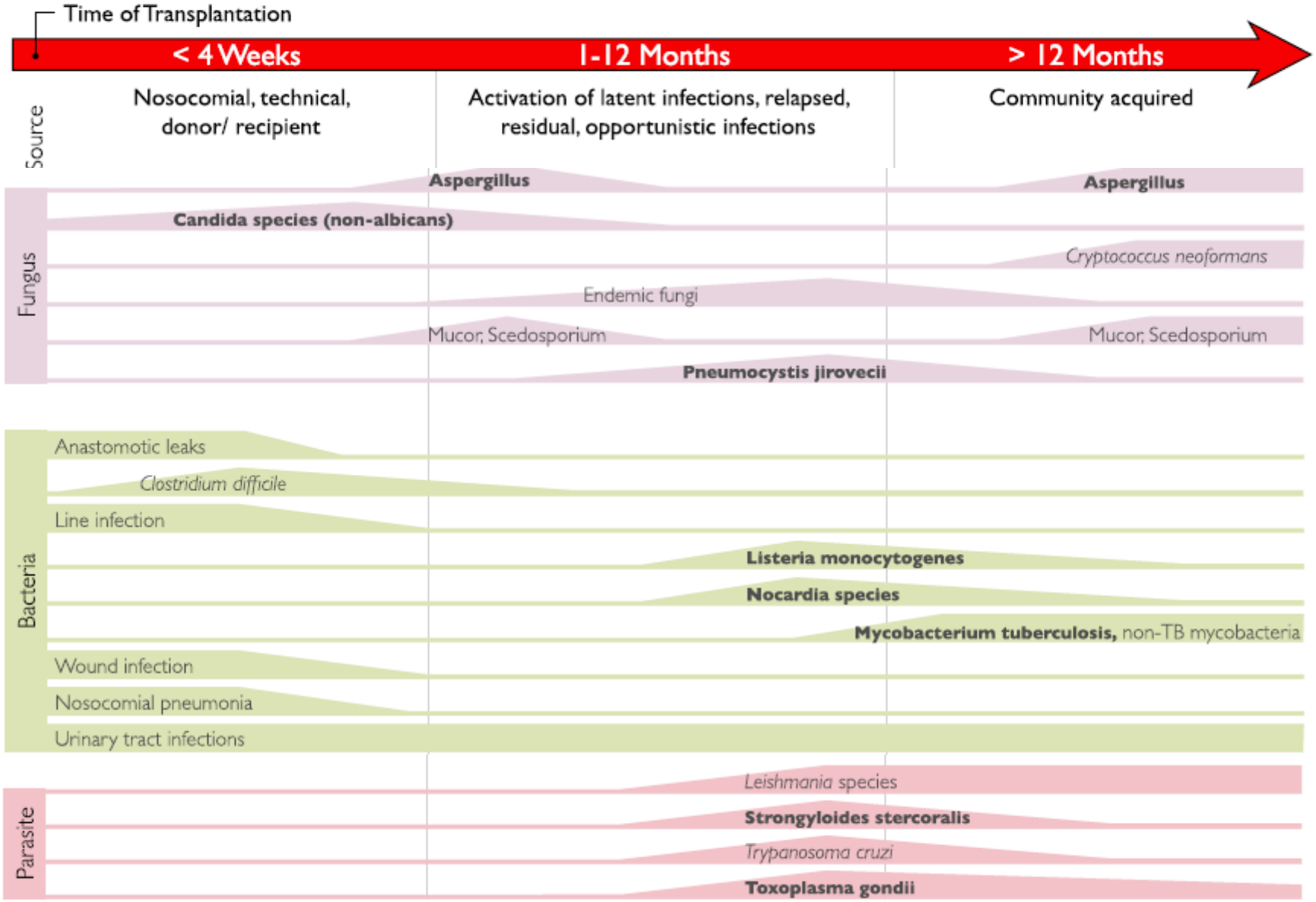
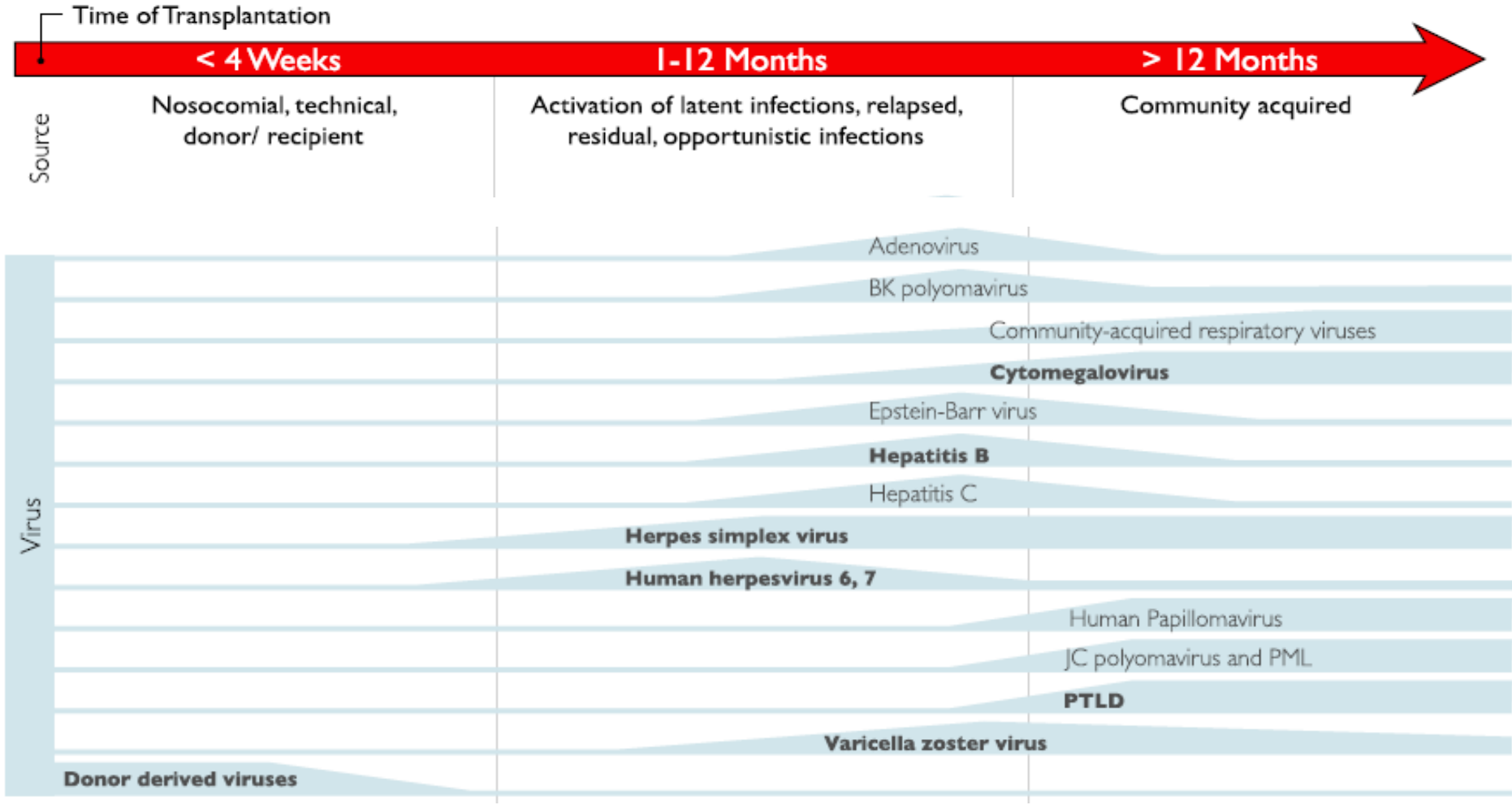
Timeline of Common Post-Transplant Infections



