SUPPLEMENTAL TABLES

Table S1. GRADE strength of recommendations and quality of the evidence[4-10]

Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable effects	Methodological quality of supporting evidence (examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Strong recommendation very-low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect for at least 1 critical outcome is very uncertain.
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low-quality evidence	Uncertainty in the estimates of Desirable effects, harms, and burden; Desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation very low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; Desirable effects may or may not be balanced with undesirable effects may be closely balanced	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain.

GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trials.

Table S2. Commercial, FDA cleared, CE marked, in-vitro diagnostic CMV quantitative molecular assays

	Abbott RealTime CMV	Alinity M CMV	Aptima CMV Quant Assay	Artus CMV RGQ MDX Kit	COBAS AmpliPrep/ COBAS TaqMan CMV Test	COBAS CMV Test
FDA approval	2017	2022	2022	2014	2012	2017
Target gene(s)	UL34 and UL80.5	UL34 and UL80.5	UL56 terminase	MIE gene	CMV DNA polymerase (UL54)	CMV DNA polymerase (UL54)
Manufacturer	Abbott Molecular, Inc.	Abbott Molecular, Inc.	Hologic, Inc.	QIAGEN	Roche Molecular Systems	Roche Molecular Systems
Source	PL (WB for non-US)	PL	PL (WB for non-US)	PL	PL	PL
Unit	IU/mL	IU/mL	IU/mL	IU/mL	IU/mL	IU/mL
LOD	31.2 (1.49 $\log_{10}$)	30 (1.48 $\log_{10}$)	40.7 (plasma, 1.61 $\log_{10}$)	77 (1.89 $\log_{10}$)	46 (1.66 $\log_{10}$)	34.5 (1.54 $\log_{10}$)
LLOQ	US: 50 (PL 1.7 $\log_{10}$) Non-US: 31.2 (PL 1.49 $\log_{10}$) 62.4 (WB 1.8 $\log_{10}$)	30 (1.48 $\log_{10}$)	53 (PL 1.72 $\log_{10}$) 176 (WB 2.24 $\log_{10}$)	159 (2.2 $\log_{10}$)	137 (2.14 $\log_{10}$)	34.5 (1.54 $\log_{10}$)
ULOQ	156.0×10^6 (PL&WB; 8.2 $\log_{10}$)	1×10^8 (8.0 $\log_{10}$)	1×10^7 (7.0 $\log_{10}$)	79.4×10^6 (7.9 $\log_{10}$)	9.1×10^6 (6.96 $\log_{10}$)	1×10^7 (7 $\log_{10}$)
Deviation from linear range and precision	Dev from linearity of ≤0.10 $\log_{10}$ IU/mL	Within-laboratory PL SD of ≤0.25 log IU/mL for CMV DNA 2.7-8.0 $\log_{10}$ IU/mL; ≤0.5 log IU/mL for CMV DNA from 1.7-<2.7 log IU/mL	Within-laboratory PL SD of 0.18 $\log_{10}$ IU/mL for CMV DNA at 2.28 log IU/mL; 0.12 $\log_{10}$ IU/mL for CMV DNA at 6.67 $\log_{10}$ IU/mL	Max dev from linearity: ≤0.15 $\log_{10}$ IU/mL	Max dev from linearity: ≤0.3 $\log_{10}$ IU/mL	Max dev from linearity: ≤0.1 $\log_{10}$ IU/mL

CE; Conformité Européenne (European Confirmity); CMV, cytomegalovirus; dev, deviation; FDA, US Food and Drug Administration; max, maximum; LLOQ; lower limit of quantitation; LOD, limit of detection; MIE, major immediate early; PL, plasma; SD, standard deviation; ULOQ; upper limit of quantitation; US, United States; WB, whole blood.

Table S3. Summary of recent clinical studies on the use of antibodies conducted in SOT recipients

