Received: 4 July 2023 | Revised: 14 November 2023 | Accepted: 27 November 2023

DOI: 10.1111/ctr.15218

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

REVIEW ARTICLE

Human cytomegalovirus-related gastrointestinal disease after kidney transplantation: A systematic review

Ilaria Elena Zais[1] | Alessandro Sirotti[2] | Samuele Iesari[2] | Edoardo Campioli[2] | Andrea Costantino[3] | Serena Delbue[4] | Andrea Collini[5] | Andrea Guarneri[6] | Federico Ambrogi[6] | Roberto Cacciola[7] | Mariano Ferraresso[2,6] | Evaldo Favi[2,6]

[1]School of Medicine, Università degli Studi di Milano, Milan, Italy

[2]General Surgery and Kidney Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[3]Division of Gastroenterology and Endoscopy, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[4]Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, Milan, Italy

[5]Renal Transplant Unit, Siena University Hospital, Siena, Italy

[6]Department of Clinical Sciences and Community Health (DISCCO), Università degli Studi di Milano, Milan, Italy

[7]Dipartimento di Scienze Chirurgiche, Università di Roma Tor Vergata, Rome, Italy

Correspondence
Samuele Iesari, General Surgery and Kidney Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza n. 28, Milan 20122, Italy.
Email: samuele.iesari@policlinico.mi.it

Abstract

Background: Human-cytomegalovirus (hCMV) infection involving the gastrointestinal tract represents a leading cause of morbidity and mortality among kidney transplant (KT) recipients (KTRs). Signs and symptoms of the disease are extremely variable. Prompt anti-viral therapy administration and immunosuppression modification are key factors for optimizing management. However, complex work-up strategies are generally required to confirm the preliminary diagnosis. Unfortunately, solid evidence and guidelines on this specific topic are not available.

We consequently aimed to summarize current knowledge on post-KT hCMV-related gastrointestinal disease (hCMV-GID).

Methods: We conducted a systematic review (PROSPERO ID: CRD42023399363) about hCMV-GID in KTRs.

Results: Our systematic review includes 52 case-reports and ten case-series, published between 1985 and 2022, collectively reporting 311 cases. The most frequently reported signs and symptoms of hCMV-GID were abdominal pain, diarrhea, epigastric pain, vomiting, fever, and GI bleeding. Esophagogastroduodenoscopy and colonoscopy were the primary diagnostic techniques. In most cases, the preliminary diagnosis was confirmed by histology. Information on anti-viral prophylaxis were extremely limited as much as data on induction or maintenance immunosuppression. Treatment included ganciclovir and/or valganciclovir administration. Immunosuppression modification mainly consisted of mycophenolate mofetil or calcineurin inhibitor minimization and withdrawal. In total, 21 deaths were recorded. Renal allograft-related outcomes were described for 26 patients only. Specifically, reported events were acute kidney injury ($n = 17$), transplant failure ($n = 5$), allograft rejection ($n = 4$), and irreversible allograft dysfunction ($n = 3$).

Conclusions: The development of local and national registries is strongly recommended to improve our understanding of hCMV-GID. Future clinical guidelines should consider the implementation of dedicated diagnostic and treatment strategies.

KEYWORDS
cytomegalovirus, gastrointestinal disease, kidney transplantation, outcome, systematic review, treatment

1 | INTRODUCTION

hCMV-GID is a major concern after KT, because of frequency and severity of this kind of infection in immunocompromised recipients.[1,2] After transplant, hCMV may occur as a primary or secondary infection.[3] Clinically, it can present as an asymptomatic infection (viremia without clinical symptoms), hCMV syndrome (viremia with systemic symptoms), or hCMV disease (tissue-invasive disease).[7] Major determinants of post-transplant hCMV disease are donor's and recipient's serostatus,[4] net state of immunosuppression,[5] administration of anti-rejection protocols containing mammalian target of rapamycin inhibitors (mTORi),[6] universal anti-viral prophylaxis,[7] and, to a lesser degree, concomitant Epstein-Barr virus or Polyomavirus BK infection.[8] Prompt diagnosis, anti-viral therapy, and immunosuppression modification are key factors in disease management.[9,10] Nevertheless, such aggressive policy entails a significant risk of drug-induced toxicity and allograft rejection.[11,12] hCMV replication in solid-organ transplant recipients is also accompanied by profound immunomodulation that, eventually, increases the risk of allograft rejection.[4,7,13]

In KTRs, hCMV can virtually replicate in every organ and tissue. However, the involvement of the gastrointestinal (GI) tract represents a particularly challenging condition. Signs and symptoms of hCMV-related gastrointestinal disease (hCMV-GID) are often vague and may overlap with those caused by other microorganisms, pre-existing conditions, or medications.[14–16] High index of suspicion, systematic work-up strategies, and invasive techniques are generally necessary to confirm the preliminary diagnosis, leading to significant delay in treatment and increased morbidity and mortality.[14–17] Unfortunately, current literature on hCMV-GID after KT is scattered in a plethora of case-reports or small case-series. Therefore, we lack solid data, and, consequently, precise guidelines, on epidemiology, clinical characteristics, diagnostic criteria, treatment options and duration, and outcomes.[18] The aim of the present study was to systematically review available information on hCMV-GID in KTRs, in order to devise informed and clinically relevant suggestions.

2 | MATERIALS AND METHODS

2.1 | Literature search

We conducted a systematic review according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist.[19] In order to avoid overlap with other studies, we searched PROSPERO® for any potentially ongoing similar reviews. Therefore, we registered our work (PROSPERO ID: CRD42023399363). In June 2023, a comprehensive search was performed using four medical databases (PubMed®, Embase®, Scopus® and Cochrane®) for any articles reporting documented hCMV-GID in KTRs. No time limits were applied to the search. The research combinations are reported in full in the Supplementary materials. Only manuscripts in English were considered. Congress proceedings and congress-related reports were excluded due to the risk of reproducing same data. This review does not cover hCMV-associated hepatobiliary disease in KTRs, a huge topic undergoing a separate review.

2.2 | Study selection and data extraction

Two different groups of authors performed the primary (IEZ, AS, EC, and AC) and secondary (AC, SD, SI, and AG) searches. Disagreements between the two teams were resolved by discussion with the senior authors (EF, SD, RC, and MF). Duplicates and non-English-edited articles were removed. The remainders articles were screened through the titles and abstracts. Only original reports on hCMV-GID in KTRs were considered. All articles potentially describing KTRs with hCMV-GID were assessed in full-text. On the contrary, articles reporting on patients with pre-transplant hCMV-GID were selectively excluded. An additional search of reference lists was performed by IEZ, AS, EC, AC, and AG.

We structured a dedicated anonymized database in which we included from the selected articles the following extracted parameters: recipient's country of origin, ethnicity, sex, primary renal disease, immunosuppressive scheme, age, previous episodes of rejection, donor's type, time from transplant to hCMV-GID onset, time from hCMV-GID presentation to final diagnosis, hCMV-GID signs and symptoms, diagnostic work-up, endoscopy, histology, anti-viral treatment, immunosuppression modification, and outcomes (including patient survival, transplant failure, allograft rejection, temporary or irreversible loss of allograft function).

2.3 | Quality assessment of the studies

The studies that we included were assessed for methodological quality using a tool based on a modification of the Newcastle–Ottawa Scale

as proposed by Murad et al.[20] Questions #4, #5, and #6 of the original questionnaires were not considered as suggested by the same authors (mostly relevant to cases of drug-induced adverse events). We made an overall evaluation considering the questions deemed most critical in the specific clinical scenario, rather than using an aggregate score. Accordingly, the quality of the studies was ranked as low, average, or high, depending on their scoring in the questionnaire: respectively, 0–2, 3–4, or 5–6 points out of a total of 6 points.

Furthermore, we used the JBI critical appraisal tool[21] to assess the quality of retrospective case-reports and retrospective case-series. More in detail, a score from 0 to 10 was attributed to retrospective case-series and a score from 0 to 8 was attributed to retrospective case-reports.

2.4 | Statistical analysis

Our systematic review mostly included single case-reports and relatively small retrospective case-series. Therefore, no meta-analysis was performed as the case-series are composed of heterogeneous patients, making any summary measure ineffective. In order to compactly describe the available literature, we used numbers for the categorical variables and ranges (min—max) for the continuous ones. The tables herein presented must also be considered as a compact way of describing the results from the literature. We acknowledge the possibility that several hCMV-GID cases after KT may not appear in our systematic review as in some circumstances various authors might have reported such cases in articles broadly referring to complications of solid organ transplantation. The statistical methods were assessed by a professional expert in biomedical statistics (Federico Ambrogi, Associate Professor of Biostatistics, University of Milan, Department of Clinical Sciences and Community Health, Laboratory of Medical Statistics and Biometry "Giulio A. Maccacaro").

2.5 | Institutional review board approval and informed consent

Data extraction and review were carried out using previously published studies. Accordingly, no Institutional Review Board approval or patient informed consent were required.

3 | RESULTS

3.1 | Included studies

The number of reports preliminarily retrieved using each of the keyword combinations previously mentioned was 4488. Following the exclusion of duplicated articles ($n = 3777$), non-English-edited articles ($n = 194$), and congress-related abstracts ($n = 0$), a pool of 517 studies remained for further evaluation. According to the inclusion criteria previously described, and after reviewing the selected studies by titles and abstracts, we identified 78 articles. Out of the 78 studies, 27 were not reporting original cases of hCMV-GID after KT. Therefore, those were excluded. We obtained further 11 reports searching through the references. At completion of the process, 62 papers were selected. There were no randomized clinical trials, prospective controlled studies, or prospective uncontrolled studies. In summary, our systematic review consists of 52 retrospective case-reports, seven single-center uncontrolled retrospective case-series, and three single-center controlled retrospective case-series,[71] that were published between 1985 and 2022. A flow diagram summarizing included articles and selection processes is reproduced in Figure 1.

