Complete Summary

GUIDELINE TITLE

Evidence-based care guideline for cytomegalovirus prophylaxis following solid organ transplants.

BIBLIOGRAPHIC SOURCE(S)

Cincinnati Children's Hospital Medical Center. Evidence-based care guideline for cytomegalovirus prophylaxis following solid organ transplants. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2007 Jul 6. 15 p. [68 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for cytomegalovirus prophylaxis following solid organ, blood and marrow transplants. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2001 Jun 7. 16 p. [145 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Cytomegalovirus (CMV) infection and disease following solid organ transplants

GUIDELINE CATEGORY

Evaluation
Prevention
Risk Assessment

CLINICAL SPECIALTY

Cardiology
Critical Care
Gastroenterology
Hematology
Infectious Diseases
Internal Medicine
Nephrology
Pediatrics
Pulmonary Medicine
Surgery

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide scientifically based recommendations for preventing or decreasing the incidence of cytomegalovirus (CMV) infection and cytomegalovirus disease

TARGET POPULATION

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 graft versus host disease (GVHD) following transplantation

These guidelines are <u>not</u> intended for use in the following:

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

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Risk Assessment for All Transplants

1. Testing pre-transplant cytomegalovirus (CMV) status of donors and recipients to stratify risk

2. Clinical assessment and treatment for conditions that may indicate risk for primary induction or reactivation of CMV disease
3. Quantitative polymerase chain reaction (PCR)

Solid Organ Transplants – Prophylactic Approach

1. Assessing patients regularly for evidence of CMV disease by clinical examination
2. Prophylactic therapy
    - Intravenous ganciclovir followed by oral ganciclovir
    - Intravenous ganciclovir in combination with CMV hyperimmune globulin
    - CMV hyperimmune globulin alone
    - Intravenous ganciclovir alone
    - Induction with oral valganciclovir (considered as an alternative in kidney recipients)

MAJOR OUTCOMES CONSIDERED

- Sensitivity and positive predictive value of cytomegalovirus (CMV) assays
- Incidence of cytomegalovirus infection following prophylactic therapy
- Adverse effects of prophylactic therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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 (Medical Subject Headings [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.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using a grading scale, and examined current local clinical practices.

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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

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.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation is followed by evidence grades (A-X) identifying the type of supporting evidence. Definitions of the evidence grades are presented at the end of the "Major Recommendations" field.

Laboratory Assessment

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

   Note: The specific laboratory tests are described (see table 3 in the original guideline document).

Prophylactic Approach

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

Solid Organ (see algorithm 1 in the original guideline document)

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 in the original guideline document for specific dosages and duration of therapy)

4. It is recommended that CMV prophylaxis be initiated for all high and intermediate risk solid organ transplant recipients (Hodson et al., 2005 [M]; Lowance et al., 1999 [A]; Merigan et al., 1992 [A]; Macdonald et al., 1995 [B]; Martin et al., 1994 [B]; Nichols & Boeckh, 2000 [S]; Patel et al., 1996 [S]). Such prophylaxis includes intravenous ganciclovir at induction doses for 14 days (Merigan et al., 1992 [A]; Cohen et al., 1993 [B]) followed by oral ganciclovir capsules for three months (Winston & Busuttil, 2003 [B], 2004 [C]; Rubin et al., 2000 [C]; Pescovitz et al., 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 et al., 1997 [A]; Flechner et al., 1998 [B]; Kletzmayr et al., 2000 [C]; Brennan et al., 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 et al., 2004 [A]). In heart recipients, valganciclovir is also presumed to be effective, but data are more limited (see Table 6 in the original guideline document, (Paya et al., 2004 [A]).

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

     Note 2: A higher incidence of neutropenia is reported in patients on valganciclovir, 8.2% versus 3.2% ganciclovir (Paya et al., 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 et al., 2004 [A]). Accordingly, the U.S. Food and Drug Administration (FDA) has cautioned against the use of valganciclovir in liver recipients (see Table 6 in the original guideline document) (Roche Pharmaceuticals 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 three months (limited data in pediatric patients): (Pescovitz et al., 1997 [C]; Local Consensus [E])
   - Intravenous ganciclovir at induction doses for 14 days in combination with CMV hyperimmune globulin (Ham et al., 1995 [D]; Bonham, 2000 [S]; Martin, 1995 [S])
   - CMV hyperimmune globulin alone (Glowacki & Smaill, 1994 [M]; Snydman et al., 1987 [A]; Saliba et al., 1989 [B]; Kathawalla et al., 1996 [D]; Basadonna et al., 1994 [D]; Arbo et al., 2000 [Q])
   - Intravenous ganciclovir daily for 30 days, followed by intravenous ganciclovir Monday through Friday until day +100 (Glowacki & Smaill, 1994 [M]; Winston et al., 1995 [A])

Note: Ganciclovir requires a dosage adjustment in patients with renal dysfunction (Taketomo, Hodding, & Kraus, 2000 [O]). (see Tables 7 through 9 in the original guideline document)

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
    - Hepatitis
    - Muscle pain
    - Gastroenteropathy
    - Leukopenia
    - Pneumonitis
    - Thrombocytopenia
    - Retinitis

8. Quantitative Polymerase Chain Reaction (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 et al., 2000 [C]; Sia et al., 2000 [C]).