	Population	Time point, outcome	Findings	Reference
CMVIG or IVIG	Cochrane Central Register of Controlled Trials. 37 trials (2185 SOT recipients)	Prophylaxis	No significant difference in CMV disease risk (16 studies, 770 patients: RR 0.80 [95% CI 0.61-1.05]), CMV infection (14 studies, 775 patients: RR 0.94 [95% CI 0.80-1.10]) with IVIG or CMVIG compared with placebo/no treatment.	[298]
		Treatment	IVIG or CMVIG significantly reduced risk of death from CMV disease (6 studies, n = 346: RR 0.33 [95% CI 0.14-0.80]). No difference in CMV disease risk with antiviral medication combined with IVIG/CMVIG vs antiviral alone (4 studies, n = 298: RR 1.17 [95% CI 0.74-1.86]).	
	Meta-analysis of 11 randomized trials (698 patients). Six randomized trials (302 patients) after kidney transplantation	Prophylaxis. Median follow-up: 12 months (range, 3-22)	CMVIG provided benefit for total survival and prevention of CMV-associated death in SOT but not kidney transplant recipients. CMV disease was significantly reduced in all recipients. No impact on CMV infections.	[286]
	Single-center, retrospective study of cardiothoracic transplantation.	CMVIG rescue therapy	CMV DNA levels were significantly reduced 1 week after therapy. After 4 weeks CMV DNA was undetectable in 73% of patients.	[287]
	Multicenter retrospective study of 22 lung transplant patients	CMVIG treatment and secondary prophylaxis. Median follow-up 174 days (range, 12-682).	No recurrence of infection (n = 11, 68%) or disease (n = 4, 66%) was observed during a median follow-up of 174 (12-682) days after treatment initiation	[294]
	Meta-analysis of 32 SOT studies (1521 CMVIG-treated patients and 1196 controls)	CMVIG prophylaxis	Average CMV infection rate of 35.8% (95% CI, 33.4-38.2) in patients receiving prophylactic CMVIG and 41.4% (95% CI, 38.6-44.2) in controls (p = 0.003).	[233]
CMVIG or IVIG in SOT with HGG	Randomized clinical trial heart transplantation. CMVIG + antiviral therapy (n = 13) vs antiviral therapy alone (n = 10)	CMVIG prophylaxis after detection of HGG; IgG <500 mg/dL vs no CMVIG	CMV disease incidence was significantly lower in CMVIG (11%) vs antiviral alone (54.5%) arm.	[238]
	Case control study heart transplantation. CMVIG + antiviral therapy vs antiviral therapy alone	CMVIG prophylaxis after detection of HGG (IgG <350 mg/dL) vs no CMVIG.	CMV disease incidence was significantly lower in CMVIG (15%) vs antiviral alone (60%) arm.	[296]
	Open clinical trial heart transplantation. IVIG + antiviral therapy (n = 12) vs antiviral therapy alone (n = 13).	IVIG prophylaxis after HGG detection (IgG <500 mg/dL) vs no IVIG. Screening starting early at day 7 after transplantation.	CMV infection (55 vs 92%, p = 0.047) and CMV disease (0% vs 38.5%, p = 0.016), was significantly lower in IVIG arm.	[295]
	Metanalysis of heart and lung transplantation. 455 patients, 4 studies.	IVIG vs no IVIG in HGG	Significant mortality reduction (OR 0.34 [95% CI 0.17-0.69]) in heart transplant with HGG receiving IVIG vs no IVIG. Mortality in lung transplant recipients with HGG receiving IVIG was comparable to no HGG.	[288]
	Single-center retrospective cohort study on lung transplantation. No HGG (n = 76), untreated HGG (n = 192) or treated HGG (n = 216)	IVIG: No HGG, untreated HGG or treated HGG	Freedom from CLAD was highest in the non-HGG group. Freedom from advanced dysfunction significantly different 2 years post-enrollment (90.5% no HGG vs 84.7% untreated HGG vs 75.4% treated HGG; p = 0.017).	[289]
	Observational study	Prophylaxis after HGG detection (IgG <600 mg/dL) vs no IVIG	IVIG achieved similar survival and CLAD-free survival in recipients with HGG vs those with normal IgG levels.	[290]
	Single center retrospective on SOT, mainly non-thoracic patients (n = 37).	CMVIG or IVIG prophylaxis after detection of HGG (IgG <400 mg/dL or IgG >400 mg/dL) vs no IgG.	No difference in survival (p = 0.44), rejection rate (p = 0.44), and graft loss censored for death (p = 0.99) at 1 year.	[291]
mAb	Randomized, double-blind, placebo-controlled study 120 D+/R- kidney transplantation	RG7667 or placebo at transplantation and 1, 4, and 8 weeks posttransplant. 24 weeks follow-up.	RG7667 was well tolerated, numerically reduced incidence of CMV infection within 12 and 24 weeks posttransplant, delayed time to CMV viremia, and was associated with less CMV disease than the placebo.	[297]
	Phase 2a randomized trial to prevent CMV infection in 120 D+/R- kidney transplant patients	4 IV doses of RG7667 vs placebo	Patients with RG7667 or component antibody exposures >median values had lower incidence of viremia at 12 and 24 weeks after transplantation and a longer delayed time to detectable CMV viremia than patients with lower exposures.	[292]
	Phase 2, randomized, double-blind, placebo-controlled study of NPC-21 in 87 D+/R- kidney transplant patients	Prophylaxis. 16 and 28 weeks	No differences in CMV viremia among groups. Significantly lower Incidence of CMV disease in patients with high dose of NPC-21 vs placebo (0% vs 13.2%)	[299]