Fishman JA. *N Engl J Med*. 2007;357:2601-14.

Timeline of Common Post-Transplant Infections



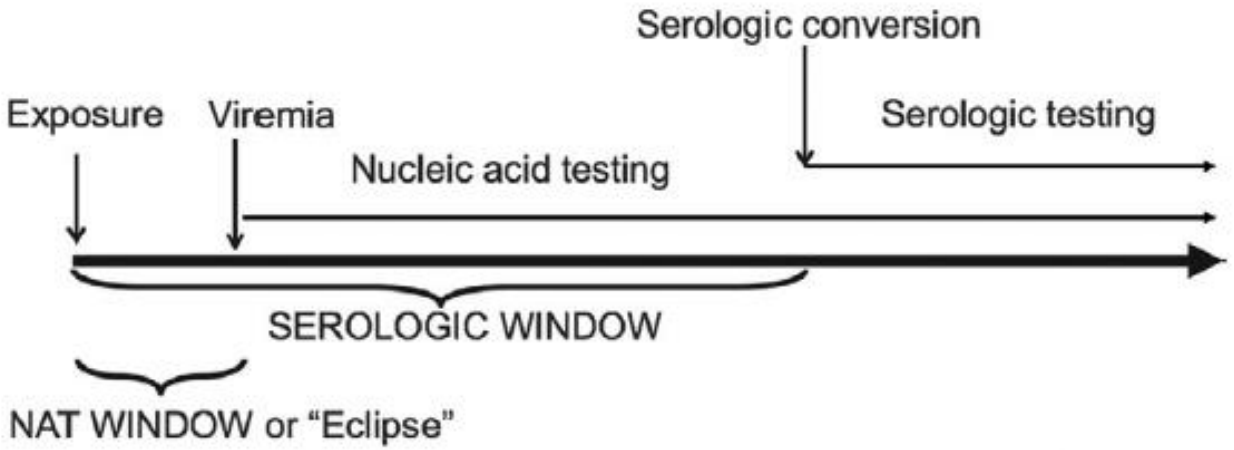
Fishman JA. *N Engl J Med*. 2007;357:2601-14.

