Cincinnati Children's Hospital Medical Center

Health Policy & Clinical Effectiveness

Evidence-Based Care Guideline

Cytomegalovirus Prophylaxis following Solid Organ Transplants [a]

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(see methods for evidence search dates)

Introduction

Cytomegalovirus (CMV) is associated with significant morbidity and mortality following solid organ or blood and marrow transplant. Although the definition of CMV infection varies in the literature, infection has been reported to occur in up to 65 percent of patients *(Sagedal 2000 [C], Ljungman 1990 [D], Ho 1994 [S]).* Symptomatic disease occurs in a smaller proportion. Direct effects of CMV disease include febrile illness, leukopenia, thrombocytopenia, hepatitis, pneumonia, gastrointestinal mucosal change, and chronic progressive retinitis. In patients with CMV disease, the risk of other opportunistic infections, chronic and acute rejection, and post-transplantation lymphproliferative disease is increased *(Falagas 1997 [C], Bronsther 1995 [D])*. CMV disease has also been implicated as a cause of prolonged hospitalization and increased hospital charges *(Kim 2000 [D]).*

The purpose of this guideline is to present scientifically based recommendations for preventing or decreasing the incidence of CMV infection and CMV disease. However, these recommendations do not apply to preemptive therapy or the treatment of established CMV disease.

Definitions:

CMV infection and CMV disease exist as a continuum. The following are working definitions developed to assist in implementing the recommendations of this guideline.

A. CMV Infection is defined as the detection of CMV in a clinical specimen *(Couchoud 1998 [M], Kidd 1993 [C]).*

B. CMV Disease, in the presence of infection, occurs as:

- **CMV Syndrome,** a clinical condition with fever, muscle pain, leukopenia and/or thrombocytopenia
- **CMV Disease with Organ and Tissue Involvement** presenting as hepatitis with a rise in liver enzymes of at least twice baseline, gastroenteropathy confirmed by endoscopic examination, pneumonitis, or retinitis *(Sagedal 2000 [C]).* The latter presentation of CMV disease requires the identification of CMV on respective pathological specimens of liver, GI tract or lung *(Muir 1998 [D])*.

Etiology

Incidence

Table 1: Presumed CMV Disease prior to routine use of prophylaxis

Transplant	Percentage of Infection
Kidney*	8%, 23%
Liver**	29%, 9.2 %
Heart***	25%, 56%
Heart-Lung****	39%
Blood&Marrow*****	58%

(Hokeberg 1995 [C], Patel 1996 [S])** *(Patel 1996 [S])
(Falagas 1997 [C], Patel 1996 [S]) *** (Ljungman 1990 [D])
***(Best 1995 [D], Patel 1996 [S])*

Note: Susceptibility to CMV infection and disease may vary between transplant type.

Etiology/Risk Factors

A. Serologic status of the donor and recipient at the time of transplant is the major risk factor associated with subsequent CMV infection. The highest risk occurs in a seronegative recipient who receives an organ from a seropositive donor *(Falagas 1997 [C], Hokeberg 1995 [C], Kirklin 1994 [C], Best 1995 [D], Patel 1996 [S], Tolkoff-Rubin 1994 [S], Stratta 1993 [S])*

Table 2: Pre-transplant serologic status and relative risk

Risk of CMV Disease	Serologic Status
High	• Donor + / Recipient – • Recipients treated with depleting anti-lymphocyte antibodies
Intermediate	• Donor + / Recipient + • Donor - / Recipient +
Low Risk	• Donor - / Recipient -

B. Use of unfiltered blood products that are not leukocyte depleted increases risk of CMV disease *(Ho 1994 [S])*.

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C. Increased immunosuppression, directly or indirectly leading to activation of latently infected cells increases risk of CMV disease *(Hokeberg 1995 [C], Kirklin 1994 [C], Best 1995 [D], Patel 1996 [S], Ho 1994 [S], Tolkoff-Rubin 1994 [S], Stratta 1993 [S])*.