CLAD, chronic allograph dysfunction; HGG, hypogammaglobulinemia

Table S4. Summary of studies evaluating the absolute lymphocyte count as a predictor of cytomegalovirus infection in solid organ transplant recipients.

Population	Timepoint, outcome	Findings	Reference
63 liver recipients	Pretransplant, posttransplant infection (CMV & others)	Pretransplant ALC <1 associated with infection (half CMV): aOR 10.1 (95% CI, 1.9-39.5); *P* = 0.005	[322]
276 liver recipients	Pretransplant, posttransplant infection	ALC <0.5 independently associated with CMV disease: aHR 4.72, (95% CI, 2.01-11.1); *P* < 0.001	[317]
226 SOT recipients (45 kidney, 84 liver, 120 lung, 14 heart, 19 other)	End of treatment, recurrence	ALC at treatment completion associated with recurrence but not significant: aHR 1.41 (95% CI, 0.95-2.10); *P* = 0.09	[194]
170 SOT recipients (79 kidney, 52 heart, 34 liver)	End of treatment, recurrence	ALC independently associated with CMV relapse. For each 100 cells/µL decrease: aHR 1.11 (95% CI, 1.03-1.20); *P* = 0.009	[200]
64 transplant (36 SOT, 28 BMT)	ALC at multiple timepoints (pretransplant, 2-4 weeks before CMV, at CMV, at clearance)	Lower ALCs in patients with CMV	[310]
423 R+ kidney recipients, ATG induction	End of prophylaxis (mostly 3 months). Day 30, 60, 90 & 180, first episode CMV	Median ALC lower in those who developed CMV: 0.66 (95% CI, 0.38-0.87) vs 0.7 (95% CI, 0.45-1.11); *P* = 0.024. ALC <0.8 associated with CMV: HR 2.27 (95% CI 1.15-4.45); *P* = 0.018	[311]
86 kidney recipients : 67 R+, 18 D+/R-, 1 D-/R- 3 months posttransplant, 7 thymo induction	ALC at day 0, 30, 90, first episode CMV	21 CMV infection. ALC <0.8 at day 90 more common in those who developed CMV infection (54% vs 46%; *P* = 0.015)	[323]
130 SOT (60 lung, 25 kidney, 45 others). 59 D+/R-, 47 R+, 10 D-/R, 2 D unknown	Post-prophylaxis. Median 264.5 days posttransplant (IQR 62-980)	Median ALC lower with CMV infection: 380 (95% CI, 240-540) vs 940 (95% CI, 551-1210) cells/mm^3; *P* < 0.001 ALC <630; sensitivity 83%, specificity 70%. CD4 subsets but not CD8 also associated with CMV	[321]
89 R+ lung recipients 6 months posttransplant	ALC nadir in 6 months prior to CMV onset	ALC <1 associated with CMV: aHR 42.5 (95% CI, 5.3-340.6); *P* < 0.001	[312]
381 kidney recipients	Repeated ALC measurements before first CMV event	ALC <0.61 associated with CMV: HR 2.25 (95% CI 1.02-4.96); *P* = 0.043	[319]
375 heart recipients	ALC at 1 month posttransplant. Composite outcome serious infection/death incl CMV	101 developed outcome including 61 CMV events. ALC<0.75 associated with outcome: HR 1.72 (95% CI, 1.08-2.75); *P* = 0.02	[318]
58 heart recipients	Day 7 posttransplant	ALC <0.5 associated with CMV infection: aOR 4.14 (95% CI, 1.16-14.77); *P* = 0.029	[313]
2999 kidney recipients; 1718 R+	Time-dependent lymphocyte count after 1 year posttransplant.	Lymphopenia associated with death, graft loss, viral infections including CMV	[314]
48 D+/R+ kidney transplant recipients	Day 28 posttransplant (excluded patients who developed CMV prior)	ALC <1.1 associated with CMV infection: HR 3.32 (95% CI, 1.08-10.2)	[320]
158 heart transplant recipients	Repeated measurements of ALC posttransplant, time varying	ALC <0.61 associated with CMV: HR 1.74 (95% CI, 1.20-2.51); *P* = 0.003	[315]
471 pancreas recipients; 262 R+, 143 D+/R-	30 days posttransplant	Low ALC associated with CMV. Per 50% decrease in R+ but not D+/R-: HR 1.39 (95% CI 1.13-1.73); *P* = 0.002. In R+ ALC <0.5 associated with CMV: HR 2.71 (95% CI, 1.29-5.66); *P* = 0.008	[316]