According to the modified Newcastle–Ottawa Scale, 37 items were ranked as low-quality, 18 as average-quality, and seven as high-quality. The application of the JBI critical appraisal tool indicates that the mean score for case-reports was 4.94/8 whereas the mean score for case-series was 6.3/10. Main characteristics and qualitative evaluations of the studies meeting the criteria for the systematic review are reported in Tables 1 and 2. Overall, our review included 311 cases of hCMV-GID after KT.

3.2 | hCMV-GID epidemiology

In none of the included studies, it is reported the number of KT performed over the same period in which the episodes of hCMV-GID were diagnosed and treated. Therefore, there are no reliable estimates of cumulative incidence or prevalence. The donor-, recipient-, and transplant-related characteristics are summarized in Table 3.

3.3 | hCMV-GID clinical characteristics

The distribution per site of CMV-GID after KT is summarized in Table 4. The time between transplantation and hCMV-GID occurrence was not available in the majority of cases included. However, in those reported, it ranged from 3 days to 22 years,[68] with various studies describing a late onset of the disease. Similarly, data regarding the time required to obtain a definitive diagnosis were rarely recorded ($n = 6$),[23,30,42,53,54] ranging from seven to 31 days. Information regarding clinical presentation could be obtained for 84/311 patients (27%). The Table 4 reports as well post-KT hCMV-GID signs, symptoms, and the rarely mentioned (32/311, 10.3%) laboratory findings. Clinical features of post-transplant hCMV-GID are also summarized in the Supplementary materials.

3.4 | hCMV-GID diagnostic work-up

The diagnostic work-up of post-KT hCMV-GID was described for most patients included in our review (298/311, 95.8%). Esophagogastroduodenoscopy and colonoscopy represented the preferred techniques. In most cases, the preliminary diagnosis was confirmed by histology. Overall, 258 biopsies were obtained, more often during endoscopic

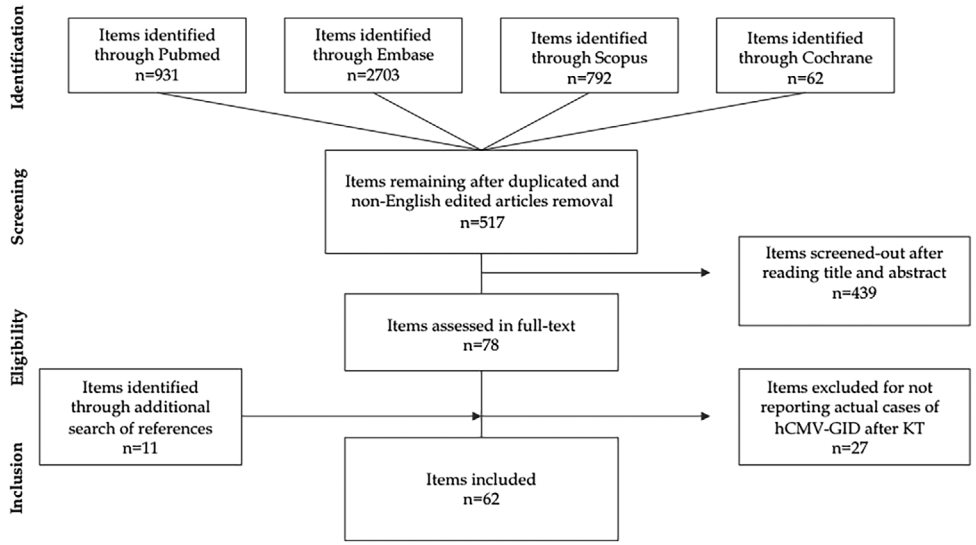

FIGURE 1 PRISMA flow diagram summarizing the identification and selection of the relevant literature on human-Cytomegalovirus-related gastrointestinal disease in kidney transplant recipients. hCMV-GID, human-cytomegalovirus-related gastrointestinal disease; KT, kidney transplantation.

TABLE 1 Studies identified through screening of online repositories.

	PubMed®	Embase®	Scopus®	Cochrane®
Esophagitis	46	90	47	0
Gastritis	28	128	47	1
Enteritis	70	317	28	24
Colitis	87	203	21	4
Proctitis	1	1	1	0
Digestive system disease	320	1798	441	32
Pancreatitis	379	166	107	1

evaluation and, less frequently, as a part of surgical exploration or autopsy. Biopsy specimens (hematoxylin/eosin, immunohistochemistry, or in situ hybridization) confirmed the presence of hCMV in 255 cases. Histology findings included mucosal hyperemia, mucosal erosion, mucosal ulceration, hemorrhagic lesions, hCMV-associated vasculitis, and ischemic lesions. In three patients with a definitive diagnosis of hCMV-GID, histology failed to demonstrate hCMV inclusions in tissue specimens.[42,59] Other reported diagnostic methods were hCMV serology, CMV DNA qPCR on blood samples, pp52 antigenemia, and pp65 antigenemia. The diagnostic work-up is summarized in Table 5.

3.5 | hCMV-GID treatment and outcomes

Overall, details on hCMV-specific anti-viral therapy were reported in 139/311 (44.7%) cases. According to the information collected, 112 patients were administered ganciclovir monotherapy,[27,83] six valganciclovir monotherapy,[25,29,31,50] and 18 a sequential combination of both drugs.[23,24,30,36,41,44,45,51,59,60,62,63,66,74] Three KTRs did not receive anti-viral therapy.[35,68] The duration of ganciclovir and valganciclovir administration ranged from 14 to 35 days and from 21 to 30 days, respectively.

For 25 patients, immunosuppression modification was recorded and included MMF withdrawal, MMF reduction, CNI minimization, and CNI suspension. Treatment-related data are summarized in Table 6.

Patient survival was available for 290/311 (93.2%) episodes of hCMV-GID. Overall, 21 deaths were recorded. More in details, reported causes of death were complications directly related to hCMV infection (n = 11),[16,56,68] sepsis (n = 4),[22,35,73] multi-organ failure (n = 4),[54,65] gastric cancer (n = 1),[31] and lung cancer (n = 1).[41] Recipients' age at the time of the death ranged from 32 to 71 years. Renal allograft-related outcomes were described for 26/311 (8.4%) patients with hCMV-GID. Particularly, reported events were not-otherwise specified acute kidney injury (n = 17),[25,27,28,30,44,46,51,62,68,71] transplant failure (n = 5),[30,44,47,71] allograft rejection (n = 4),[28,62,72] and irreversible allograft dysfunction (n = 3).[62] Patient- and transplant-related outcomes are synthetically described in Table 6.

TABLE 2 Studies meeting the criteria for the systematic review.

Study	Design	Period	Size P/D	Disease	NOS	JBI
Abderrahim et al.[22]	CR	2003	2/2	Colitis	L	4
Alhyraba et al.[23]	CR	2007	1/1	Enteritis	L	6
Baek et al.[24]	CR	2015	1/1	Gastritis	H	7
Baradhi et al.[25]	CR	2018	1/1	Colitis	L	4
Canbakan et al.[26]	CR	2005	1/1	Gastritis	A	4
Chang et al.[27]	CR	2005	1/1	Upper GI	L	4
Chang et al.[28]	CR	2004	1/1	Colitis	L	5
Chen et al.[29]	CR	2008	1/1	Gastritis	A	4
Dahman et al.[15]	CR	2010	1/1	Colitis	L	6
De Andrade et al.[16]	SUCS	2012	407/23	Esophagitis	I	6
				Gastritis		
				Colitis		
De Bartolomeis et al.[30]	CR	2005	1/1	Colitis	L	6
Di Cocco et al.[31]	CR	2012	1/1	Gastritis	A	6
Dumoulin et al.[32]	CR	2003	1/1	Colitis	L	5
Durand et al.[33]	SCCS	2011	11/11	Unspecified GID	H	8
Ensaroglu et al.[34]	SUCS	2015	1/1	Colitis	A	6
Fernández-Cruz et al.[35]	CR	1989	5/2	Pancreatitis	I	4
Florescu et al.[36]	CR	2011	1/1	Colitis	L	5
Fung et al.[37]	CR	2020	1/1	Duodenitis	L	3
Giladi et al.[38]	CR	1998	3/2	Upper Gi	A	5
				Gastritis		
Gioco et al.[39]	SUCS	2020	4/4	Colitis	A	4
Gorsane et al.[40]	CR	2013	1/1	Colitis	L	6
Gueguen et al.[41]	CR	2019	1/1	Colitis	L	6
Gupta et al.[43]	CR	2014	1/1	Upper GI	L	3
Hogan et al.[44]	CR	2022	1/1	Lower GI	I	5
Ishaque et al.[14]	SUCS	2015	200/23	Esophagitis	I	7
				Gastritis		
				Enteritis		
				Colitis		
				Proctitis		
Joo et al.[45]	CR	2013	1/1	Esophagitis	L	5
Ju et al.[46]	CR	2001	1/1	Upper GI	L	5
				Lower GI		
Kaplan et al.[47]	SUCS	2010	10/10	Upper GI	H	6
Karagiannis et al.[48]	CR	2007	1/1	Lower GI	L	3
Kato et al.[49]	CR	2019	1/1	Enteritis	I	6
Kazanji et al.[50]	CR	2015	1/1	Duodenitis	L	4
Keskar et al.[51]	CR	2015	2/2	Gastritis	A	5
Kim et al.[52]	SCCS	2016	26/26	Unspecified GID	A	8
Klein Nulend et al.[59]	CR	2022	1/1	Proctitis	H	7
Kodama et al.[53]	CR	1985	2/2	Gastritis	L	3

(Continues)

TABLE 2 (Continued)