- Antithymocyte immunoglobulins (ATG, ALG, OKT3) for either induction therapy or rejection treatment.
- Anti-rejection therapy in the past 14 days *(Best 1995 [D])*, which includes high doses of corticosteroids *(Stratta 1993 [S]).*
- Mycophenolate mofetil (MMF) used in doses of 3g/d instead of 2g/d, in conjunction with doses of CSA (8-10 mg/kg/d) and prednisone (0.5mg/kg/d before surgery and tapering to 0.1 mg/kg/d) *(Moreso 1998 [B]).*

D. Environmental exposure such as being in crowds or public places or in a child care setting increases the risk of CMV for the immunocompromised transplant patient *(CentersforDiseaseControlandPrevention. 2000 [E]).*

Target Population

Inclusion: These guidelines are intended for use in the following types of transplant patients of all ages:

- Patients undergoing primary infection prophylaxis following solid organ transplant
- Patients treated for graft rejection or GVHD following transplantation

Exclusion: These guidelines are not intended for use in the following:

- Patients with CMV disease
- Patients receiving experimental CMV vaccine
- Non-transplant patients who are immunosuppressed

GUIDELINE RECOMMENDATIONS

References in parentheses ( ) Evidence strengths in [ ]

Laboratory Assessment

1. It is recommended that CMV status of donors and recipients be tested pre-transplant to stratify risk *(Badley 1997 [B], Flechner 1999 [C], Humar 1999a [C], Blok 1998 [C], Sakamaki 1997 [C], Solans 1995 [C], Muir 1998 [D], Abecassis 1996 [D], Martin 1995 [S], Snydman 1994 [S])*.

Note: The specific laboratory tests are described (see Table 3).

Prophylactic approach

Recommendations for CMV disease prophylaxis in solid organ transplant recipients are based on the previously defined risk levels (see Table 2) and treatment effectiveness (see Table 4).

Solid Organ (see Algorithm 1)

Laboratory evaluation

2. It is recommended that patients receiving prophylaxis for CMV be assessed regularly for evidence of CMV disease by clinical examination *(Local Consensus [E]).*

3. No specific recommendations regarding laboratory screening for CMV disease in patients receiving prophylaxis are made because of lack of evidence.

Prophylactic therapy (see Table 5)

4. It is recommended that CMV prophylaxis be initiated for all high and intermediate risk solid organ transplant recipients *(Hodson 2005 [M], Lowance 1999 [A], Merigan 1992 [A], Macdonald 1995 [B], Martin 1994 [B], Nichols 2000 [S], Patel 1996 [S])*. Such prophylaxis includes intravenous ganciclovir at induction doses for 14 days *(Merigan 1992 [A], Cohen 1993 [B])* followed by oral ganciclovir capsules for three months *(Winston 2003 [B], Winston 2004 [C], Rubin 2000 [C], Pescovitz 1997 [C], Local Consensus [E]).*

Note 1: In adult renal and liver transplant recipients oral ganciclovir therapy has been reportedly used for the entire 3 month period *(Gane 1997 [A], Flechner 1998 [B], Kletzmayr 2000 [C], Brennan 1997 [C]).*

- In kidney recipients, oral valganciclovir for 100 days has been shown to be as clinically effective as oral ganciclovir for CMV prevention.*(Paya 2004 [A]).* In heart recipients, valganciclovir is also presumed to be effective, but data are more limited (see Table 6, *(Paya 2004 [A])*).

Note 1: Oral valganciclovir has been shown to have equivalent bioavailability to IV ganciclovir in adult liver transplant recipients *(Pescovitz 2000 [B]).* Preliminary data suggest similar results in children.*(Bouw R 2006 [B]).*

Note 2: A higher incidence of neutropenia is reported in patients on valganciclovir, 8.2% versus 3.2% ganciclovir *(Paya 2004 [A]).*

Note 3: In the liver transplant subpopulation, there was a higher incidence of overall CMV disease and a significant increase in tissue-invasive CMV disease in the valganciclovir arm vs the ganciclovir arm (14% vs 3%)*(Paya 2004 [A]).* Accordingly, the FDA has cautioned against the use of valganciclovir in liver recipients (see Table 6, ***(RochePharmaceuticals 2003 [E]))***.