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

Wolfe CR, Ison MG. *Clin Transplant*. 2019;33(9):e13547. doi:10.1111/ctr.13547

Potential donor-derived disease transmission –Risk Criteria



Virus	Serology	NAT
HIV	22 days	5-10 days
HBV	38 - 50 days	20 – 26 days
HCV	38 - 94 days	6 - 9 days

- Pre-transplant testing For HIV, HCV, HBV –ALL recipients during hospitalization for transplant
- Post-transplant testing at 4-6 weeks post-transplant: HIV, HBV, HCV NAT
- Risk for undetected infection (from recent exposure to day of negative NAT) is fewer than one per 1 million donors for:
  - HIV after 14 days
  - HBV after 35 days,
  - HCV after 7 days

Wolfe CR, Ison MG. *Clin Transplant*. 2019;33(9):e13547. doi:10.1111/ctr.13547
Grossi PA, Wolfe C and Peghin M; 2024.Transpl Int 37:12803. doi: 10.3389/ti.2024.12803
Jones JM, Kracalik I, Levi ME, et al., 2020. MMWR Recomm Rep 2020;69(No. RR-4):1–16.

Potential donor-derived disease transmission

- 5%–7% of donors have bacteremia at the time of procurement
  - Risk to recipient is low mainly due to microorganisms resistant to perioperative antibiotics
  - Donors with positive blood cultures
    - Used if they have received appropriate antimicrobials for at least 24–48 h

- Non-bacteremic localized infections from other sites only require antibiotic treatment if transmission in the transplanted organ

Wolfe CR, Ison MG. *Clin Transplant*. 2019;33(9):e13547. doi:10.1111/ctr.13547
Grossi PA, Wolfe C and Peghin M; 2024.Transpl Int 37:12803. doi: 10.3389/ti.2024.12803

Potential donor-derived disease transmission

- Recipients of organs from donors with MDR-GNB
  - Early microbiological diagnosis
  - Peri-transplant targeted antibiotic therapy
  - Inter-institutional communication and prolonged treatment after transplantation

- Untreated candidemia is not recommended
  - Can be accepted only after 24–48 h of effective antifungal therapy & recipients should receive a minimum 14-days of antifungals
  - Candida auris colonization?

Wolfe CR, Ison MG. *Clin Transplant*. 2019;33(9):e13547. doi:10.1111/ctr.13547
Grossi PA, Wolfe C and Peghin M; 2024.Transpl Int 37:12803. doi: 10.3389/ti.2024.12803

Case Presentation #2

42 yo LURT 2015 CMV D-/R-, EBV D+/R+; h/o norovirus last year and c. diff last year

Brother (with whom she lives) sick with “mono” 2 weeks before presentation

Patient develops fatigue, myalgias, fever, followed eventually by watery diarrhea, & headache

Labs notable for WBC 4.9 (8-10) Plts 120 (250’s); Cr 2.9 (1.5-1.7); elevated AST/ALT 60s-70s; Norovirus PCR +

Case Presentation #2

What do you think is going on here?

A. The patient has norovirus alone
B. The patient has c. diff and norovirus
C. The patient has acute EBV infection
D. The patient has acute CMV & norovirus (infection/colonization)

Case Presentation #2

What do you think is going on here?

A. The patient has norovirus alone
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D. The patient has acute CMV & norovirus (infection/colonization)

Cytomegalovirus in Kidney Transplant

- Donor/Recipient status predicts risk
  - High: D+/R-; Mod: D+/R+ & D-/R+; Low: D-/R-
  - Confirm negative recipient at time of transplant

Comparison of prophylaxis versus preemptive therapy

	Prophylaxis VGCV	Prophylaxis LET[a]	Preemptive therapy
Early CMV DNAemia/infection	Rare	Rare	Common
Prevention of CMV disease	Good efficacy	Good efficacy	Good efficacy
Late CMV (infection/disease)	Common	Common	Rare
Resistance to the agent being used	Uncommon	Rare	Uncommon (with weekly testing)
Ease of implementation	Relatively easy	Relatively easy	More difficult
Prevention of other herpes viruses	Prevents HSV, VZV	Does not prevent	Does not prevent
Other opportunistic infections	May prevent	Unknown	Unknown
Costs	Cost of drug	Cost of drug is significant[b]	Cost of monitoring
Safety	Myelosuppression	Drug interactions	Less drug toxicity
Prevention of rejection	May prevent	Unknown	Unknown
Graft survival	May improve	Unknown	May improve

Kotton CN, Kumar D, Manuel O, et al. *Transplantation*. 2025;109(7):1066-1110.