Study	Design	Period	Size P/D	Disease	NOS	JBI
Lee et al.[54]	CR	2004	1/1	Colitis	L	7
Lempinen et al.[75]	SUCS	2009	82/8	Upper GI	H	6
Li et al.[55]	CR	2009	1/1	Gastritis	A	5
Lin et al.[56]	CR	2008	1/1	Gastritis	A	4
Moustafellos et al.[57]	CR	2006	1/1	Gastritis	L	4
Muldoon et al.[58]	CR	1996	1/1	Colitis	L	7
Papadimitriou et al.[60]	CR	2012	1/1	Enteritis	L	5
Peixoto et al.[61]	CR	2016	1/1	Upper GI	L	4
Posadas Salas et al.[62]	CR	2019	6/5	Colitis	H	5
Posen et al.[63]	CR	2013	1/1	Appendicitis	L	4
Ríos et al.[64]	CR	2016	1/1	Lower GI	L	4
Santoro-Lopes et al.[42]	CR	2011	1/1	Colitis	L	6
Sarkio et al.[76]	SCCS	2005	89/34	Upper GI	H	6
Scully et al.[65]	CR	2001	1/1	Upper GI	L	4
				Lower GI		
Shim et al.[66]	CR	2019	1/1	Colitis	L	4
Shrestha et al.[67]	CR	1995	1/1	Colitis	L	3
Sinha et al.[68]	CR	2002	5/2	Pancreatitis	A	4
Slifkin et al.[69]	CR	2001	5/2	Enteritis	A	5
				Colitis		
Smak Gregoor et al.[70]	CR	1997	1/1	Colitis	L	5
Stas et al.[71]	CR	1996	1/1	Colitis	L	8
Tapan et al.[72]	CR	2012	1/1	Gastritis	A	4
Toogood et al.[73]	CR	1996	3/3	Colitis	L	6
Toussaint et al.[74]	CR	2005	1/1	Upper GI	L	5
				Lower GI		
Trappe et al.[77]	CR	2007	1/1	Colitis	L	5
Veroux et al.[78]	CR	2007	1/1	Colitis	L	6
Wadhwa et al.[17]	SUCS	2018	1770/106	Esophagitis	L	6
				Gastritis		
				Colitis		
Yazawa et al.[79]	CR	2019	1/1	Colitis	L	4

Abbreviations: CR, retrospective case-report; D, disease; GID, gastrointestinal disease.; NOS, New-Castle Ottawa Scale; P, patient; SCCS, single-center controlled retrospective case-series; SUCS, single-center uncontrolled retrospective case-series.

4 | DISCUSSION

hCMV represents a leading cause of post-KT morbidity and mortality.[80,81] Considering the high seroprevalence of the virus in the general population,[82] its ability to establish life-long latency into the host,[83] the increasing use of powerful immunosuppressive protocols,[84] and the overwhelming number of frail or sensitized ESRD patients,[85] the incidence of hCMV-related complications is expected to rise in the future.

GI involvement may account for up to 70% of post-transplant hCMV tissue-invasive infections,[86,87] and hCMV-GID appears to be relatively frequent among KTRs. However, most reports available in the literature are driven by publication bias and do not provide comprehensive data on incidence or prevalence, thus limiting the opportunity to explore the real epidemiology of the disease. The proportion of recipients experiencing post-KT hCMV-GID with GI symptoms severe enough to require endoscopy nominally ranges from 15.5%[17] to 68%,[75] while De Andrade and Lempinen suggested that post-transplant hCMV-GID proportion might exceed 10%.[16,75] Altogether, the creation

TABLE 3 Summary of the characteristics of the kidney transplant patients with hCMV-GID described in the case-reports and case-series constituting the systematic review.[a]

Variables	Number or range (min–max)
Recipients	311
Country of origin:	
Somalia	1
N/A	310
Ethnicity:	
Caucasian	2
Afro-Caribbean	2
Asian	2
N/A	305
Sex:	
Male	80
Female	48
N/A	183
Age at diagnosis (years)	8-73
Primary renal disease:	
Primary or secondary glomerulopathy[16,23,24,31,35,49,55,57,62,66,68,71]	20
Hypertensive nephropathy[16,45,50,59,70]	13
Diabetic nephropathy[15,16,27,36,50]	8
ADPKD[41,64,65,73]	5
Cystinosis[62]	1
Reflux nephropathy[74]	1
Renal malformation[25]	1
Nephrosclerosis[30]	1
Recurrent pyelonephritis[44]	1
N/A	260
hCMV serostatus:	
hCMV IgG+	74
hCMV IgG−	19
N/A	218
Time from transplant to hCMV-GID onset (years)	0-22
Donor type:	
Living donor[16,22,24,46,51,53,55,57,68,69,71]	26
Deceased donor[15,16,23,25–31,35,37–40,42,44,45,50,58–60,62,65,70,72–74]	63
N/A	222
Donors	
Donor's ethnicity:	
N/A	311
Donor's sex:	
N/A	311
Donor's age:	
N/A	311
Donor's hCMV serostatus:	
hCMV IgG+	76
hCMV IgG−	14
N/A	221
Transplants	
HLA mismatch:	
N/A	311
hCMV serostatus matching:	
D+/R-[16,24,38,50,60,73]	9
D+/R+[16,22,23,30,32,42,51,55,56,58,59,68,74]	65
D-/R+[16,24,38,50,60,69,73]	5
D-/R-[16,31,36,41,44,57,66,69]	7
N/A	214
Induction immunosuppression:	
Basiliximab[25,27,30,31,55,59,60,62,72]	12
rATG[23,25,26,40,43]	19
OKT3[58,69]	2
Alemtuzumab[57]	1
Methilprednisolone[25,26,30,46,56]	7
No induction[24,51,70]	3
N/A	276
Maintenance immunosuppression:	
Tacrolimus[23,26,36,37,40,42,45,49–51,55,57,59,61–63,66]	38
Cyclosporin[15,22,27,28,30–32,38,41,46,54,56,58,60,64,6	34
MMF[15,16,22,24–28,30,31,36,40,41,43,45,50,51,54–56,57,59,61,62,65,70,72,74]	85
Azathioprine[22,35,36,38,58,68,69,71,73,74]	15
Everolimus[23,42]	5
Steroid[15,16,22–28,30–32,35–43,45,46,49–56,57–63,66,6	101
N/A	206

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; hCMV-GID, human-cytomegalovirus-related gastrointestinal disease; N/A, not available; D, donor; R, recipient; rATG, rabbit anti-thymocyte globulin; OKT3, muromonab-CD3; MMF, Mycophenolate mofetil.

[a]Summaries based on individual cases should not be considered as an estimate of the "real world".

of registries should be promoted to collect inclusive epidemiological data and to support effective strategies of prevention and screening.

The country of origin or ethnicity of the patients experiencing post-transplant hCMV-GID were seldom recorded. On the contrary, data regarding sex and age were available in most cases. Disparities in the

TABLE 4 Summary of the clinical characteristics of the episodes of hCMV-GID after kidney transplantation described in the case-reports and case-series constituting the systematic review.[a]

Variables	Number or range (min–max)
Episodes of hCMV-GID	311
hCMV-GID variant:	
Esophagitis[14,16,17,29,45,46,65,74]	17
Gastritis[14,16,17,24,31,46,51,53,55,56,57,65,72,74]	29
Duodenitis 14,37,50	3
Upper-GI disease[27,38,43,47,61,76]	56
Enteritis[23,49,60,69]	4
Colitis[14–17,22,25,28,30,32,34,36,39–42,54,58,62,66,67,69–71,73,77–79]	136
Appendicitis[63]	1
Proctitis[14,59]	3
Lower-GI disease[44,48,64,]	3
Pancreatitis[35,68]	4
Not-otherwise specified GID[16,33,46,52,65,74]	55
Time from onset to diagnosis (days):	7-31
Symptoms:	
Abdominal pain	42
Epigastric pain	39
Chest wall pain	1
Perianal pain	2
Dysphagia	2
Odynophagia	1
Nausea	6
Reflux	2
Malaise	8
Signs:	
Fever	28
Vomiting	29
Diarrhea	40
GI bleeding	25
Weight loss	9
Anorexia	2
Laboratory findings:	
Leukopenia[27,40,41,58,59,63,69,73,74]	15
Anaemia[15,27,28,30,31,41,42,50,60,64,74]	13
Elevated serum creatinine[25,27,28,30,44,46,51,62,68,71]	17
Elevated CRP[28]	2
Elevated amilase[35]	2
Elevated lipase[35]	2
hCMV viremia[15,23–25,27,28,30,31,36,40,41,43,44,49,50,54–56,57–64,66,69,72,74]	47

Abbreviations: hCMV-GID, human-Cytomegalovirus-related gastrointestinal disease; N/A, not available; CRP, C-Reactive Protein.
[a]Summaries based on individual cases should not be considered as an estimate of the "real world".

TABLE 5 Summary of the diagnostic work-ups performed for the episodes of hCMV-GID after kidney transplantation described in the case-reports and case-series constituting the systematic review.[a]

Variables	Number or range (min–max)
Episodes of hCMV-GID	311
Laboratory analysis:	
WCC	15
Renal function tests	17
CRP	2
Amylase	2
Lipase	2
hCMV-specific blood tests:	
hCMV serology[42,59]	2
hCMV DNA qPCR[15,23–25,27,28,30,31,36,40,41,43,44,49,50,54–56,57–64,66,69,72,74]	47
p52 antigenemia[50,76]	34
pp65 antigenemia[30,55,57,65,67,73,75,76]	62
Endoscopy:	
Esophagogastroduodenoscopy[14,16,17,23,24,26–29,31,37,38,43,45–48,50,51,53,55,58,61,64,68,72,74,76]	95
Colonoscopy[14,17,25,28,32,36,40–42,44,46,48–51,58,60,62,64,67,70,74]	137
Histology:	
Endoscopic biopsy	232
Others	26
Histological findings	
Mucosal hyperemia[23,24,28,31,44,46,48,49,53,58]	11
Mucosal erosion[24,29,31,38,48,51,53,55,57,76]	21
Mucosal ulceration[15,16,26–32,36,37,40,42,43,45,46,48,50,51,54,56,60,61,63–66,68,71,74]	57
Haemorragic lesions[15,58,64,68,71,74]	8
hCMV-associated vasculitis[70,74]	3
Ischemic lesions[40,58,70,74]	4

Abbreviations: hCMV-GID, human-cytomegalovirus-related gastrointestinal disease; WCC, white cell count; N/A, not available Abbreviations: CRP, C-Reactive Protein.

