



James M. Anderson Center for Health
Systems Excellence

Evidence-Based Care Guideline

Cytomegalovirus Prevention following Solid Organ Transplantation^a

Reviewed and Revised: September 30, 2013; July 6, 2007
Original Publication Date: June 07, 2001

Target Population

Inclusions: These recommendations are intended for use in patients with solid organ transplant (SOT), ages birth to young adults.

Exclusions: These recommendations are NOT intended for use in the following:

- Patients with CMV disease
- Patients with non-solid organ transplants

Target Users

Include but are not limited to (in alphabetical order):

- Clinicians caring for inpatients and outpatients
- Patient care staff, including:
 - nurse practitioners
 - nurses
- Patients and families
- Pharmacists
- Primary care providers
- Residents
- Transplant teams

Introduction

References in parentheses () Evidence level in [] (See [link](#) for definitions)

Cytomegalovirus (CMV) is a significant cause of morbidity and mortality after solid organ transplantation. CMV presents along a continuum of symptoms ranging from asymptomatic replication of virus to a viral syndrome with malaise and fever to end-organ disease including hepatitis, colitis, pneumonitis and retinitis. CMV in adults has also been associated with opportunistic infections including fungal infections. In

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pediatrics, the indirect effects of CMV are less clear but concerns include potential associations with late graft failure (kidney) (*Li 2007 [4b (risk factors)]*), early mortality (lung, small bowel) (*Danziger-Isakov 2009 [3a (incidence)]*, *Florescu 2012 [4b (risk factors)]*) and coronary artery vasculopathy (heart) (*Mahle 2009 [3a (incidence)]*, *Potena 2006 [3b (treatment)]*, *Simmonds 2008 [4a (risk factors)]*). Therefore, prevention of CMV disease aims to decrease post-transplant morbidity and mortality.

Definitions: adapted from (*Kotton 2013 [5a]*, *Humar 2006 [5a]*)

CMV Infection and Disease:

- *CMV infection:* evidence of CMV replication by CMV DNA polymerase chain reaction (PCR) in the absence of symptoms
- *CMV disease:* evidence of CMV infection with attributable symptoms; CMV disease can be further categorized as either:
 - *CMV syndrome* with fever, malaise, leukopenia, and/or thrombocytopenia
 - *CMV disease* with evidence of tissue invasive disease (hepatitis, colitis, pneumonitis, etc.)

CMV Prevention Strategies:

- *Prophylaxis:* antiviral medication for a specified period of time (usually 3 to 12 months). Prophylaxis can be **universal** (given to all recipients) or **targeted** (given based on risk profile to selected groups of recipients).
- *Preemptive therapy:* serial monitoring for CMV replication with initiation of therapy at a pre-determined threshold viral load prior to the onset of symptoms
- *Sequential (hybrid) therapy:* short-course prophylaxis (2 to 4 weeks) followed by serial monitoring and preemptive therapy as above

Abbreviations for CMV IgG Serologic Status before Transplant

- D-: donor CMV negative
- D+: donor CMV positive
- R-: recipient CMV negative
- R+: recipient CMV positive

Challenges in the prevention of CMV include

- **Monitoring:**
 - Variability exists between laboratory assays (*Pang 2009 [5a (Diagnostics)]*). Until all assays are normalized to international WHO standards, consistency in laboratory and assay use is desirable.
 - Treatment thresholds for preemptive therapy are unknown (*Ghisetti 2004 [2a (prognosis)]*).

- Optimal specimen type (whole blood vs. plasma) to predict CMV is unknown (*Lisboa 2011 [4b (diagnosis)]*).
- Prevention strategies:
 - Adherence to medications and monitoring are critical to the success of all prevention strategies.
 - Prophylaxis, preemptive, and sequential strategies have risks and benefits to be weighed by each individual transplant team.

The objective of this guideline is to:

- Prevent CMV disease in at-risk solid organ transplant recipients through risk stratification and targeted and cost-effective prevention strategies.

Etiology

Epidemiology

Although definitions vary within the literature, recent data report continued CMV infection and disease in pediatric SOT despite the use of prevention strategies (Table 1).