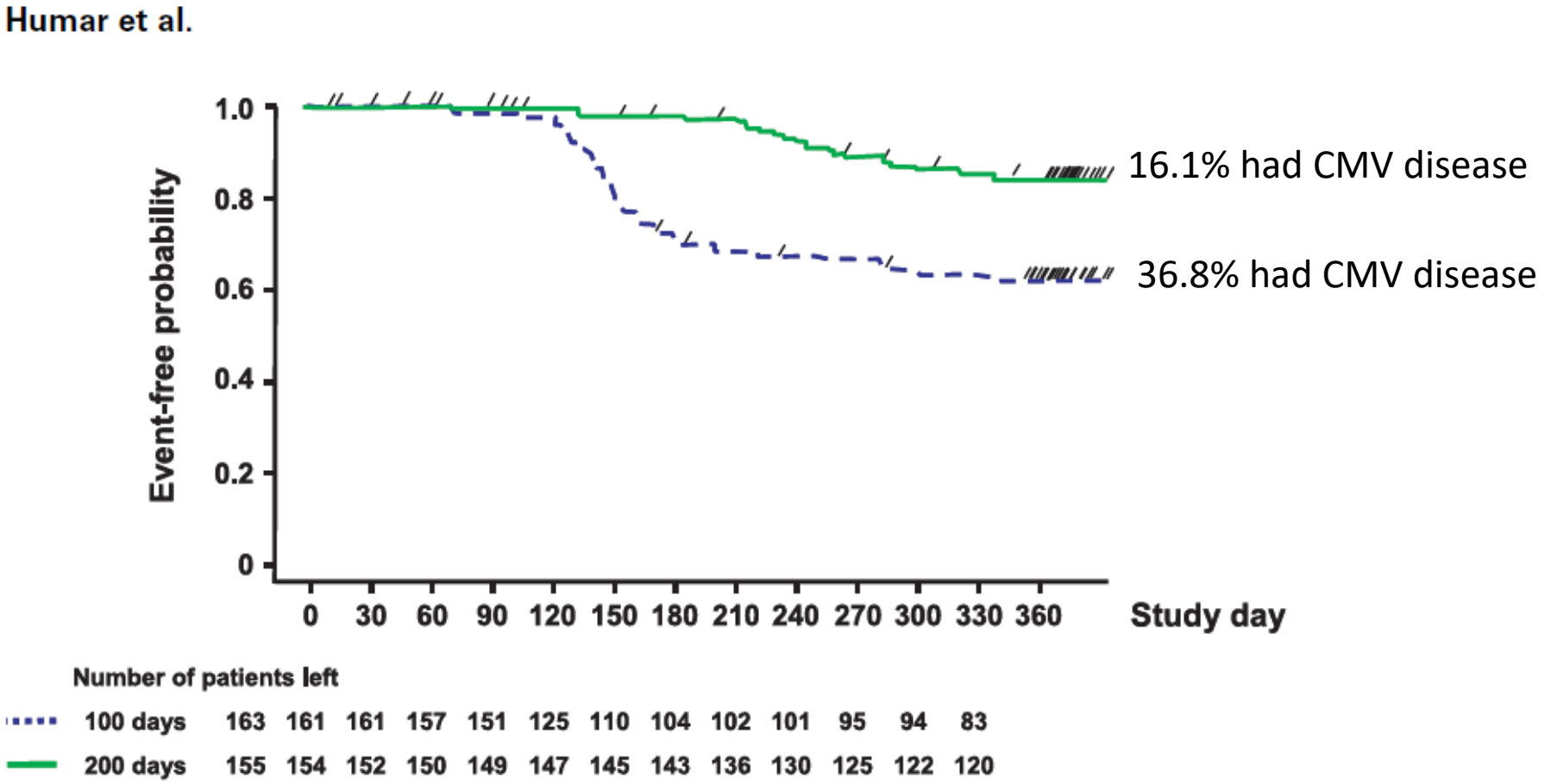
Duration of Prophylaxis: The Impact Trial

- Study design: prospective, randomized, double-blind study
- Purpose: To compare safety and efficacy of 200 days valganciclovir vs. 100 days valganciclovir in D+/R- renal transplant recipients (N=326)
- 3 months valcyte + 3 months placebo vs. 6 months valcyte 900 mg /day dose (according to renal function)
- Primary outcome was development of CMV disease within 52 weeks

Humar A, et al. Am J Transplant. 2010 May;10(5):1228-37.