[a]Summaries based on individual cases should not be considered as an estimate of the "real world".

access to the transplant waiting list or in the number of transplants performed between different subgroups of patients may actually explain the predominance of adult males among KTRs with hCMV-GID.[88]

The primary renal disease of KTRs with hCMV-GID is generally underreported and there is no demonstrable clustering between the cause of ESRD and post-transplant hCMV-GID susceptibility.[89]

The net state of immunosuppression represents the major determinant of hCMV infection susceptibility after KT.[90] However, the role of specific maintenance immunosuppressive agents in the development of post-transplant hCMV tissue-invasive disease remains debated.[91] Unfortunately, data regarding induction immunosuppression in patients with hCMV-GID are scarce, thus preventing any meaningful descriptive analysis. Sensibly, patients who had received T- or B-cell depleting antibodies may deserve more aggressive diagnostic and treatment approaches in case of suspected hCMV-GID. Data on maintenance immunosuppression were more consistently reported, and they indicate a predominance of CNI (both tacrolimus and cyclosporine), MMF, and steroid use among KTRs who experience hCMV-GID. The association between chronic exposure to tacrolimus or MMF and post-transplant hCMV infection has been extensively investigated. Both drugs may increase the risk of hCMV tissue-invasive disease compared to cyclosporine or azathioprine, respectively.[92–95] As no direct comparison can be made between patients with or without hCMV-GID who receive different immunosuppressive schemes, the value of our findings in confirming this theory is limited. mTORi may reduce the incidence and severity of various post-transplant viral infections, including hCMV.[6] However, the small proportion of patients on mTORi with hCMV-GID might simply reflect the preferred use of MMF over mTORi in most transplant centers.[96] The impact of acute or chronic steroid administration on the incidence of hCMV-GID after KT is unclear because of a lack of comparative data. Nevertheless, similarly to hCMV-related lung disease, rapid steroid withdrawal or steroid-free immunosuppressive protocols may be associated with a reduced incidence of hCMV-GID.[97] Indeed, patients with recent acute

TABLE 6 Summary of treatments and outcomes of hCMV-GID after kidney transplantation described in the case-reports and case-series constituting the systematic review.[a]

Treatment	Patients ($n = 311$)	Length (range)	Remission	No response	Relapse	Death	Graft loss	Rejection	Allograft Dysfunction
Anti-viral tp:									
Ganciclovir	112	14–35 d	32	5	8	15	3	4	6
Valganciclovir	6	21–30 d	5		1	1			3
Both drugs	18	7–90 d	17		2	1	2		6
Untreated	3					3			2
N/A	172					1			
IS modification:	25								
MMF reduction	7								
MMF discontinuation	9								
CNI reduction	3								
CNI discontinuation	4								
AZA discontinuation	4								
mTORi	0								
N/A	3								

Abbreviations: hCMV-GID, human-cytomegalovirus-related gastrointestinal disease; tp, therapy; d, days; N/A, not available; IS, immunosuppression; MMF, Mycophenolate mofetil; ↓, reduction; ≠, withdrawal; CNI, calcineurin inhibitors; AZA, azathioprine; mTORi, mTOR inhibitors.
[a]Summaries based on individual cases should not be considered as an estimate of the "real world".

rejection episodes receiving steroid pulses often experience transient or prolonged hCMV reactivation.[98]

The average interval between transplantation and hCMV-GID is variable, though the risk of hCMV tissue-invasive disease is highest within six months of transplant.[99] hCMV-GID should be considered during the entire post-transplant follow-up, especially in patients not receiving universal prophylaxis, with recent episodes of rejection, or sustained exposure to high-dose immunosuppressive therapy.

The diagnostic workup can be challenging. Since hCMV can break through prophylaxis, KTRs with GI signs and symptoms should underwent a systematic workup, regardless of the strategy for the control of hCMV infection, that is, prophylaxis,[100,101] pre-emptive therapy,[80] or surveillance.[7] Post-transplant hCMV infection can present with a broad spectrum of signs and symptoms.[12] In particular, the clinical picture of hCMV-GID may be elusive, often remaining vague until the occurrence of severe and life-threatening complications. Most patients complain of non-localized abdominal pain or epigastric pain. Frequently, they present with fever, diarrhea, vomiting, or episodes of GI bleeding. First-line laboratory tests are of limited use in guiding the diagnosis. Findings include various combinations and degrees of leukopenia, thrombocytopenia, anemia, and elevated SCr concentration. Furthermore, symptoms, signs, and laboratory findings of hCMV-GID may overlap with those observed in several other conditions commonly occurring in KTRs, such as drug-induced side effects, bacterial or fungal infections, gastro-esophageal reflux disease, stress-induced gastritis, colonic diverticulitis, or malignancy.[102] Cases of severe hCMV tissue-invasive disease with low-level or absent viremia are relatively rare.[103] Thus, routine nuclear antigen testing (NAT) or DNA qPCR assays for the detection of hCMV replication in blood samples should be promptly requested in all KTRs with GI symptoms, especially those presenting with diffuse abdominal pain, vomiting, diarrhea, or GI bleeding. However, we identified fifteen cases with discordant blood and tissue CMV replication assays, in which tissue sample analysis was necessary to make a diagnosis.[28,29,32,42,45,51,54,60,69–71,73] When KTRs present with GI signs and symptoms and hCVM is not detectable in blood, cross-sectional imaging, such as abdomen CT or MRI, has a role,[104] but, more significantly, endoscopy with tissue sampling might speed diagnosis and targeted treatment start,[75,105] especially in KTRs with recent episodes of GI bleeding. The major advantages of endoscopy are the possibility to obtain tissue specimens, and to promptly treat active sources of bleeding.[106] Considering the higher incidence of procedure-related adverse events observed in the KTR population,[101] the theoretical benefit of early endoscopy use should be weighed against the risk of complications on an individual basis.[107]

As stated, histology is a valuable tool to confirm the preliminary diagnosis of hCMV-GID, regardless of the specific organ involved. The details on the techniques used for specimens' analysis were omitted in most studies. hCMV-specific immunohistochemistry and in situ hybridization procedures are probably more reliable than direct microscopy and hematoxylin-eosin staining,[108] but the cost-effectiveness of these methods and the theoretical advantage of combining multiple diagnostic modalities have yet to be assessed.[87]

The first-line treatment in the majority of post-transplant hCMV-GID episodes consisted of intravenous ganciclovir administration,

eventually followed by valganciclovir as secondary prophylaxis in some cases. Even if the bioavailability of ganciclovir and valganciclovir is almost equivalent,[109] the intravenous drug administration is reportedly preferred because the occurrence of nausea, vomiting, diarrhea, or bleeding can require prolonged fasting periods or restricted oral intake, the presence of abnormal bowel function or bowel inflammation can reduce the absorption of oral formulations,[109] and, lastly, in patients with acute kidney injury or "creeping" creatinine, oral valganciclovir is generally contraindicated for an higher risk of drug-induced adverse reactions.[110]

The reported duration of hCMV-specific anti-viral therapy is extremely variable and criteria for treatment discontinuation are not always clearly reported. In general, ganciclovir administration is switched to valganciclovir as soon as the patient is able to restore normal oral intake or renal function recovers.[111] The length of treatment is usually guided by continuous clinical evaluations, serial hCMV viral load testing in blood samples, and assessment of hCMV-specific T-cell immunity.[112] Only imaging or endoscopy can actually confirm complete recovery,[113] though this approach is not always practical. Secondary prophylaxis with a three-to-six-month course of valganciclovir has been suggested in patients with severe forms of hCMV-GID, early recurrence after anti-viral therapy discontinuation, and weak hCMV-specific T-cell immunity.[7,18,114,115]

Clinical guidelines recommend reducing the net state of immunosuppression in all transplant recipients with hCMV-related tissue-invasive disease.[97,116] Unfortunately, the management of immunosuppressive therapy was marginally addressed in most of the studies included in our review. The limited data available indicate that following a step-by-step approach may be appropriate. MMF reduction or withdrawal can be considered in most cases, at a very early stage. On the contrary, CNI minimization or discontinuation should be reserved to critically ill patients or those with sustained hCMV-GID after proper anti-viral treatment and first line reduction of immunosuppression. Unless contraindicated by concomitant comorbidities, previous episodes of drug-induced toxicity, or exceedingly high risk of rejection, temporary or definitive mTORi use can be considered.[117,118] Both sirolimus and everolimus have been demonstrated to interfere with viral replication and virus-specific immunity, in several in vitro[119] and in vivo studies.[120] In case of prolonged fasting, intravenous formulations of CNI and steroids can be proposed, aiming to optimize absorption and bioavailability.[121]

Despite the recent advancements in prevention, diagnosis, and treatment of post-transplant hCMV infection,[99] the available literature, fraught with the known publication bias, displays that the outcomes of KTRs with hCMV-GID remain suboptimal. In particular, the mortality rate observed among patients developing bowel perforation or presenting with acute pancreatitis appears high.[22,30,35,37,49,68,73] The occurrence of transplant failure and irreversible allograft dysfunction are relatively frequent.[62] The reasons behind are difficult to ascertain. Late diagnosis plays a role as it inevitably leads to significant delay in treatment. The lack of systematic protocols for the evaluation of KTRs with GI symptoms represents a major issue, and it should be formally addressed in future consensus conferences or upcoming clinical guidelines.[99] The limited options of specific anti-viral treatment,[125] the toxicity profiles of currently available anti-hCMV drugs,[121–123] and the emergence of drug-resistant hCMV strains[124,125] are other relevant contributing factors. The FDA has recently approved maribavir, a novel compound acting on hCMV enzyme pUL97, for the treatment of refractory forms of hCMV disease. However, to date, there are no reports describing its efficacy and safety in the setting of post-KT hCMV-GID.[121]

hCMV tissue-invasive disease can virtually affect any parts of the GI tract. Colitis, gastritis, and esophagitis represent the most reported forms of the disease, while duodenitis or pancreatitis are less frequent but potentially lethal. However, altogether, colon hCMV involvement is the most commonly detected, accounting for 94% of cases of GID[126,127] (Figure 2). Several hypotheses have been advanced to explain the specific hCMV tropism for the GI tract. First, this tropism might depend on the infected cell type. Since CMV spreads through blood, tissues with greater vascularization and mesenchymal representation will sensibly be the most affected. Secondly, the expression, on specific cell populations, of the surface proteins serving as viral dock stations might favour viral entry.[128] Lastly, the prevalence of colonic hCMV disease might be partly explained by local exposure to proinflammatory microbiota.