Table 1: Epidemiology by Organ Type

Organ	CMV Infection	CMV Disease	References
Kidney	8 to 38%	8 to 12%	(<i>Martin-Pena 2009 [2a (incidence)]</i> , <i>Kranz 2008 [3a (incidence)]</i> , <i>Robinson 2002 [3a (incidence)]</i> , <i>Bock 1997 [3a (incidence)]</i> , <i>Ginevri 1998 [3b (incidence)]</i>)
Liver	15 to 30%	12 to 22%	(<i>Krampe 2010 [3b (prevention)]</i> , <i>Bedel 2012 [4a (incidence)]</i> , <i>Turmelle 2009 [4a (prevention)]</i> , <i>Kullberg-Lindh 2003 [4b (risk factors)]</i>)
Heart	38%	8 to 18%	(<i>Mahle 2009 [3a (incidence)]</i> , <i>Simmonds 2008 [4a (risk factors)]</i>)
Lung	30%	22 to 38%	(<i>Danziger-Isakov 2009 [3a (incidence)]</i> , <i>Danziger-Isakov 2003 [3a (incidence)]</i> , <i>Metras 1999 [3b (incidence)]</i>)
Small Bowel	13%	8 to 24%	(<i>Mazariegos 2008 [4b (prevention)]</i> , <i>Florescu 2012 [4b (risk factors)]</i> , <i>Bueno 1997 [4b (risk factors)]</i>)

Risk Factors

CMV serostatus 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. However, even CMV D-/R- pediatric SOT are at risk from nosocomial or community acquisition of CMV (*Danziger-Isakov 2009 [3a (incidence)]*). Risk is further stratified by D/R serostatus and organ type in [Table 2](#).

Additional risks include:

- Use of unfiltered blood products that are not leukocyte-depleted (*Ho 1994 [5b]*)
- Increased immunosuppression, directly or indirectly leading to activation of latently infected cells (*Hokeberg 1995 [2b (incidence)]*, *Kirklın 1994 [3a (incidence)]*, *Best 1995 [4b (risk factors)]*, *Patel 1996 [5a]*, *Ho 1994 [5b]*, *Tolkoff-Rubin 1994 [5b]*, *Stratta 1993 [5b]*). This therapy may be:
 - antithymocyte immunoglobulins (ATG, ALG, OKT3) for either induction therapy or rejection treatment, or
 - anti-rejection therapy in the past 14 days (*Best 1995 [4b (risk factors)]*), which includes high doses of corticosteroids (*Stratta 1993 [5b]*).
- Environmental exposures, including child care settings (*Centers for Disease Control and Prevention 2000 [5a]*).

Guideline Recommendations

Assessment

Laboratory Assessment/Monitoring

1. It is recommended
 - that whole blood CMV DNA PCR be used for monitoring (*Lisboa 2011 [4b (diagnosis)]*), and
 - that monitoring occur at specified intervals (see [Table 2](#)) (*Local Consensus 2013 [5]*).
2. It is recommended, to assure consistent results, that the same laboratory facility and assay be used for serial samples (*Local Consensus 2013 [5]*, *Pang 2009 [5a (Diagnostics)]*).

Note 1: The laboratory facility at Cincinnati Children's Hospital Medical Center (CCHMC) will be used for CCHMC patients.

Note 2: Inconsistent test results may be the result of testing being performed:

 - at different laboratory facilities,
 - using different assays, or

- on a different specimen type (e.g. whole blood vs. plasma) (*Lisboa 2011 [4b (diagnosis)]*).
- Contributing factors may be:
 - patient use of different laboratory facility due to geographic need or insurance
 - the designated laboratory facility transitions to use a different assay
 - unreliable implementation processes (see [Appendix](#)).