5. If a patient is unable to tolerate the above regimen due to adverse effects of the medication or inability to take capsules, the following options may be considered:

- Intravenous ganciclovir at induction doses for 14 days, followed by oral ganciclovir suspension for

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three months - limited data in pediatric patients: *(Pescovitz 1997 [C], Local Consensus [E]).*

- Intravenous ganciclovir at induction doses for 14 days in combination with CMV hyperimmune globulin. *(Ham 1995 [D], Bonham 2000 [S], Martin 1995 [S])*
- CMV hyperimmune globulin alone *(Glowacki 1994 [M], Snydman 1987 [A], Saliba 1989 [B], Kathawalla 1996 [D], Basadonna 1994 [D], Arbo 2000 [Q]).*
- Intravenous ganciclovir daily for 30 days, followed by intravenous ganciclovir Monday-Friday until day +100 *(Glowacki 1994 [M], Winston 1995 [A]).*

  Note: Ganciclovir requires a dosage adjustment in patients with renal dysfunction *(Taketomo 2000 [O]).* (see Tables 7 , 8 , and 9)

6. In low risk solid organ transplant recipients there is insufficient evidence to make specific recommendations regarding the use of antiviral agents for CMV prophylaxis *(Local Consensus [E]).* Instead, ongoing clinical surveillance for signs and symptoms of CMV disease appears reasonable *(Local Consensus [E]).*

Clinical Assessment

7. It is recommended that patients with any of the following clinical conditions be considered at risk for primary infection or reactivation of CMV disease and be treated accordingly.

- fever
- muscle pain
- leukopenia
- thrombocytopenia
- hepatitis
- gastroenteropathy
- pneumonitis
- retinitis

8. Quantitative PCR

Note 1: Measurement of quantitative CMV viral load (PCR) may have the potential to identify patients at imminent risk of CMV disease and may be a useful monitoring tool during antiviral treatment, a determinant of adequacy of treatment, and a predictor of CMV relapse *(Emery 2000 [C], Sia 2000 [C]).*

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Table 3: CMV Assay Sensitivities and Predictive Values

Test Name	Sensitivity for CMV Infection	Positive predictive value for CMV Disease	Typical Specimen Type	Comments
Qualitative PCR	100%	25-45%	Blood, tissue, BAL, others	Suggested for routine monitoring; limited usefulness once positive
Quantitative PCR	78-100%	64%	Blood	Appropriate for serial monitoring of qualitative PCR (+) patients
Conventional viral culture of blood, tissue, urine, BAL	70%	33% - 54% blood, urine, throat	Blood, Tissue, Urine, BAL	Prolonged turnaround time
Shell vial culture of urine, BAL	60-66%		Urine, BAL	Rapid; not suitable for blood
CMV serology (IgG, IgM)	47-54%		Blood	
Histopathologic exam with in-situ hybridization	75%	100%	Tissue	
pp65 Antigen	100%	45% - 61%	Blood	Not widely available

(Sagedal 2000 [C], Flechner 1999 [C], Humar 1999b [C], Blok 1998 [C], Sakamaki 1997 [C], Solans 1995 [C], Muir 1998 [D], Abecassis 1996 [D])

(See appendix A for CHMC-specific test names and availability)

Note: Determination of viral load by tests such as pp65 antigen or Quantitative PCR may be helpful in predicting disease *(Fisher 2002 [C], Ferreira-Gonzalez 1999 [C], Humar 1999a [C], Kusne 1999 [C], CentersforDiseaseControlandPrevention. 2000 [E]),* however the utility of pp65 antigen testing is limited due to specimen instability with off-site testing.

Table 4: Number Needed to Treat (NNT) to prevent 1 episode of infection or disease

NNT Infection	Organ	Treatment[1]	Reference
6	Liver	IV GCV vs ACV	*(Singh 1994 [B])*
6	Kidney	GCV vs placebo	*(Hibberd 1995 [A])*
2.8	Kidney	Oral GCV vs ACV	*(Flechner 1998 [B])*
NNT Disease	**Organ**	**Treatment**	**Reference**
7	Liver	IV/oral GCV x 98 d	*(Gane 1997 [A])*
9.1	BMT	CMV Ig	*(Messori 1994 [M])*
4.5	Liver	Oral ACV x 16 wk vs placebo	*(Gavalda 1997 [B])*
2.5	BMT	IV GCV vs placebo	*(Goodrich 1991 [B])*
14	Liver	IV GCV vs ACV x 100d	*(Winston 1995 [A])*
2.7	Liver	CMV Ig +GCV vs CMV Ig	*(Bonham 2000 [S])*
in D+/R- 5	Liver, Kidney, Heart	GCV vs ACV or placebo	*(Couchoud 1998 [M])*
3.7	Heart	GCV vs placebo	*(Merigan 1992 [A])*

1 = GCV=ganciclovir, ACV=acyclovir, CMVIg=cytomegalovirus immunoglobulin

See http://www.cebm.net/nnts.asp for definitions and use of NNT.