To our knowledge, this is the first systematic review on hCMV-GID after KT. All possible variables were included, aiming to summarize available information on the major aspects of the disease. The main limitation of our review consists in the inability to provide a structured meta-analysis because of the nature of the available studies. Moreover, we have summarized four decades of post-KT hCMV-GID experiences, during which immunosuppression practices, antiviral drugs, diagnostic tools have also evolved along with CMV strains. We are not entirely sure that early results apply still today. Nonetheless, the updated references herein reported are a basis for further research projects, and offer a comprehensive insight to the transplant physicians who deal with post-KT hCMV-GID.

5 | CONCLUSIONS

Current evidence shows that post-KT hCMV-GID is a major threat to both patient and allograft survival. Although esophagitis, gastritis, and colitis represent the most frequently observed forms of the disease, hCMV-tissue-invasive infection can virtually affect any part of the GI tract, with exceedingly high mortality in case of bowel perforation or pancreatitis. The signs and symptoms of hCMV-GID may be subtle and variable, frequently overlapping with those determined by other common conditions such as bacterial infections, drug-induced side effects, or malignancies. The occurrence of new-onset abdominal pain, vomiting, diarrhea, or GI bleeding, especially in KTRs with recent episodes of rejection, should prompt a systematic work-up, aiming to prevent delays in diagnosis and treatment. A combination of hCMV DNA qPCR testing in whole blood samples, endoscopy, and his-

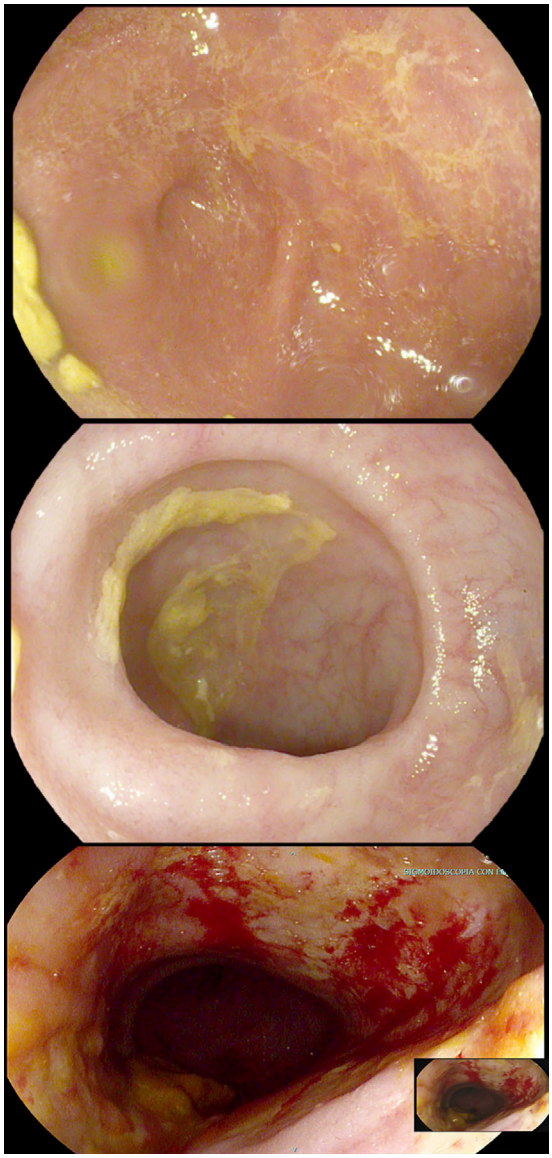

FIGURE 2 Cases of human-cytomegalovirus-related colon disease in kidney transplant recipients, with an example of hemorrhagic CMV colitis (bottom picture).

tology generally yields a definitive diagnosis. Intravenous ganciclovir is the mainstay of treatment. Anti-viral therapy withdrawal should be guided by serial clinical evaluations and repeated assessments of hCMV viremia. Dynamic testing of hCMV-specific T-cell immunity is useful. In case of clinical remission, a course of secondary anti-viral prophylaxis with oral valganciclovir may be considered. A multi-step reduction of the net state of immunosuppression or the selective use of mTORi may improve viral clearance capacity, but a tailored approach is suggested to minimize the risk of rejection or allograft dysfunction. Considered the relatively low quality of the studies available and the limited amount of data provided, dedicated registries should be implemented to improve our understanding of post-KT hCMV-GID. Also, future clinical guidelines should focus on dedicated diagnostic and treatment strategies.

AUTHOR CONTRIBUTIONS

Zais IE: literature review, data collection, data review, drafting the article, and editing; Sirotti A: literature review, data collection, data review, drafting the article, and editing; Iesari S: research strategy, data review, drafting the article, editing the article, critical revision, and final approval; Campioli E: literature review, data collection, and data review; Costantino A: data interpretation, critical revision, and final approval; Delbue S: literature review, data interpretation, critical revision, and final approval; Collini A: literature review, data interpretation, and critical revision; Guarneri A: literature review, data collection, and data review; Ambrogi F: statistics, revision, and final approval; Cacciola R: data interpretation, critical revision, drafting the article, and final approval; Ferraresso M: supervision, data interpretation, critical revision, and final approval; Favi E: vision, study design, literature review, data interpretation, drafting the article, critical revision, and final approval.

We acknowledge participation in the Transplant Peer Review Network and complied with the journal's author guidelines and policies.

ACKNOWLEDGMENTS

Final language revision was kindly performed by Nicholas Raison, Department of Urology, Guy's and St Thomas' NHS Foundation Trust, London, UK, MRC Centre for Transplantation, Guy's Hospital, King's College London, London, UK (nicholas.raison@kcl.ac.uk). Publication costs were funded through the grant *Ricerca* Corrente by the Italian Ministry of Health.

Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicting interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Ilaria Elena Zais https://orcid.org/0000-0002-4085-1884
Alessandro Sirotti https://orcid.org/0009-0002-6635-0006
Samuele Iesari https://orcid.org/0000-0002-6918-945X
Edoardo Campioli https://orcid.org/0009-0006-6864-0938
Andrea Costantino https://orcid.org/0000-0003-4345-6051
Serena Delbue https://orcid.org/0000-0002-3199-9369
Andrea Collini https://orcid.org/0000-0002-3307-524X
Andrea Guarneri https://orcid.org/0000-0001-6542-4953
Federico Ambrogi https://orcid.org/0000-0001-9358-011X
Roberto Cacciola https://orcid.org/0000-0001-8363-1358
Mariano Ferraresso https://orcid.org/0000-0003-3410-9090
Evaldo Favi https://orcid.org/0000-0001-6465-428X

REFERENCES

1. Vanichanan J, Udomkarnjananun S, Avihingsanon Y, Jutivorakool K. Common viral infections in kidney transplant recipients. *Kidney Res Clin Pract*. 2018;37(4):323-337. doi:10.23876/j.krcp.18.0063