Table 2: Prophylaxis and Monitoring Recommendations for CMV Prevention

Organ	Serostatus*	Risk Level	Recommended Prophylaxis and Monitoring	Citations
Kidney	D-/R-	Low [†]	Prophylaxis: none Monitoring: for clinical symptoms (see Recommendation #3 for list)	(<i>Melgosa Hijosa 2004 [2b (prognosis)]</i>), (<i>Bock 1997 [3a (incidence)]</i>), (<i>Jongsma 2013 [3a (prognosis)]</i>), (<i>Ginevri 1998 [3b (incidence)]</i>), (<i>Lapidus-Krol 2010 [4a (prevention)]</i>), (<i>Camacho-Gonzalez 2011 [4a (risk)]</i>), (<i>Local Consensus 2013 [5]</i>)
	R+ or D+/R-	Intermediate to High	Prophylaxis: 3 to 6 months of VGCV [‡] (as recommended in adults) Monitoring: for clinical symptoms (see Recommendations #3)	(<i>Krampe 2010 [3b (prevention)]</i>), (<i>Bedel 2012 [4a (incidence)]</i>), (<i>Saitoh 2011 [4a (prevention)]</i>), (<i>Lapidus-Krol 2010 [4a (prevention)]</i>), (<i>Madan 2009 [4a (prevention)]</i>), (<i>Local Consensus 2013 [5]</i>)
Liver	D-/R-	Low [†]	Prophylaxis: GCV IV once daily until able to take acyclovir orally [§] to complete 120 days of antiviral therapy post-transplant. Serial monitoring: every 2 weeks × 3 months and then once monthly to 12 months post-transplant	(<i>Krampe 2010 [3b (prevention)]</i>), (<i>Bedel 2012 [4a (incidence)]</i>), (<i>Saitoh 2011 [4a (prevention)]</i>), (<i>Lapidus-Krol 2010 [4a (prevention)]</i>), (<i>Madan 2009 [4a (prevention)]</i>), (<i>Local Consensus 2013 [5]</i>)
	R+ or D+/R-	Intermediate to High	Prophylaxis: GCV IV once daily until able to take VGCV orally until 120 days post-transplant [‡] (VGCV not FDA approved in liver) Serial monitoring: every 2 weeks × 3 months and then once monthly to 12 months post-transplant	(<i>Krampe 2010 [3b (prevention)]</i>), (<i>Bedel 2012 [4a (incidence)]</i>), (<i>Saitoh 2011 [4a (prevention)]</i>), (<i>Lapidus-Krol 2010 [4a (prevention)]</i>), (<i>Madan 2009 [4a (prevention)]</i>), (<i>Local Consensus 2013 [5]</i>)
Heart	D-/R-	Low [†]	Prophylaxis: none Serial monitoring: every 2 weeks × 3 months and then once monthly to 12 months post-transplant	(<i>Mahle 2009 [3a (incidence)]</i>), (<i>Lin 2012 [3b (incidence)]</i>), (<i>Snydman 2010 [4a (prevention)]</i>), (<i>Local Consensus 2013 [5]</i>)
	R+ or D+/R-	Intermediate to High	Prophylaxis: GCV IV once daily until able to take VGCV orally to complete 6 months post-transplant [‡] Serial monitoring: every 2 weeks × 12 months	(<i>Mahle 2009 [3a (incidence)]</i>), (<i>Lin 2012 [3b (incidence)]</i>), (<i>Snydman 2010 [4a (prevention)]</i>), (<i>Local Consensus 2013 [5]</i>)
Lung	D-/R-	Low [†]	Prophylaxis: none Serial monitoring: every 2 weeks × 3 months and then once monthly to 12 months post-transplant	(<i>Palmer 2010 [2a (treatment)]</i>), (<i>Danziger-Isakov 2009 [3a (incidence)]</i>), (<i>Ranganathan 2009 [4a (prevention)]</i>), (<i>Local Consensus 2013 [5]</i>)
	R+ or D+/R-	High	Prophylaxis: GCV IV once daily until able to take VGCV orally to complete 12 months post-transplant [‡] Serial monitoring: every 2 weeks × 12 months	(<i>Palmer 2010 [2a (treatment)]</i>), (<i>Danziger-Isakov 2009 [3a (incidence)]</i>), (<i>Ranganathan 2009 [4a (prevention)]</i>), (<i>Local Consensus 2013 [5]</i>)
Small Bowel**	D-/R-	Low [†]	Prophylaxis: GCV IV once daily for 8 weeks Serial monitoring: at CCHMC laboratory facility every 2 weeks × 6 months and then once monthly	(<i>Mazariegos 2008 [4b (prevention)]</i>), (<i>Florescu 2012 [4b (risk factors)]</i>), (<i>Bueno 1997 [4b (risk factors)]</i>), (<i>Local Consensus 2013 [5]</i>)
	R+ or D+/R-	High	Prophylaxis: GCV IV once daily for 8 weeks and then transition to oral VGCV if on full feeds to complete 6 months total prophylaxis. Serial monitoring: at CCHMC laboratory facility every 2 weeks × 8 months and then once monthly	(<i>Mazariegos 2008 [4b (prevention)]</i>), (<i>Florescu 2012 [4b (risk factors)]</i>), (<i>Bueno 1997 [4b (risk factors)]</i>), (<i>Local Consensus 2013 [5]</i>)