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Table 5: Prophylactic Drugs and Dosages for Solid Organ Transplant Recipients

Induction Dosing*	Duration of Induction	Maintenance Dosing*	Duration of Maintenance	References
Primary Regimen Recommendation				
Ganciclovir 5 mg/kg/dose IV every 12 hours	14 days	Ganciclovir Capsules: 30-40 mg/kg/dose PO every 8 hours (Max. dose 1000mg)	Until day +100	*(Merigan 1992 [A], Cohen 1993 [B], Pescovitz 1997 [C], Local Consensus [E])*
Alternative Regimens				
Ganciclovir 5 mg/kg/dose IV every 12 hours	14 days	Ganciclovir Suspension: 30-40 mg/kg/dose PO every 8 hours (Max. dose 1000mg)	Until day +100	*(Merigan 1992 [A], Cohen 1993 [B], Pescovitz 1997 [C], Local Consensus [E])*
Ganciclovir 6 mg/kg/dose IV every 24 hours	30 days	Ganciclovir 6 mg/kg/dose IV every 24 hours Monday – Friday	Until day +100	*(Winston 1995 [A])*
Ganciclovir 5 mg/kg/dose IV every 12 hours + CMV hyperimmune globulin 150 mg/kg/dose on Day 0	14 days _____	CMV Hyperimmune globulin: 100 mg/kg/dose on weeks 2, 4, 6, and 8, and 50 mg/kg/dose on weeks 12 and 16 post transplant	_____	*(Ham 1995 [D], Bonham 2000 [S])*
CMV hyperimmune globulin 150 mg/kg/dose on Day 0	_____	CMV Hyperimmune globulin: 100 mg/kg/dose on weeks 2, 4, 6, and 8, and 50 mg/kg/dose on weeks 12 and 16 post transplant	_____	*(Snydman 1987 [A])*
Valganciclovir		Dose (mg) to provide a ganciclovir exposure similar to that known to be safe and effective in adults (max. 900 mg once daily): 7 x BSA x CrCLS where 7 represents the ratio between a 900 mg Valganciclovir dose and a typical adult CrCL of 125 ml/min. BSA is body surface area and CrCLS is the calculated creatinine clearance using the Schwartz formula.	Until day +100	*(Paya 2004 [A], Vaudry 2006 [B])*

Note: Ganciclovir requires dosage adjustments in patients with renal impairment *(Taketomo 2000 [O])*.
(See Tables 7 and 8 below or CHMC formulary for dosage adjustments).

Table 6: Percentage of Patients with CMV Disease and Tissue-Invasive CMV Disease by Organ Type *

	CMV Disease		Tissue-Invasive CMV Disease		CMV Syndrome	
Organ	VGCV (N=239)	GCV (N=125)	VGC (N=239)	GCV (N=125)	VGCV (N=239)	GCV (N=125)
Liver	19% (22/118)	12% (7/59)	14% (16/118)	3% (2/59)	5% (6/118)	9% (5/59)
Kidney	6% (5/81)	23% (9/39)	1% (1/81)	5% (2/39)	5% (4/81)	18% (7/39)
Heart	6% (2/35)	10% (2/21)	0% (0/35)	5% (1/21)	6% (2/35)	5% (1/21)

VGCV=valganciclovir; GCV=oral ganciclovir

*Valganciclovir HCl tablet prescribing information
(See Roche Pharmaceuticals at http://www.rochetransplantation.com/product/valcyte/sot/default.aspx)

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Table 7: Estimated creatinine clearance based on serum creatinine and body length (Schwartz equation)

CLcr = K * L / Scr	
CLcr = creatinine clearance in mL/min/1.73 m2	L = length (height) in cm
K = Constant of proportionality that is age specific (see below)	Scr = Serum creatinine concentration in mg/dL

Age	K
Low birth weight ≤ 1 year	0.33
Full term ≤ 1 year	0.45
2 – 12 years	0.55
13 – 21 year female	0.55
13 – 21 year male	0.7

Table 8: Ganciclovir Dosage Adjustment for Renal Impairment ***(Taketomo 2000 [O])***