2. Alfieri CM, Molinari P, Gandolfo M, et al. Cytomegalovirus disease in renal transplanted patients: prevalence, determining factors, and influence on graft and patients outcomes. *Pathogens*. 2021;10(4):473. doi:10.3390/pathogens10040473
3. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis*. 2017;64(1):87-91. doi:10.1093/cid/ciw668
4. Raval AD, Kistler KD, Tang Y, Murata Y, Snydman DR. Epidemiology, risk factors, and outcomes associated with cytomegalovirus in adult kidney transplant recipients: a systematic literature review of real-world evidence. *Transpl Infect Dis*. 2021;23(2):e13483. doi:10.1111/tid.13483
5. Bataille S, Moal V, Gaudart J, et al. Cytomegalovirus risk factors in renal transplantation with modern immunosuppression. *Transpl Infect Dis*. 2010;12(6):480-488. doi:10.1111/j.1399-3062.2010.00533.x
6. Kaminski H, Marseres G, Yared N, et al. mTOR inhibitors prevent CMV infection through the restoration of functional $\alpha\beta$ and $\gamma\delta$ T cells in kidney transplantation. *J Am Soc Nephrol*. 2022;33(1):121-137. doi:10.1681/ASN.2020121753
7. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*. 2018;102(6):900-931. doi:10.1097/TP.0000000000002191
8. Blazquez-Navarro A, Dang-Heine C, Wittenbrink N, et al. BKV, CMV, and EBV interactions and their effect on graft function one year post-renal transplantation: results from a large multi-centre study. *EBioMedicine*. 2018;34:113-121. doi:10.1016/j.ebiom.2018.07.017
9. Tang Y, Guo J, Li J, Zhou J, Mao X, Qiu T. Risk factors for cytomegalovirus infection and disease after kidney transplantation: a meta-analysis. *Transpl Immunol*. 2022;74:101677. doi:10.1016/j.trim.2022.101677
10. Sener M, Rogozinski T, George J, Mital D, Slakey D. Cytomegalovirus and kidney transplantation: an update. *OBM Transplant*. 2023;7(1):174, [doi:10.21926/obm.transplant.2301174
11. Asberg A, Jardine AG, Bignamini AA, et al. Effects of the intensity of immunosuppressive therapy on outcome of treatment for CMV disease in organ transplant recipients. *Am J Transplant*. 2010;10(8):1881-1888. doi:10.1111/j.1600-6143.2010.03114.x
12. Azevedo LS, Pierrotti LC, Abdala E, et al. Cytomegalovirus infection in transplant recipients. *Clinics (Sao Paulo)*. 2015;70(7):515-523. doi:10.6061/clinics/2015(07)09
13. Yoon SH, Cho JH, Jung HY, et al. Clinical impact of BK virus surveillance on outcomes in kidney transplant recipients. *Transplant Proc*. 2015;47(3):660-665. doi:10.1016/j.transproceed.2014.11.051
14. Ishaque M, Rashid R, Mubarak M. Gastrointestinal complications in renal transplant recipients detected by endoscopic biopsies in a developing country. *Indian J Gastroenterol*. 2015;34(1):51-57. doi:10.1007/s12664-015-0537-8
15. Dahman M, Krell R, Brayman K, et al. Simultaneous Clostridium difficile-associated colitis and late-onset intestinal cytomegalovirus disease in a renal transplant recipient. *Ann Transplant*. 2010;15(4):72-76.
16. de Andrade LG, Rodrigues MA, Romeiro FG, Carvalho MF. Gastrointestinal cytomegalovirus disease in renal transplant recipients: a case series. *Clin Transplant*. 2012;26(2):345-350. doi:10.1111/j.1399-0012.2011.01514.x
17. Wadhwa RK, Nazeer A, Rai AA, Luck NH. Role of endoscopic findings and biopsies in renal transplant recipients with gastrointestinal complications: a tertiary care experience. *Exp Clin Transplant*. 2018;16(5):522-527. doi:10.6002/ect.2017.0132
18. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of transplantation infectious diseases community of practice. *Clin Transplant*. 2019;33(9):e13512. doi:10.1111/ctr.13512
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2535
20. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med*. 2018;23(2):60-63. doi:10.1136/bmjebm-2017-110853
21. Barker TH, Stone JC, Sears K, et al. The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials. *JBI Evid Synth*. 2023;21(3):494-506. doi:10.11124/JBIES-22-00430
22. Abderrahim E, Bouhamed L, Raies L, et al. Intestinal perforation following renal transplantation: report of 2 cases related to cytomegalovirus disease. *Transplant Proc*. 2003;35(7):2706-2707. doi:10.1016/j.transproceed.2003.08.063
23. Alhyraba M, Grim SA, Benedetti E, Clark NM. Unusual presentation of cytomegalovirus enteritis after liver and kidney transplantation. *Transpl Infect Dis*. 2007;9(4):343-346. doi:10.1111/j.1399-3062.2007.00276.x
24. Baek HS, Choe BH, Kim HK, Huh S, Cho MH. Coincidence of late-onset cytomegalovirus-induced myositis and gastritis in a pediatric renal transplant recipient. *Transpl Infect Dis*. 2015;17(6):864-867. doi:10.1111/tid.12468
25. Baradhi KM, Aure RL, El-Amm JM. High-dose valganciclovir treatment for resistant cytomegalovirus colitis due to UL97 and UL54 mutations. *Transplant Proc*. 2018;50(1):142-144. doi:10.1016/j.transproceed.2017.11.013
26. Canbakan B, Mizrak D, Keven K, et al. Gastric ulcer despite no acid in a renal allograft recipient: what is the link? *Nephrol Dial Transplant*. 2005;20(10):2279-2281. doi:10.1093/ndt/gfi080
27. Chang HR. Posttransplant cytomegalovirus disease presenting with pyloric obstruction. *Transplantation*. 2005;79(10):1462-1463. doi:10.1097/01.tp.0000144329.53119.4e
28. Chang HR, Lian JD, Chan CH, Wong LC. Cytomegalovirus ischemic colitis of a diabetic renal transplant recipient. *Clin Transplant*. 2004;18(1):100-104. doi:10.1046/j.0902-0063.2003.00108.x
29. Chen YJ, Huang HC, Chen TC, Cheng HT. Cytomegalovirus esophagitis with symptoms of gastroesophageal reflux disease in a kidney transplant recipient. *Kaohsiung J Med Sci*. 2020;36(10):859-860. doi:10.1002/kjm2.12264
30. De Bartolomeis C, Collini A, Barni R, Ruggieri G, Bernini M, Carmellini M. Cytomegalovirus infection with multiple colonic perforations in a renal transplant recipient. *Transplant Proc*. 2005;37(6):2504-2506. doi:10.1016/j.transproceed.2005.06.082
31. Di Cocco P, Soker T, Clemente K, et al. Cytomegalovirus and gastric cancer after renal transplantation: a possible interplay. *Transplant Proc*. 2012;44(7):1912-1915. doi:10.1016/j.transproceed.2012.06.051
32. Dumoulin A, Boulmerka H, Tran Van Nhieu J, Lang P, Baron C. Severe recurrent cytomegalovirus disease revealed by a colocutaneous fistula in a kidney transplant recipient. *Transpl Infect Dis*. 2003;5(3):147-150. doi:10.1034/j.1399-3062.2003.00014.x
33. Durand CM, Marr KA, Arnold CA, et al. Detection of cytomegalovirus DNA in plasma as an adjunct diagnostic for gastrointestinal tract disease in kidney and liver transplant recipients. *Clin Infect Dis*. 2013;57(11):1550-1559. doi:10.1093/cid/cit521
34. Ensaroğlu F, Harmancı Ö, Öcal S, et al. Significance of colonoscopic findings in patients after kidney graft. *Exp Clin Transplant*. 2015;13 Suppl 3:55-57. doi:10.6002/ect.tdtd2015.O45
35. Fernández-Cruz L, Targarona EM, Cugat E, Alcaraz A, Oppenheimer F. Acute pancreatitis after renal transplantation. *Br J Surg*. 2005;76:1132-1135. doi:10.1002/BJS.1800761108
36. Florescu DF, Mindru C, Chambers HE, Kalil AC. Clostridium difficile and cytomegalovirus colitis co-infection: search for the hidden 'bug'. *Transpl Infect Dis*. 2011;13(4):411-415. doi:10.1111/j.1399-3062.2011.00605.x