The Impact Trial: Results

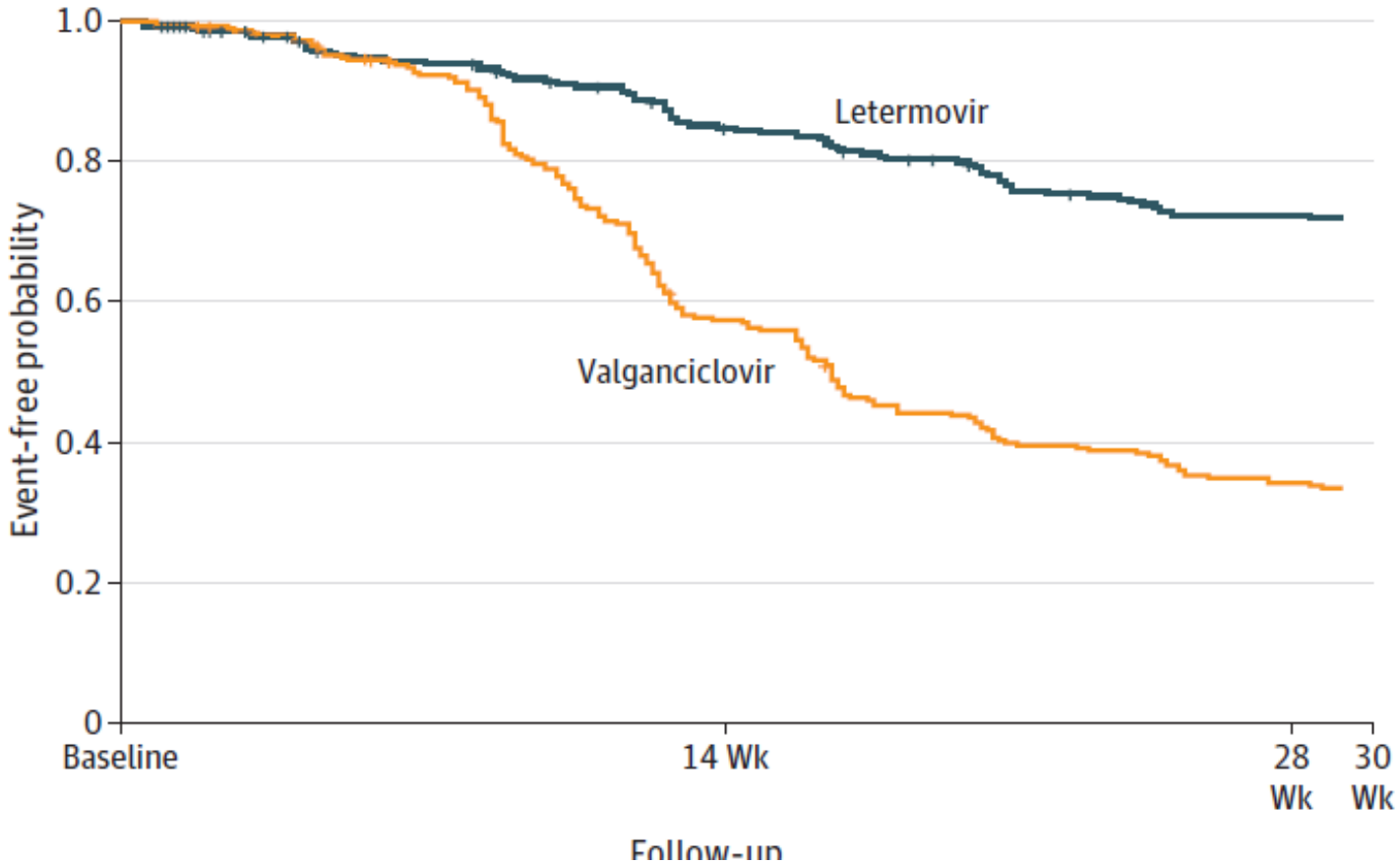
Kaplan–Meier plot of time to cytomegalovirus disease up to month 12 post transplant.



Humar A, et al. Am J Transplant. 2010 May;10(5):1228-37.

Letermovir Prevention of Cytomegalovirus in Kidney Transplant

- Letermovir non-inferior to valganciclovir
- 11.3% vs 37.0% for leukopenia and 2.7% vs 16.5% for neutropenia



Limaye AP, Budde K, Humar A, et al.. *JAMA*. 2023;330(1):33-42.
Kotton CN, Kumar D, Manuel O, et al. *Transplantation*. 2025;109(7):1066-1110.