Note: There are no randomized studies indicating that CMV immunoglobulin is any more effective than GCV or VGCV alone for intermediate- and higher-risk recipients. These regimens represent local consensus and do not imply an exclusive course of action.

* Refer to [Table 3](#) serostatus recommendation for infants less than 12 months of age.

[†] Risk of CMV infection in D-/R- is approximately 5% to 7% within 12 months of transplantation (*Danziger-Isakov 2009 [3a (incidence)]*), (*Danziger-Isakov 2003 [3a (incidence)]*).

[‡] T-cell depleting induction is associated with increased risk of CMV DNAemia and disease; consider prolonged prophylaxis or more intensive monitoring (*Camacho-Gonzalez 2011 [4a (risk)]*).

[§] Acyclovir is given for risk of Herpes Simplex Virus reactivation in D-/R- liver recipients (*Wilck 2013 [5a (treatment)]*).

** Use caution with VGCV in patients with small bowel transplants due to concerns for malabsorption (*Florescu 2012 [4b (risk factors)]*).

Abbreviations: CCHMC = Cincinnati Children's Hospital Medical Center; CMV = cytomegalovirus; D- = donor CMV negative serologic status before transplant; D+ = donor CMV positive serologic status before transplant; FDA = Federal Drug Administration; GCV = ganciclovir; IV = intravenous; R- = recipient CMV negative serologic status before transplant; R+ = recipient CMV positive serologic status before transplant; VGCV = valganciclovir

Clinical Assessment

3. It is recommended that patients with any of the following clinical conditions be evaluated for CMV by examination, whole blood PCR and end-organ histopathology if indicated (*Local Consensus 2013 [5], Kotton 2013 [5a]*).
 - fever
 - muscle pain
 - leukopenia
 - thrombocytopenia
 - anemia
 - hepatitis
 - gastroenteropathy
 - pneumonitis
 - retinitis

8. It is recommended that valganciclovir be dosed around a meal (*Villeneuve 2013 [3a (treatment)], Pescovitz 2010 [3a (treatment)]*).

Management Recommendations

General

Recommendations for CMV disease prevention in solid organ transplant recipients are based on the organ transplanted and previously defined risk levels ([Table 2](#)).

Primary strategy

4. It is recommended that **targeted prophylaxis** be the primary strategy for prevention of CMV disease at CCHMC (*Local Consensus 2013 [5]*). See definition page 1.

Risk stratification

5. It is recommended that targeted prophylaxis be risk stratified based on donor/recipient CMV serostatus ([Table 2](#)) (*Local Consensus 2013 [5], Kotton 2013 [5a]*).
6. It is recommended to assign infants < 12 months of age to the high risk category unless D-/R-, as serology in infants <12 months of age may be confounded by maternal antibody ([Table 3](#)) (*Local Consensus 2013 [5], Kotton 2013 [5a]*).

Table 3: Assignment of Donor/Recipient Serostatus in Infants < 12 months of age

Donor	Recipient	Highest Risk Assignment
+	+ or -	D+/R-*
-	+	D-/R+
-	-	D-/R-

*If recipient confirmed positive by CMV culture or NAT (nucleic acid amplification testing), assign D+/R+

Medications

7. It is recommended to use age- and weight-based antiviral dosing ([Table 4](#)) (*Villeneuve 2013 [3a (treatment)], Launay 2012 [3a (treatment)], Pescovitz 2010 [3a (treatment)], Vaudry 2009 [3a (treatment)], Local Consensus 2013 [5]*).