Definitions:

Evidence Based Grading Scale:

M: Meta-analysis or systematic review
A: Randomized controlled trial: large sample
B: Randomized controlled trial: small sample
C: Prospective trial or large case series
D: Retrospective analysis
O: Other evidence
S: Review article
E: Expert opinion or consensus
F: Basic laboratory research
L: Legal requirement
Q: Decision analysis
X: No evidence

CLINICAL ALGORITHM(S)

A clinical algorithm is provided in the original guideline document for "Solid Organ Transplant Prophylactic Approach."

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is identified and classified for each recommendation (see "Major Recommendations") using the following scheme:

Evidence Based Grading Scale:

M: Meta-analysis or systematic review
A: Randomized controlled trial: large sample
B: Randomized controlled trial: small sample
C: Prospective trial or large case series
D: Retrospective analysis
O: Other evidence
S: Review article
E: Expert opinion or consensus
F: Basic laboratory research
L: Legal requirement
Q: Decision analysis
X: No evidence

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Prevent or decrease the incidence of cytomegalovirus (CMV) infection and cytomegalovirus disease and its associated significant morbidity and mortality

POTENTIAL HARMS

A higher incidence of neutropenia is reported in patients on valganciclovir, 8.2% versus 3.2% ganciclovir.

CONTRAINDICATIONS

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The U.S. Food and Drug Administration (FDA) has cautioned against the use of valganciclovir in liver recipients.

QUALIFYING STATEMENTS

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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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

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 cytomegalovirus (CMV) disease is an outcome measure monitored and reviewed by the transplant teams.

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Jun 7 (revised 2007 July 6)

GUIDELINE DEVELOPER(S)

Cincinnati Children's Hospital Medical Center - Hospital/Medical Center

SOURCE(S) OF FUNDING

Cincinnati Children's Hospital Medical Center

GUIDELINE COMMITTEE

Cardiac Clinical Pathway Team, Renal & Liver Transplant Teams 2007 Revision

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Cincinnati Children's Hospital Medical Center Physicians: Peter Manning, MD, Cardiac Surgery; Catherine Dent, MD, Cardiac Intensive Care/Transplant; William Border, MD, Cardiology; James Spaeth, MD, Anesthesia; Michael Alice Moga, MD, Cardiology/Fellow; Jeffrey Anderson, MD, Cardiology/Fellow; Pirooz Eghtesady, MD, Cardiac Surgery/Transplant; Jens Goebel, MD, Nephrology/Transplant; Kathleen Campbell, MD, Liver Transplant

Patient Services: Karen Uzark, PhD, CPNP, Cardiology/Transplant; Joyce Slusher, CPNP, Cardiology/Transplant; Christa Barlow, CNP, Cardiac Surgery; Melissa Magness, RN, Cardiac ICU; Tammy Lingsch, RN, A6 Central; Cynthia Wedekind, Pharm D, Clinical Pharmacy; Jenni Raake, RRT, Respiratory Care; Shawna Kirkendall, RN, Manager, A 6 Central

Clinical Effectiveness Services: Eduardo Mendez, RN, MPH, Dir. Evidence-Based Care, Facilitator; Eloise Clark, MPH, Guideline Program Administrator; Danette Stanko, MA, MPH, Epidemiologist; Kate Rich, Lead Decision Support Analyst; Carol Frese, RN, Medical Reviewer; Edward Donovan, MD, Medical Director, Clinical Effectiveness; Carol Tierney, MSN, RN, Education Specialist

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cincinnati Children's Hospital Medical Center Web site.

For information regarding the full-text guideline, print copies, or evidence based practice support services contact the Children's Hospital Medical Center Health Policy and Clinical Effectiveness Department at HPCEInfo@chmcc.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

The following Health Topics are available:

- Cytomegalovirus (CMV). Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2006 Oct. 2 p.
- Cytomegalovirus (CMV) in the immunocompromised patient. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2007 Jan. p. 3

Electronic copies: Available from the Cincinnati Children's Hospital Medical Center.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on March 11, 2004. This NGC summary was updated by ECRI Institute on February 26, 2008.

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