Pearls of Prevention/Treatment of Cytomegalovirus in KT

- Ganciclovir/Valganciclovir side effects
  - Dose-dependent leukopenia/neutropenia common after prolonged dosing
  - With leukopenia due to valganciclovir:
    - Do not dose reduce or stop
    - Adjust dose only for changes in renal function
- CMV treatment/prevention with sub-optimally dosed valganciclovir can lead to resistance
  - Parenteral treatment options for ganciclovir-resistant CMV: parenteral medications (foscarnet and cidofovir)
  - Oral option/less toxic: maribavir

Kotton CN, Kumar D, Manuel O, et al. *Transplantation*. 2025;109(7):1066-1110.
Limaye AP, Budde K, Humar A, et al.. *JAMA*. 2023;330(1):33-42.

Treatment of Refractory/Resistant Cytomegalovirus-Maribavir

- Mechanism: targets viral kinase (UL97)
- Phase 3 treatment trial maribavir 400 BID vs. standard care for resistant/refractory CMV in SOT and HCT recipients→ 55.7% vs. 23.9% cleared CMV viremia by 8 weeks
- FDA approved for treatment of resistant/refractory CMV in November 2021
- No clinical efficacy against other herpes viruses
- Oral formulation
- Dysgeusia
- May need to adjust tacrolimus dosing due to minor drug-drug interaction
- Poor CNS penetration so not a good choice for systemic treatment of retinitis
- Case reports describe treatment failures

Kotton CN, Kumar D, Manuel O, et al. *Transplantation*. 2025;109(7):1066-1110.
Avery RK, Alain S, Alexander BD, et al. Clin Infect Dis. 2023 Feb 8;76(3):560.
Razonable RR. *Drug Des Devel Ther*. 2024;18:3987-4001.

Case Presentation #3

- 48yo man with congenital bladder dysfunction c/b CKD due to reflux nephropathy and h/o childhood colonic bladder augmentation with native ureter reimplantation s/p LURT in 2019

- Significant PMH: Insulin dependent Diabetes; Obesity; BPH
- Works as a correctional officer

- About 18 months post transplant, admitted with sepsis due to transplant pyelonephritis due to *E. coli* after having 2 previous episodes of acute cystitis

- Graft function – excellent with Cr 0.8-1.2

Case Presentation #3

- Urinary retention found – Started on CIC
- Job prevented frequent sufficient bathroom breaks
- Rotating antimicrobials started
  - Stopped after weight loss with euglycemia off meds and retirement
- Successful for 4 years

- Recurrent UTIs (different each time bacteria) x 3 in 2 months
- Repeat evaluation: Mucinous adenocarcinoma found in colonic bladder augmentation-now s/p resection

Case Presentation #3

Why are his UTIs back despite antibiotic prophylaxis?

1. He isn’t really taking the antibiotics
2. He has a prostate infection
3. There is a new anatomic issue
4. He really isn’t performing CIC

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1. He isn't really taking the antibiotics
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Repeat evaluation: Mucinous adenocarcinoma found in colonic bladder augmentation

Case Presentation #4

- 54 yo woman with Type 1 DM since age of 5 who underwent LRKT in 2018 and Pancreas transplant in 2020
- Significant PMH: Peripheral artery disease c/b diabetic foot & multiple amputations; CVA
- Hormone replacement Rx (after menopause) with transdermal estrogen and oral progesterone discontinued due to CVA risk
- Graft function excellent: Cr 0.8; No diabetes
- Over the next 9 months, patient experiences acute cystitis x 4 with *E. coli, Klebsiella, Citrobacter* and *Enterococcus*

Case Presentation #4

What is the *best* management of this patient?

1. Rotating daily antibiotic suppression/prophylaxis
2. Vaginal estrogens
3. Increased hydration
4. Daily methenamine

Case Presentation #4

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Case Presentation #4

- Evaluations by Gyn, Heme-Onc and Neurology
- Vaginal estrogens started
- UTIs resolved

Antimicrobial prophylaxis

- Trimethoprim-sulfamethoxazole (TMP/SMX) as PJP ppx can also prevent UTI
- Metanalysis 2011
  - 6 studies
  - Graft loss/function = Primary
  - Infection = Secondary
  - 3 studies: Antibiotic vs Placebo
  - 2 studies: Antibiotic vs TMP/SMX or placebo
  - 1 study: Ciprofloxacin vs Placebo

Goldman JD, Julian K. *Clin Transplant*.2019;33:e13507. https ://doi.org/10.1111/ctr.13507
Green H, Rahamimov R, et al. *Transpl Infect Dis*. 2011;13(5):441-447. http://doi:10.1111/j.1399-3062.2011.00644.x