Health Topics on CCHMC’s website:

[Cytomegalovirus \(CMV\) in the Immunocompromised Patient](#)

[Medications to Prevent Infections Following Kidney Transplant](#)

Future Research Agenda

1. Among children with SOT, what is the efficacy of prevention strategies, and what are the important differences between prophylaxis, preemptive therapy, and sequential/hybrid strategies?
2. Among children with SOT, what economic and safety concerns are important to consider when anticipating use of antiviral medications?
3. Among children with SOT, what is the optimal schedule for antiviral dosing and therapeutic drug monitoring?
4. Among children with SOT, what novel options are effective for the prevention and treatment of CMV infection and disease?
5. Among children with SOT, what indirect effects are associated with CMV infection?
6. Among children with SOT, what are the clinically relevant viral load thresholds to guide risk stratification, preemptive therapy, and therapeutic assessments?
7. Among children with SOT, which assays for the assessment of T cell immunity to CMV are able to predict the development of CMV disease, thereby allowing better risk stratification of patients and more targeted prevention strategies?

Table 4: Valganciclovir and Ganciclovir**A. Valganciclovir and Ganciclovir Dosing by Age**

Age	Valganciclovir (oral)	Ganciclovir (IV)
< 6 months	14 to 16 mg/kg daily	
6 months to 3 years	7 × BSA × GFR* daily Monitor for signs of toxicity†	All ages: 5 mg/kg IV every 24 hours‡
3 to 18 years	7 × BSA × GFR* daily Up to 900 mg daily‡	
≥ 18 years	900 mg daily‡	

* See GFR calculations below

† Toxicity includes neutropenia, thrombocytopenia and renal dysfunction

‡ Requires dose adjustments with renal dysfunction, see below

B. *GFR Calculations:

Patient	Equation	Comment
6 to 12 months	Cystatin C-based, using the Larsson equation: • $77.239 \times \text{CysC in mg/L}^{-1.2623}$ ◦ calculate to a maximum GFR of 100 mL/min/1.73m ²	<ul style="list-style-type: none"> • Consultation with nephrology may be appropriate in this age group. • By 1 year of age normal GFR is in the range of 100 mL/min/1.73 m². • This equation has not been validated below age 2 years. • See comments below on cystatin C-based alternative GFR calculation.
1 to 18 years	Bedside Schwartz equation: • $0.413 \times \text{height (cm)} / \text{SCr (mg/dL)}$ ◦ calculate to a maximum GFR of 120 mL/min/1.73m ²	<ul style="list-style-type: none"> • This equation has not been validated below age 2 years. It was developed in children with chronic kidney disease but is reasonable to use in this population. • This equation will underestimate GFR in children with markedly decreased muscle mass (see cystatin C-based alternative below).
≥ 18 years with renal dysfunction	Modification of Diet in Renal Disease (MDRD) • $175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203}$ × 1.212 (if patient is black) × 0.742 (if female) ◦ calculate to a maximum GFR of 120 mL/min/1.73m ²	<ul style="list-style-type: none"> • See renal dose adjustments below for this population. ‡
Alternatives	Cystatin C-based, using the Larsson equation: • $77.239 \times \text{CysC in mg/L}^{-1.2623}$ ◦ calculate to a maximum GFR of 120 mL/min/1.73m ²	<ul style="list-style-type: none"> • This is a muscle mass-independent alternative for GFR estimation for children older than 1 year of age (though this equation has not been validated below age 2 years). • With this method there is a risk of underdosing valganciclovir and ganciclovir in patients exposed to high dose steroids and calcineurin inhibitors; an elevated cystatin C in these patients will result in falsely low calculated GFR (<i>Muto 2010 [3a (prognosis)]</i>, <i>Risch 2001 [4b (prognosis)]</i>).
	Consultation	<ul style="list-style-type: none"> • Consultation with nephrology may be appropriate if there is uncertainty about the utility of creatinine- or cystatin C-based GFR calculations, or discrepancies between methods.
	Nuclear Medicine • calculated GFR in mL/min/1.73m ²	<ul style="list-style-type: none"> • A measured GFR (nuclear medicine) remains the gold standard for the precise assessment of kidney function, but it is somewhat complicated, costly, and it involves radiation.