GFR (mL/min/1.73m2)	IV Dosage	PO Dosage
> 70	5 mg/kg/dose every 12 hours	30-40 mg/kg/dose every 8 hours (Max. dose 1000 mg)
50 - 70	2.5 mg/kg/dose every 12 hours	15-20 mg/kg/dose every 8 hours (Max. dose 500 mg)
25 - 50	2.5 mg/kg/dose every 24 hours	15-20 mg/kg/dose every 12 hours (Max. dose 500 mg)
< 25	1.25 mg/kg/dose every 24 hours	15-20 mg/kg/dose every 24 hours (Max. dose 500 mg)

Table 9: Foscarnet Dosage Adjustment for Renal Impairment ***(Taketomo 2000 [O])***

Induction Therapy		Maintenance Therapy	
Clcr (mL/min/kg)	mg/kg/dose	Clcr (mL/min/kg)	mg/kg/dose
≥ 1.6	60	≥ 1.4	90 - 120
1.5	56.5	1.2 - 1.4	78 - 104
1.4	53	1 - 1.2	75 - 100
1.3	49.4	0.8 - 1	71 - 94
1.2	45.9	0.6 - 0.8	63 - 84
1.1	42.4	0.4 - 0.6	57 - 76
1	38.9		
0.9	35.3		
0.8	31.8		
0.7	28.3		
0.6	24.8		
0.5	21.2		
0.4	17.7		

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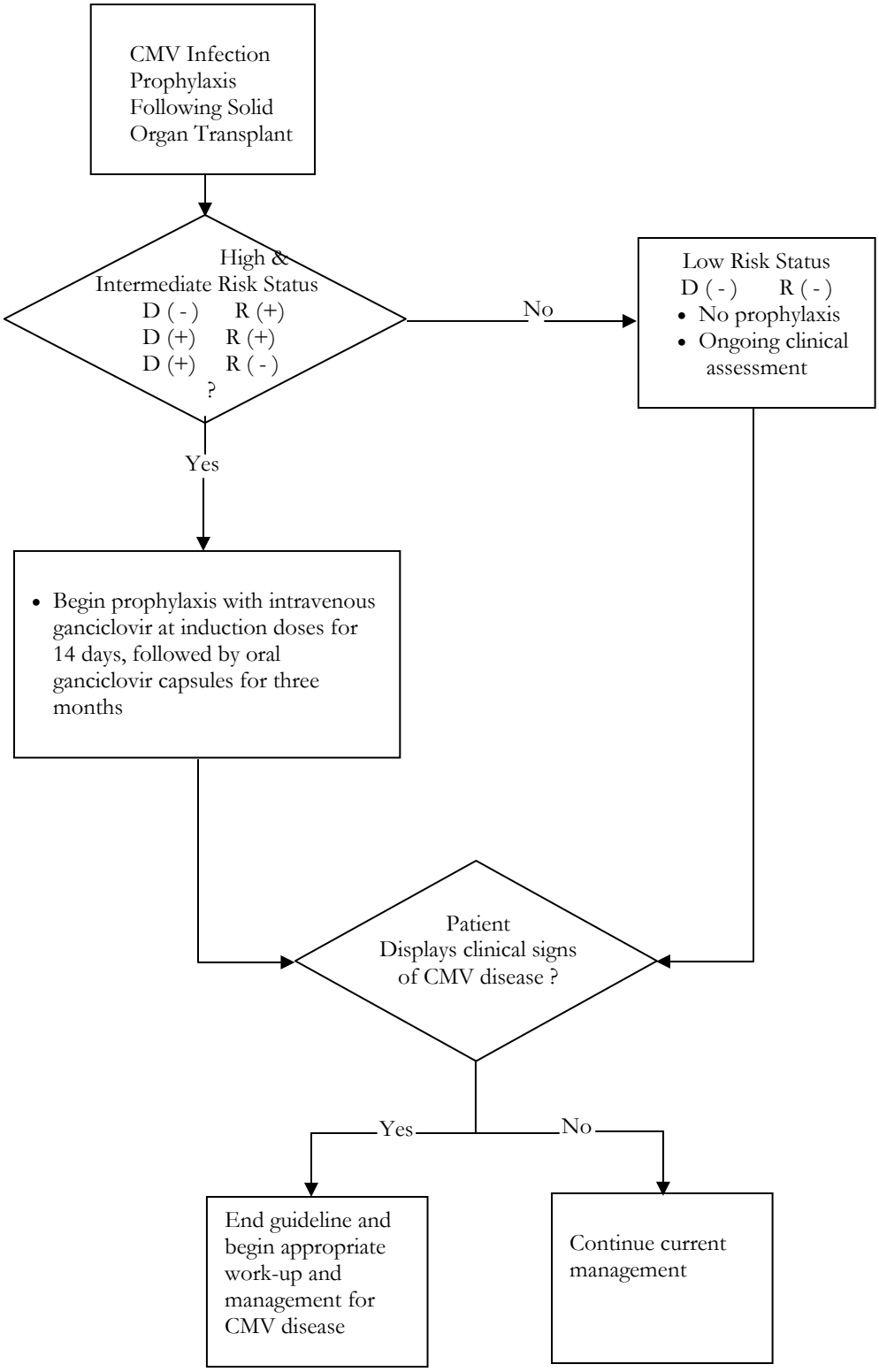
Algorithm 1 for Solid Organ Transplant Prophylactic Approach