37. Fung WW, Chi WK, Szeto CC, Li PK, Chow KM. Lessons of the month 3: duodenal perforation after polystyrene sulfonate. *Clin Med (Lond)*. 2020;20(1):107-109. doi:10.7861/clinmed.2019-0327
38. Giladi M, Lembo A, Johnson BL Jr. Postural epigastric pain: a unique symptom of primary cytomegalovirus gastritis? *Infection*. 1998;26(4):234-235. 10.1007/BF02962370
39. Gioco R, Puzzo L, Patanè M, et al. Post-transplant colitis after kidney transplantation: clinical, endoscopic and histological features. *Aging (Albany NY)*. 2020;12(24):24709-24720. doi:10.18632/aging.202345
40. Gorsane I, Aloui S, Letaif A, et al. Cytomegalovirus ischemic colitis and transverse myelitis in a renal transplant recipient. *Saudi J Kidney Dis Transpl*. 2013;24(2):309-314. doi:10.4103/1319-2442.109588
41. Gueguen J, Bailly E, Machet L, et al. CMV disease and colitis in a kidney transplanted patient under pembrolizumab. *Eur J Cancer*. 2019;109:172-174. doi:10.1016/j.ejca.2018.12.027
42. Santoro-Lopes G, de Lemos Ados S, Halpern M, Gonçalves RT, Santos MA, Valiante PM. Simultaneous cytomegalovirus and Mycobacterium tuberculosis infection presenting as hemorrhagic colitis 3 years after a kidney transplant. *Exp Clin Transplant*. 2011;9(5):340-343.
43. Gupta A, Rai P. Odynophagia in a renal transplant recipient. *Indian J Gastroenterol*. 2014;33(5):496-497. doi:10.1007/s12664-013-0400-8
44. Hogan JI, Steiner KL, Sifri CD. First report of sexually transmitted primary cytomegalovirus proctocolitis in a renal transplant recipient. *Transpl Infect Dis*. 2022;24(1):e13680. doi:10.1111/tid.13680
45. Joo YB, Jung HS, Baeg MK, Lee WH, Lee HJ, Yang CW. Cytomegalovirus esophagitis presents as chest pain in a renal transplant recipient. *Korean J Intern Med*. 2013;28(4):497-499. doi:10.3904/kjim.2013.28.4.497
46. Ju JH, Park HS, Shin MJ, et al. Successful treatment of massive lower gastrointestinal bleeding caused by mixed infection of cytomegalovirus and mucormycosis in a renal transplant recipient. *Am J Nephrol*. 2001;21(3):232-236. doi:10.1159/000046253
47. Kaplan B, Meier-Kriesche HU, Jacobs MG, et al. Prevalence of cytomegalovirus in the gastrointestinal tract of renal transplant recipients with persistent abdominal pain. *Am J Kidney Dis*. 1999;34(1):65-68. doi:10.1016/s0272-6386(99)70110-1
48. Karagiannis S, Kosmadakis G, Goulas S, Boletis J, Mavrogiannis C. Education and imaging. Gastrointestinal: cytomegalovirus enterocolitis. *J Gastroenterol Hepatol*. 2007;22(4):594. doi:10.1111/j.1440-1746.2007.04886.x
49. Kato K, Cooper M. Small bowel perforation secondary to CMV-positive terminal ileitis postrenal transplant. *BMJ Case Rep*. 2019;12(11):e231662. doi:10.1136/bcr-2019-231662
50. Kazanji N, Davila F, Manickam P, Wang Y, Bossory L. A case of invasive cytomegalovirus duodenitis in an immunosuppressed patient 15 months after renal transplantation. *Infection*. 2015;43(3):383-385. doi:10.1007/s15010-014-0714-1
51. Keskar V, Jamale T, Karegar M, et al. Late-onset cytomegalovirus gastritis in low-risk renal allograft recipients. *Exp Clin Transplant*. 2015;13(3):279-282. doi:10.6002/ect.2013.0301
52. Kim T, Lee YM, Lee SO, et al. Differences of cytomegalovirus diseases between kidney and hematopoietic stem cell transplant recipients during preemptive therapy. *Korean J Intern Med*. 2016;31(5):961-970. doi:10.3904/kjim.2015.079
53. Kodama T, Fukuda S, Takino T, Omori Y, Oka T. Gastroduodenal cytomegalovirus infection after renal transplantation. Fiberscopic observations. *Endoscopy*. 1985;17(4):157-158. doi:10.1055/s-2007-1013001
54. Lee CJ, Lian JD, Chang SW, et al. Lethal cytomegalovirus ischemic colitis presenting with fever of unknown origin. *Transpl Infect Dis*. 2004;6(3):124-128. doi:10.1111/j.1399-3062.2004.00063.x
55. Li W, Fan H, Yiping L. Postural epigastric pain as a sign of cytomegalovirus gastritis in renal transplant recipients: a case-based review. *Transplant Proc*. 2009;41(9):3956-3958. doi:10.1016/j.transproceed.2009.05.034
56. Lin CJ, Pan CF, Wu CJ, Chen HH, Kao CR, Lee CC. A giant gastric ulcer mimicking carcinoma in a renal transplant recipient with CMV infection. *South Med J*. 2008;101(3):327. doi:10.1097/SMJ.0b013e318164700f
57. Moustafellos P, Hadjianastasiou V, Gray D. Postural epigastric pain as a sign of CMV gastritis: a case report. *Transplant Proc*. 2006;38(5):1357-1358. doi:10.1016/j.transproceed.2006.05.067
58. Muldoon J, O'Riordan K, Rao S, Abecassis M. Ischemic colitis secondary to venous thrombosis. A rare presentation of cytomegalovirus vasculitis following renal transplantation. *Transplantation*. 1996;61(11):1651-1653. doi:10.1097/00007890-199606150-00018
59. Klein Nulend R, Singla A, De Silva R, et al. A first case report of cytomegalovirus infection presenting with perianal fistula and abscess formation in a kidney transplant recipient. *Exp Clin Transplant*. 2022;20(8):771-775. doi:10.6002/ect.2022.0190
60. Papadimitriou G, Koukoulaki M, Vardas K, et al. Small bowel obstruction caused by inflammatory cytomegalovirus tumor in a renal transplant recipient: report of a rare case and review of the literature. *Transpl Infect Dis*. 2012;14(5):E111-E115. doi:10.1111/j.1399-3062.2012.00784.x
61. Peixoto A, Santos-Antunes J, Silva M, Macedo G. Esophageal and gastric ulceration due to synchronous herpes simplex virus, cytomegalovirus and Epstein-Barr virus infection. *Acta Gastroenterol Belg*. 2016;79(2):271-272.
62. Posadas Salas MA, Thompson J, Kadian M, Ngo T, Bruner E, Self S. Cytomegalovirus renal infection: rare manifestation of a common post-transplant viral infection-A case series. *Transpl Infect Dis*. 2019;21(6):e13169. doi:10.1111/tid.13169
63. Posen A, Renckens I, Sagaert X, Kuypers D. Subacute cytomegalovirus appendicitis in a renal transplant recipient. *Transpl Infect Dis*. 2013;15(1):96-97. doi:10.1111/tid.12021
64. Ríos A, Ruiz J, Rodríguez JM, Parrilla P. Sever lower gastro-intestinal bleeding by CMV in a kidney transplant with low-dose immunosuppression. *Nefrologia*. 2016;36(4):454-455. doi:10.1016/j.nefro.2016.01.001
65. Scully RE, Eugene JM, William FM, et al. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 25-2001. A 71-year-old man with gastric ulcers and ileocecal thickening eight years after renal transplantation. *N Engl J Med*. 2001;345(7):526-532. doi:10.1056/NEJMcpc010025
66. Shim HG, Huh A, Dickstein A. Cecal bascule as a rare presentation of cytomegalovirus colitis in a kidney transplant recipient. *ACG Case Rep J*. 2019;6(9):e00197. doi:10.14309/crj.0000000000000197
67. Shrestha BM, Darby C, Fergusson C, Lord R, Salaman JR, Moore RH. Cytomegalovirus causing acute colonic pseudo-obstruction in a renal transplant recipient. *Postgrad Med J*. 1996;72(849):429-430. doi:10.1136/pgmj.72.849.429
68. Sinha S, Jha R, Lakhtakia S, Narayan G. Acute pancreatitis following kidney transplantation—role of viral infections. *Clinical transplantation* 2003;17:32-36. doi:10.1034/J.1399-0012.2003.02041.X
69. Slifkin M, Tempesti P, Poutsiaka DD, Snydman DR. Late and atypical cytomegalovirus disease in solid-organ transplant recipients. *Clin Infect Dis*. 2001;33(7):E62-E68. doi:10.1086/322663
70. Smak Gregoor PJ, van Gelder T, Abraham Tanis A, Chadha-Ajwani S, Klaassen RJ, Weimar W. Cytomegalovirus colitis in a CMV-seropositive renal transplant recipient on triple drug therapy (including mycophenolate). *Nephrol Dial Transplant*. 1997;12(12):2766-2767. doi:10.1093/ndt/12.12.2766
71. Stas KJ, Louwagie PG, Van Damme BJ, Coosemans W, Waer M, Vanrenterghem YF. Isolated zygomycosis in a bought living unre-

lated kidney transplant. *Transpl Int*. 1996;9(6):600-602. doi:10.1007/BF00335563

72. Tapan U, Kutlugun AA, Arici M, Altun B. Postural epigastric pain: a challenging symptom for cytomegalovirus (CMV) gastritis. *Ren Fail*. 2012;34(2):235-236. doi:10.3109/0886022X.2011.646883
73. Toogood GJ, Gillespie PH, Gujral S, et al. Cytomegalovirus infection and colonic perforation in renal transplant patients. *Transpl Int*. 1996;9(3):248-251. doi:10.1007/BF00335394
74. Toussaint N, Goodman D, Langham R, Gock H, Hill P. Haemorrhagic Campylobacter jejuni and CMV colitis in a renal transplant recipient. *Nephrol Dial Transplant*. 2005;20(4):823-826. doi:10.1093/ndt/gfh687
75. Lempinen M, Halme L, Sarkio S, et al. CMV findings in the gastrointestinal tract in kidney transplantation patients, patients with end-stage kidney disease and immunocompetent patients. *Nephrol Dial Transplant*. 2009;24(11):3533-3539. doi:10.1093/ndt/gfp408
76. Sarkio S, Halme L, Arola J, Salmela K, Lautenschlager I. Gastroduodenal cytomegalovirus infection is common in kidney transplantation patients. *Scand J Gastroenterol*. 2005;40(5):508-514. doi:10.1080/00365520510012262
77. Trappe R, Pohl H, Forberger A, Schindler R, Reinke P. Acute esophageal necrosis (black esophagus) in the renal transplant recipient: manifestation of primary cytomegalovirus infection. *Transpl Infect Dis*. 2007;9(1):42-45. doi:10.1111/j.1399-3062.2006.00158.x
78. Veroux M, Puzzo L, Corona D, et al. Cytomegalovirus and Clostridium difficile ischemic colitis in a renal transplant recipient: a lethal complication of anti-rejection therapy? *Urol Int*. 2007;79(2):177-179; discussion 180. doi:10.1159/000106334
79. Yazawa M, Sasaki H, Sakurai Y, et al. Early post-transplant diagnosis of cytomegalovirus esophagitis in an ABO-incompatible kidney transplant recipients: a case report. *Transpl Infect Dis*. 2018;20(2):e12827. doi:10.1111/tid.12827
80. De Keyzer K, Van Laecke S, Peeters P, Vanholder R. Human cytomegalovirus and kidney transplantation: a clinician's update. *Am J Kidney Dis*. 2011;58(1):118-126. doi:10.1053/j.ajkd.2011.04.010
81. Selvey LA, Lim WH, Boan P, et al. Cytomegalovirus viraemia and mortality in renal transplant recipients in the era of antiviral prophylaxis. Lessons from the western Australian experience. *BMC Infect Dis*. 2017;17(1):501. doi:10.1186/s12879-017-2599-y
82. Fowler K, Mucha J, Neumann M, et al. A systematic literature review of the global seroprevalence of cytomegalovirus: possible implications for treatment, screening, and vaccine development. *BMC Public Health*. 2022;22:1-15. [doi:10.1186/S12889-022-13971-7
83. Reeves M, Sinclair J. Aspects of human cytomegalovirus latency and reactivation. *Curr Top Microbiol Immunol*. 2008;325:297-313. doi:10.1007/978-3-540-77349-8_17
84. Muntean A, Lucan M. Immunosuppression in kidney transplantation. *Clujul Med*. 2013;86(3):177-180.
85. Wallace D, Robb M, Hughes W, et al. Outcomes of patients suspended from the national kidney transplant waiting list in the United Kingdom between 2000 and 2010. *Transplantation*. 2020;104(8):1654-1661. doi:10.1097/TP.0000000000003033
86. Eid AJ, Razonable RR. Cytomegalovirus disease in solid organ transplant recipients: advances lead to new challenges and opportunities. *Current opinion in organ transplantation*. 2007;12:610-617. [doi:10.1097/MOT.0B013E3282F0D386
87. Dioverti MV, Razonable RR. Cytomegalovirus. *Microbiol Spectr*. 2016;4(4). doi:10.1128/microbiolspec.DMIH2-0022-2015
88. Segev DL, Kucirka LM, Oberai PC, et al. Age and comorbidities are effect modifiers of gender disparities in renal transplantation. *J Am Soc Nephrol*. 2009;20(3):621-628. doi:10.1681/ASN.2008060591
89. Boenink R, Astley ME, Huijben JA, et al. The ERA registry annual report 2019: summary and age comparisons. *Clin Kidney J*. 2021;15(3):452-472. doi:10.1093/ckj/sfab273
90. Fisher RA. Cytomegalovirus infection and disease in the new era of immunosuppression following solid organ transplantation. *Transpl Infect Dis*. 2009;11(3):195-202. doi:10.1111/j.1399-3062.2009.00372.x
91. Gane E, Saliba F, Valdecasas GJ, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group [corrected]. *Lancet*. 1997;350(9093):1729-1733. doi:10.1016/s0140-6736(97)05535-9
92. Kizilbash SJ, Rheault MN, Bangdiwala A, Matas A, Chinnakotla S, Chavers BM. Infection rates in tacrolimus versus cyclosporine-treated pediatric kidney transplant recipients on a rapid discontinuation of prednisone protocol: 1-year analysis. *Pediatr Transplant*. 2017;21(4). doi:10.1111/petr.12919
93. Ong PW, Kee T, Ho QY. Impact of tacrolimus versus cyclosporine on one-year renal transplant outcomes: a single-centre retrospective cohort study. *Proc Sing Healthcare*. 2020;29(4):217-222. [doi:10.1177/2010105820957370
94. Sarmiento JM, Dockrell DH, Schwab TR, Munn SR, Paya CV. Mycophenolate mofetil increases cytomegalovirus invasive organ disease in renal transplant patients. *Clin Transplant*. 2000;14(2):136-138. doi:10.1034/j.1399-0012.2000.140206.x
95. Song AT, Abdala E, Bonazzi PR, Bacchella T, Machado MC. Does mycophenolate mofetil increase the risk of cytomegalovirus infection in solid organ transplant recipients?–A mini-review. *Braz J Infect Dis*. 2006;10(2):132-138. doi:10.1590/s1413-86702006000200011
96. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med*. 2004;351(26):2715-2729. doi:10.1056/NEJMra033540
97. Axelrod D, Leventhal JR, Gallon LG, Parker MA, Kaufman DB. Reduction of CMV disease with steroid-free immunosuppresssion in simultaneous pancreas-kidney transplant recipients. *Am J Transplant*. 2005;5(6):1423-1429. doi:10.1111/j.1600-6143.2005.00855.x
98. Rabbani A, Aliabbar S, Nikeghbalian S, Malek-Hosseini A, Baziboroun M. Immunosuppressive regimens on conversion of cytomegalovirus infection to disease in liver transplant recipients. *Caspian J Intern Med*. 2022;13(4):721-727. doi:10.22088/cjim.13.4.721
99. Gabardi S, Asipenko N, Fleming J, et al. Evaluation of low- versus high-dose valganciclovir for prevention of cytomegalovirus disease in high-risk renal transplant recipients. *Transplantation*. 2015;99(7):1499-1505. doi:10.1097/TP.0000000000000570
100. Kidney disease: improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9 Suppl. 3:S1-S155. doi:10.1111/j.1600-6143.2009.02834.x
101. Palamuthusingam D, Kunarajah K, Pascoe EM, Johnson DW, Hawley CM, Fahim M. Postoperative outcomes of kidney transplant recipients undergoing non-transplant-related elective surgery: a systematic review and meta-analysis. *BMC Nephrol*. 2020;21(1):365. doi:10.1186/s12882-020-01978-4
102. Behrend M. Adverse gastrointestinal effects of mycophenolate mofetil: aetiology, incidence and management. *Drug Saf*. 2001;24(9):645-663. doi:10.2165/00002018-200124090-00002
103. Eid AJ, Arthurs SK, Deziel PJ, Wilhelm MP, Razonable RR. Clinical predictors of relapse after treatment of primary gastrointestinal cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant*. 2010;10(1):157-161. doi:10.1111/j.1600-6143.2009.02861.x
104. Calogero A, Gallo M, Sica A, et al. Gastroenterological complications in kidney transplant patients. *Open Med (Wars)*. 2020;15(1):623-634. doi:10.1515/med-2020-0130
105. Wetwittayakhlang P, Rujeerapaiboon N, Wetwittayakhlung P, et al. Clinical features, endoscopic findings, and predictive factors for mortality in tissue-invasive gastrointestinal cytomegalovirus disease between immunocompetent and immunocompromised patients.