Antimicrobial prophylaxis

- No difference in graft loss
- No difference in all cause mortality
- Reduced the risk for sepsis due to bacteremia by 87%
- Reduced risk for developing bacteriuria by 60%
- Two studies comparing TMP/SMX to placebo: More UTIs in the treatment group were due to TMP/SMX-resistant bacteria (62% vs. 18%, p<0.001)

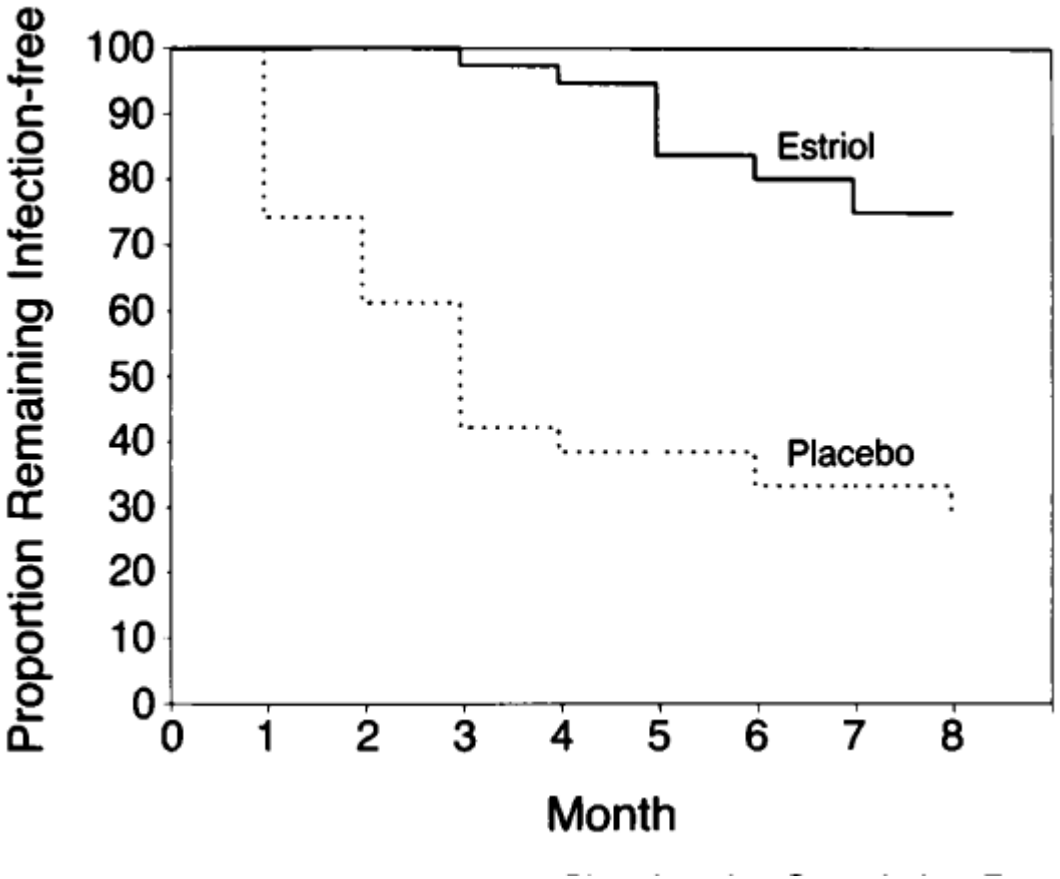
Goldman JD, Julian K. *Clin Transplant*.2019;33:e13507. https ://doi.org/10.1111/ctr.13507
Green H, Rahamimov R, et al. *Transpl Infect Dis*. 2011;13(5):441-447. http://doi:10.1111/j.1399-3062.2011.00644.x