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Appendix A
Children's Hospital Medical Center
Cincinnati, Ohio
Laboratory Tests (1-2007)

Test Name	CHMC Name (KIDS SYSTEM)
Qualitative PCR	(CMV PCR)
Quantitative PCR	(CMV PCR quantitative)
Conventional culture of blood	(VIRUS BLOOD CULTURE)
Conventional culture of non-blood specimen	(VIRUS ISOLATION/CULTURE)
Shell vial culture	(CMV ANTIGEN RAPID)

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Development Process

The process by which this guideline was developed is documented in the Guideline Development Process Manual; a Team Binder maintains minutes and other relevant development materials. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using the grading scale that follows, and examined current local clinical practices.

1. To select evidence for critical appraisal by the group for the update of this guideline, the Medline, EmBase and the Cochrane databases were searched. Evidence from 2000 and before was verified for inclusion in the guidelines. **Evidence from January 2001 to January 2007 were reviewed** to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to cytomegalovirus and solid organ transplantation and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles were identified. December, 2000 was the last date for which literature was reviewed for the previous version of this guideline. The details of that review strategy are not documented. However, all previous citations were reviewed for appropriateness to this revision.

CCHMC Evidence Grading Scale			
M	Meta-analysis or Systematic Review	S	Review Article
A	Randomized controlled trial: large sample	E	Expert opinion or consensus
B	Randomized controlled trial: small sample	F	Basic Laboratory Research
C	Prospective trial or large case series	L	Legal requirement
D	Retrospective analysis	Q	Decision analysis
O	Other evidence	X	No evidence

Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline. Experience with the implementation of earlier publications of this guideline has provided learnings which have been incorporated into this revision. Incidence of CMV Disease is an outcome measure monitored and reviewed by the transplant teams. Once the guideline has been in place for four years, the development team reconvenes to explore the continued validity of the guideline. This phase can be initiated at any point that evidence indicates a critical change is needed.

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

The guidelines have been reviewed and approved by clinical experts not involved in the development process, senior management, Risk Management & Corporate Compliance, other appropriate hospital committees, and other individuals as appropriate to their intended purposes. The guideline was developed without external funding. All Team Members and Clinical Effectiveness support staff listed have declared whether they have any conflict of interest and none were identified.

Copies of this Evidence-based Care Guideline (EBCG) and its companion documents are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm Examples of approved uses of the EBCG include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care guidelines;
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Notification of CCHMC at HPCEInfo@cchmc.org for any EBCG, or its companion documents, adopted, adapted, implemented or hyperlinked by the organization is appreciated.

Important Information

NOTE: These recommendations result from review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this pathway is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

For more information about this guideline and the supporting evidence contact the Heart Center, Division of Cardiothoracic Surgery at 513-636-4200 or thc@cchmc.org .

Additionally for more information about CCHMC guidelines and the guideline development process, contact the Health Policy & Clinical Effectiveness office at: 513-636-2501 or HPCEInfo@chmcc.org.

Additional Suggested Readings

(Note Guideline References are listed on pages 13 - 16)

(References included in this listing are not cited in the guidelines and are included for those interested in pursuing a further in-depth review of these subjects. Author names in blue font can be clicked on to access PubMed Abstracts)

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