Gastroenterol Res Pract. 2021;2021:8886525. doi:10.1155/2021/8886525
106. Wilkins T, Khan N, Nabh A, Schade RR. Diagnosis and management of upper gastrointestinal bleeding. *Am Fam Physician*. 2012;85(5):469-476.
107. Nass KJ, Zwager LW, van der Vlugt M, et al. Novel classification for adverse events in GI endoscopy: the AGREE classification. *Gastrointest Endosc*. 2022;95(6):1078-1085.e8 doi:10.1016/j.gie.2021.11.038
108. Alacam S, Karabulut N, Bakir A, et al. Diagnostic significance of cytomegalovirus DNA quantitation in gastrointestinal biopsies: comparison with histopathological data and blood cytomegalovirus DNA. *Eur J Gastroenterol Hepatol*. 2021;33(1):40-45. doi:10.1097/MEG.0000000000001840
109. Franck B, Autmizguine J, Marquet P, Ovetchkine P, Woillard JB. Pharmacokinetics, pharmacodynamics, and therapeutic drug monitoring of valganciclovir and ganciclovir in transplantation. *Clin Pharmacol Ther*. 2022;112(2):233-276. doi:10.1002/cpt.2431
110. Perrottet N, Decosterd LA, Meylan P, Pascual M, Biollaz J, Buclin T. Valganciclovir in adult solid organ transplant recipients: pharmacokinetic and pharmacodynamic characteristics and clinical interpretation of plasma concentration measurements. *Clin Pharmacokinet*. 2009;48(6):399-418. doi:10.2165/00003088-200948060-00006
111. Czock D, Scholle C, Rasche FM, Schaarschmidt D, Keller F. Pharmacokinetics of valganciclovir and ganciclovir in renal impairment. *Clin Pharmacol Ther*. 2002;72(2):142-150. doi:10.1067/mcp.2002.126306
112. Abate D, Saldan A, Mengoli C, et al. Comparison of cytomegalovirus (CMV) enzyme-linked immunosorbent spot and CMV quantiferon gamma interferon-releasing assays in assessing risk of CMV infection in kidney transplant recipients. *J Clin Microbiol*. 2013;51(8):2501-2507. doi:10.1128/JCM.00563-13
113. Yokose T, Obara H, Shinoda M, et al. Colon perforation due to antigenemia-negative cytomegalovirus gastroenteritis after liver transplantation: a case report and review of literature. *World J Gastroenterol*. 2019;25(15):1899-1906. doi:10.3748/wjg.v25.i15.1899
114. Humar A, Lebranchu Y, Vincenti F, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am J Transplant*. 2010;10(5):1228-1237. doi:10.1111/j.1600-6143.2010.03074
115. Luan FL, Stuckey LJ, Park JM, Kaul D, Cibrik D, Ojo A. Six-month prophylaxis is cost effective in transplant patients at high risk for cytomegalovirus infection. *J Am Soc Nephrol*. 2009;20(11):2449-2458. doi:10.1681/ASN.2008111166
116. Gómez E, de Oña M, Mélon S, et al. Control of cytomegalovirus disease in renal transplant patients treated with prednisone, azathioprine and cyclosporine using intensive monitoring and decreased immunosuppression. *Nephron*. 1999;82(3):238-245. doi:10.1159/000045408
117. Andrassy J, Hoffmann VS, Rentsch M, et al. Is cytomegalovirus prophylaxis dispensable in patients receiving an mTOR inhibitor-based immunosuppression? a systematic review and meta-analysis. *Transplantation*. 2012;94(12):1208-1217. doi:10.1097/TP.0b013e3182708e56
118. Pascual J, Royuela A, Fernández AM, et al. Role of mTOR inhibitors for the control of viral infection in solid organ transplant recipients. *Transpl Infect Dis*. 2016;18(6):819-831. doi:10.1111/tid.12601
119. Havenith SH, Yong SL, van Donselaar-van der Pant KA, van Lier RA, ten Berge IJ, Bemelman FJ. Everolimus-treated renal transplant recipients have a more robust CMV-specific CD8+ T-cell response compared with cyclosporine- or mycophenolate-treated patients. *Transplantation*. 2013;95(1):184-191. doi:10.1097/TP.0b013e318276a1ef
120. Nashan B, Gaston R, Emery V, et al. Review of cytomegalovirus infection findings with mammalian target of rapamycin inhibitor-based immunosuppressive therapy in de novo renal transplant recipients. *Transplantation*. 2012;93(11):1075-1085. doi:10.1097/TP.0b013e31824810e6
121. Gandhi RG, Kotton CN. Evaluating the safety of maribavir for the treatment of cytomegalovirus. *Ther Clin Risk Manag*. 2022;18:223-223. [doi:10.2147/TCRM.S303052
122. Hayes M, Boge CLK, Sharova A, et al. Antiviral toxicities in pediatric solid organ transplant recipients. *Am J Transplant*. 2022;22(12):3012-3020. doi:10.1111/ajt.17171
123. van der Wekken-Pas LC, Totté JEE, Lunel FV, van Zuilen AD, van Luin M. Therapeutic drug monitoring of ganciclovir in cytomegalovirus-infected patients with solid organ transplants and its correlation to efficacy and toxicity. *Ther Drug Monit*. 2022. doi:10.1097/FTD.0000000000001054
124. Guermouche H, Burrel S, Mercier-Darty M, et al. Characterization of the dynamics of human cytomegalovirus resistance to antiviral drugs by ultra-deep sequencing. *Antiviral Res*. 2020;173:104647. doi:10.1016/j.antiviral.2019.104647
125. Wong DD, van Zuylen WJ, Novos T, et al. Detection of ganciclovir-resistant cytomegalovirus in a prospective cohort of kidney transplant recipients receiving subtherapeutic valganciclovir prophylaxis. *Microbiol Spectr*. 2022;10(3):e0268421. doi:10.1128/spectrum.02684-21
126. Fakhreddine AY, Frenette CT, Konijeti GG. A practical review of cytomegalovirus in gastroenterology and hepatology. *Gastroenterol Res Pract*. 2019;6156581:1-11.
127. You DM, Johnson MD. Cytomegalovirus infection and the gastrointestinal tract. *Curr Gastroenterol Rep*. 2012;14(4):334-342. doi:10.1007/s11894-012-0266-4
128. Sun L, Chen JM, Yang K et al. Cytomegalovirus cell tropism and clinicopathological characteristics in gastrointestinal tract of patients with HIV/AIDS. *Diagn Pathol*. 2022;17:9.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zais IE, Sirotti A, Iesari S, et al. Human cytomegalovirus-related gastrointestinal disease after kidney transplantation: A systematic review. *Clin Transplant*. 2024;38:e15218. https://doi.org/10.1111/ctr.15218