Evaluation of recurrent UTI

Reference	UTI rate	Recurrent UTI rate[e]	Study period	No. of patients	Patients with UTI	% Female	Age (year)	Follow-up (month)	Location
54,a	-	36%	2001-2011	99	-	69%	53.3	54	Taiwan
42,a	-	72%	2010-2011	154	-	48%	51.3	12	Portugal
134,a	-	18%	1976-1994	307	-	87.5%	46	180	UK
22	7%	-	1985-1999	954	68	24%	32.8	-	Turkey
46	13%[g]	32%[c]	1987-1999	1387	180	30%	44	>12	France
43	15%	46%	2000-2010	344	50	72%	41.1	36	Korea
135,h	15%	15%	2003-2005	2174	150	33%[b]	50[b]	24	Spain
136	16%	-	2005-2007	158	25	31%	47	6	USA
39	17%[g]	23%[c]	1994-2004	1022	169	19%	34	>6	India
52	18%	-	2002-2004	189	34	40%	49.7	36	Spain
17	20%	-	2005-2007	343	69	44%	52	12	Netherlands
9	21%	-	2005-2010	1166	247	39%	53	60	USA
137	23%	-	2005-2013	9038	2100	39%	51	24	USA
75,h	24%	52%	2001-2004	127	31	40%	47.1	20	USA
48	28%	-	2012-2013	417	115	37%	55	12	Netherlands
138,f	31%	4%	2001-2007	598	185	35%	54	12	Austria
11	32%	-	2000-2011	60702	19213	40%	-	54	USA
66	33%	-	2009-2010	236	77	39%	52	12	USA
12	34%	-	2013-2014	120	41	38%	47.2	1	Poland
25	34%	14%	2007-2009	301	101	41%	56.7	10	USA
50,h	34%	44%	2010	105	36	36%	47.9	12	Brazil
139	36%	-	2003-2007	176	63	46%	37	12	Mexico
140,h	37%	37%	1999-2001	52	19	42%	11-47	1	Mexico
108	41%	36%	1999-2006	136	56	35%	31	38	Turkey
7	43%	64%[c]	1996-2002	500	213	34%	44	42	USA
141	43%	-	1996-2000	28924	12508	40%	45.4	36	USA
36,h	45%	12%	2000-2001	163	73	40%	38	24	Brazil
142	55%	51%	2009	89	49	42%	48	12	Poland
51,d	61%	47%	1998-2008	122	74	38%	43.8	68	Greece
49	75%	-	2000-2005	172	133	32%	46.5	22	France
23	80%[g]	-	1972-1991	576	464	45%	37.8	>60	Germany

Hollyer I, Ison MG. *Transpl Infect Dis*. 2018;20:e12828. https://doi.org/10.1111/tid.12828

Vaginal Estrogens



At 4 month –

Probability of being infection free:

0.95 estradiol
0.3 placebo

Raz R, Stamm WE. *N Engl J Med*. 1993;329(11):753-756. doi:10.1056/NEJM199309093291102
Rahn DD, Carberry C, Sanses TV, et al*Obstet Gynecol*. 2014;124(6):1147-1156. doi:10.1097/AOG.0000000000000526

Methenamine – Kidney Transplant

- Single center, retrospective; 2006-2017
- Adult renal transplant recipients
- 1 gram daily with Vitamin C
- 38 patients (Median Age: 50; 84% female)
- Followed for a median of 314 days

	Pre-methenamine	Post-methenamine	*P*-value
UTI rate, n/1000 follow-up days	9.16	5.01	**0.0001**
Length of antibiotic therapy to treat UTI, n/1000 follow-up days	152	88	**0.0022**
Length of antibiotic suppressive therapy, n/1000 follow-up days	13.7	0	**<0.0001**
Length of therapy for non-UTI antibiotics, n/1000 follow-up days	69	83	0.8655
TMP-SMX prophylaxis length of therapy, n/1000 follow-up days	849	895	0.7080
Hospitalizations due to UTI, n/1000 follow-up days	2.64	1.07	**0.0456**
Hospitalizations (other cause), n/1000 patient days	3.72	2.03	0.1244

Hollyer I, Varias F, Ho B, Ison MG.*Transpl Infect Dis*. 2019;21:e13063. https://doi.org/10.1111/tid.13063

Methenamine – Kidney Transplant

	Pre-methenamine	Post-methenamine	*P*-value
Creatinine, median	1.24	1.21	0.8723
GFR mL/min/1.73 m^2, median	50.5	51.0	0.9942
Urinary pH, median	5.50	6.00	0.3203
MDR organisms isolated, % of positive bacteria cultures	0.08	0.07	0.6145

Hollyer I, Varias F, Ho B, Ison MG.*Transpl Infect Dis*. 2019;21:e13063. https://doi.org/10.1111/tid.13063

TAKE HOME MESSAGES

- Infections in KT are common
- KT recipient infection: Comorbidities, time from transplant and status of immunosuppression are key
- Donor Derived Infections are rare:donor status testing/infections can help prevent transmission
- CMV is the troll of transplant
  - Prophylaxis works
- UTIs in KT are very common
  - PJP ppx with Trimethoprim/Sulfamethoxazole can help prevent early
  - Can consider other agents
- Recurrent UTIs happen
  - Prevention strategies-no one size fits all

Contact: bblair@mgb.org

SELCTED REFERENCES

1. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med*. 2007;357(25):2601-2614. doi:10.1056/NEJMra064928

2. Wolfe CR, Ison MG; AST Infectious Diseases Community of Practice. Donor-derived infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13547. doi:10.1111/ctr.13547

3. Kotton CN, Kumar D, Manuel O, et al. The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation. *Transplantation*. 2025;109(7):1066-1110. doi:10.1097/TP.0000000000005374