C. ‡ Renal Dose Adjustments**Valganciclovir (≥18 years or who meet maximum daily dosing based on weight)**

- GFR 40 to 59 mL/min: 450 mg once daily
- GFR 25 to 39 mL/min: 450 mg every 2 days
- GFR 10 to 24 mL/min: 450 mg twice weekly

Ganciclovir

- GFR 50 to 69 mL/min: 2.5 mg/kg/dose every 24 hours
- GFR 25 to 49 mL/min: 1.25 mg/kg/dose every 24 hours
- GFR 10 to 24 mL/min: 0.625 mg/kg/dose every 24 hours
- GFR <10 mL/min: 0.625 mg/kg/dose 3 times/week following hemodialysis

Abbreviations: BSA = body surface area, cm = centimeters, CysC = cystatin C; dL = deciliter, GFR = glomerular filtration rate, IV = intravenous, kg = kilogram, L = liter, mg = milligrams, mL/min = milliliters per minute, m² = meters squared, SCr = serum creatinine

Appendix: Implementation Issues for CMV Monitoring Related to External Laboratory Facility Use

Attempts to implement Recommendation #2 may encounter difficulties when use of external laboratory facilities cannot be avoided. Under such circumstances, a reliable process to document the following relevant details will enable appropriate interpretation of assay results.

Specifics to be documented for each specimen

1. Laboratory facility
2. Specimen type (whole blood or plasma)
3. Unit of measure for results (copies/mL, IU/mL, etc.)
4. Assay used (if available)

In addition, implementation of this interpretation requires reliable access to these details within the context of clinic flow.

Members of CMV Prevention following Solid Organ Transplantation Team 2013

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Development Process

The process by which this guideline was developed is documented in the [Guideline Development Process Manual](#); relevant development materials are kept electronically. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic search and critical appraisal of the literature, using the [Table of Evidence Levels](#) described following the references, and examined current local clinical practices.

To select evidence for critical appraisal by the group for this guideline, the Medline, EmBase and the Cochrane databases were searched for dates of January 2007 to August 2013 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 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, review articles, and non-English articles. The resulting abstracts were reviewed 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. January, 2007 was the last date for which literature was reviewed for the previous version of this guideline. All previous citations were reviewed for appropriateness to this revision.

Once the guideline has been in place for five 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 recommendations have been reviewed and approved by clinical experts not involved in the development process and distributed to other parties as appropriate to their intended purposes.

The guideline was developed without external funding. All Team Members and Professional Support staff listed have declared whether they have any conflict of interest and none were identified. Conflict of interest declaration forms are on file with the Evidence group of the James M. Anderson Center for Health Systems Excellence.

Copies of this Evidence-Based Care Guideline (EBCG) and any available implementation tools 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/service/j/anderson-center/evidence-based-care/default/> 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;
- hyperlinks to the CCHMC website may be placed on the organization’s website;
- the EBCG may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at EBDMInfo@cchmc.org for any EBCG, or its companion documents, adopted, adapted, implemented or hyperlinked by the organization is appreciated.

NOTE: These recommendations result from review of literature and practices current at the time of their formulations. This guideline 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 recommendations to meet the specific and unique requirements of individual patients. Adherence to this guideline is voluntary. The clinician 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, its supporting evidence and the guideline development process, contact Lara Danziger-Isakov, MD, MPH in Infectious Diseases at (513) 636-9101 or Lara.Danziger-Isakov@cchmc.org.

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Note: When using the electronic version of this document,  indicates a hyperlink to the PubMed abstract.

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Note: Full tables of evidence grading system available in separate document:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (abbreviated table below)

Table of Evidence Levels (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5, 5a or 5b	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

<i>Strength</i>	<i>Definition</i>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (*direct benefit*)
4. Burden to patient of adherence to recommendation (*cost, hassle, discomfort, pain, motivation, ability to adhere, time*)
5. Cost-effectiveness to healthcare system (*balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis*)
6. Directness (*the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]*)
7. Impact on morbidity/mortality or quality of life