a, adjusted; ALC, absolute lymphocyte count; CMV, cytomegalovirus; D, donor; HR, hazard ratio; R, recipient; OR, odds ratio.

Table S5. Clinical studies on potential indirect effects of CMV in pediatric SOT recipients by organ transplanted

Organ	Study info	Findings	Reference
Kidney	Single center prospective 2000-2005, N = 55	CMV DNAemia associated with decreased renal function at 2 years posttransplant and development of moderate to severe interstitial fibrosis and tubular atrophy.	514
	Single center retrospective 1973-2010, N = 104	Chronic allograft insufficiency which was identified as major risk factor for graft loss correlated with CMV infection	293
	Multicenter registry retrospective 2000-2013, N = 242	CMV antiviral prophylaxis associated with preservation of transplant function 3 years posttransplant. CMV replication (DNAemia or pp65 antigenemia) associated with decline in graft function	515
	Multicenter prospective 2009-2013, N = 106	Pretransplant CMV serostatus and DNAemia were NOT related to biopsy-proven acute rejection or de novo donor-specific antibody formation.	525
	Multicenter (Japan) retrospective 2011-2014, N = 163	CMV infection or disease not associated with acute rejection renal function or other infections at 2 years posttransplant.	526
	Single center retrospective 2002-2018, N = 100	No association between CMV and graft function in the first 5 years posttransplant	527
Heart	Single center retrospective 1989-2003, N = 165	Pretransplant CMV seropositivity associated with coronary artery disease all-cause mortality and coronary death	520
	Multicenter retrospective 1993-2007, N = 1598	No association between pretransplant CMV seropositivity and coronary artery vasculopathy or mortality.	517
	Single center retrospective 2010-2016, N = 91	No association between CMV risk stratification and overall graft loss but CMV high risk status associated with decreased rejection-free survival compared to intermediate or low risk groups	499
	Multicenter registry retrospective 1987-2015, N = 4968	CMV seropositive transplants who received no antiviral prophylaxis had impaired graft survival compared to those who received antivirals or seronegative recipients	521
Liver	Single center retrospective 2007-2008, N = 62	No association between seropositivity before transplantation or CMV DNAemia after transplantation with rejection	522
	Single center retrospective 2005-2015, N = 337	CMV antigenemia was associated with rejection but ~ 60% of rejection episodes were prior to CMV	494
	Single center retrospective 2008-2014, N = 100	No association between CMV and EBV infection sepsis biliary and vascular complications	491
	Single center retrospective 1998-2018, N = 118	No association between CMV infection or disease with acute or chronic rejection survival fungal infection EBV infection PTLD or biliary complications.	496
	Single center retrospective 2001-2020, N = 126	Association between CMV infection and acute cellular rejection. No effect of CMV infection on EBV infection or development of PTLD	157
Lung	Multicenter retrospective 1988-2005, N = 555	CMV D+/R- serostatus was associated with pulmonary fungal infections	523
	Multicenter retrospective 2004-2007, N = 577	CMVIG administration was associated with increased mortality in the first year posttransplant but was not associated with acute rejection respiratory fungal or viral infections	511
	Multicenter retrospective 1988-2005, N = 576	CMV serostatus or infection was not associated with respiratory viral infections	524
All Organs	Single center retrospective 2011-2018, N = 687	CMV DNAemia was associated with rejection in liver transplant recipients only but not with mortality or other organ-specific adverse outcomes.	184
	Multicenter retrospective 2016-2019, N = 749	Breakthrough CMV DNAemia was associated with rejection with highest risk among liver transplant recipients. Bacteremia adenovirus and EBV DNAemia were more common in patients with breakthrough CMV DNAemia compared to no CMV.	501

CMV, cytomegalovirus; CMVIG, CMV immunoglobulin; EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorders.