Complete Summary

GUIDELINE TITLE

Evidence based clinical practice guideline for cytomegalovirus prophylaxis following solid organ, blood and marrow transplants.

BIBLIOGRAPHIC SOURCE(S)

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]

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SCOPE

DISEASE/CONDITION(S)

Cytomegalovirus infection and disease following solid organ or blood and marrow transplants

GUIDELINE CATEGORY

Evaluation
Prevention
Risk Assessment

CLINICAL SPECIALTY

Cardiology
Critical Care
Gastroenterology
Hematology
Infectious Diseases

Nephrology
Pediatrics
Pulmonary Medicine

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 or blood and marrow transplant
- Patients that are 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 cytomegalovirus vaccine
- Non-transplant patients who are immunosuppressed

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/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

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
    - Valganciclovir (considered as an alternative but not recommended)
    - Intravenous ganciclovir in combination with CMV hyperimmune globulin

Solid Organ Transplants – Pre-emptive Approach

Ongoing assessment for clinical signs and symptoms of CMV disease

Blood and Marrow Transplants -- Prophylactic Approach

Ganciclovir prophylaxis (not routinely recommended for blood and marrow transplant recipients secondary to a relatively low attack rate of CMV disease and a high incidence of ganciclovir-induced neutropenia; intravenous immunoglobulin alone also not recommended)

Blood and Marrow Transplants –Pre-emptive Approach

1. Regular scheduled screening of recipients for CMV infection using qualitative polymerase chain reaction (PCR)
2. Intravenous ganciclovir therapy for patients with viremia or deoxyribonucleic acid (DNA) positivity detected by screening
3. Restarting ganciclovir at induction doses for blood and marrow recipients if, while on maintenance regimen, a positive qualitative PCR recurs and clinical symptoms are absent
4. Consultation with an infectious disease specialist if ganciclovir resistance is suspected (i.e., positive antigenemia or a positive qualitative PCR persists or if the level of antigenemia continues to rise)
5. Monitoring of absolute neutrophil counts and management of ganciclovir neutropenia with granulocyte colony-stimulating factor (G-CSF)
6. Considering use of foscarnet

MAJOR OUTCOMES CONSIDERED

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

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

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

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.

During formulation of these guidelines, 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

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines have been reviewed and approved by senior management, Legal Services, the Institutional Review Board, the hospital's Pharmacy and Therapeutics, Clinical Practices, Executive, and other 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]; Snydman, 1994 [S]; Martin, 1995 [S]; Flechner et al., 1999 [C]; Abecassis et al., 1996 [D]; Muir et al., 1998 [D]; Blok et al., 1998 [C]; Sakamaki et al., 1997 [C]; Solans et al., 1995 [C]; Humar et al., 1999 [C]).

   Note: The laboratory evaluation selected post transplant is dependent on whether a prophylactic or pre-emptive approach is selected as described below. The specific laboratory tests are described (see table 3 in the original guideline document).

Prophylactic Approach

Recommendations for CMV disease prophylaxis in solid organ or blood and marrow 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

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

2. It is recommended that CMV prophylaxis be initiated for all high and intermediate risk solid organ transplant recipients (Lowance et al., 1999 [A]; Macdonald et al., 1995 [B]; Martin et al., 1994 [B]; Merigan et al.,1992 [A]; Nichols & Boeckh, 2000 [S]; Patel et al., 1996 [S]). Such prophylaxis includes intravenous ganciclovir at induction doses for 14 days (Cohen et al., 1993 [B]; Merigan et al., 1992 [A]) followed by oral ganciclovir capsules for three months (Pescovitz et al., 1997 [C]; Local Expert Consensus [E]).

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

Note 2: It should be noted that the use of oral valganciclovir has been shown to have equivalent bioavailability to intravenous ganciclovir (IV GCV) in adult liver transplant recipients (Pescovitz et al., 2000 [B]) but there is not data for its use in children. Valganciclovir might be considered an alternative to IV GCV in the future, pending results of its use in the pediatric population.

3. 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:
    - IV GCV 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 Experience [E])
    - IV GCV at induction doses for 14 days in combination with CMV hyperimmune globulin (Bonham, 2000 [S]; Ham et al., 1995 [D]; Martin, 1995 [S])
    - CMV hyperimmune globulin alone (Saliba et al., 1989 [B]; Glowacki & Smaill, 1994 [M]; Kathawalla et al., 1996 [D]; Basadonna et al., 1994 [D]; Arbo et al., 2000 [Q]; Snydman et al., 1987 [A])
    - IV GCV daily for 30 days, followed by IV GCV Monday through Friday until day +100 (Winston et al., 1995 [A]; Glowacki & Smaill, 1994 [M])

    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)

4. 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 Expert Consensus [E]).

Blood & Marrow

5. Ganciclovir prophylaxis is not routinely recommended for blood and marrow transplant recipients secondary to a relatively low attack rate of CMV disease and a high incidence of ganciclovir-induced neutropenia (Goodrich et al., 1991 [B]; Goodrich et al., 1993 [B]; Winston et al., "Ganciclovir prophylaxis," 1993[B]; Locatelli et al., 1994 [C]; Przepiorka et al., 1994 [D]; Canpolat et al., 1996 [C]; Verdonck et al., 1997 [B]). Intravenous immunoglobulin (IVIG) alone is also not recommended to prevent CMV disease (Winston et al., " Intravenous immunoglobulin," 1993 [B]; "Guidelines for preventing opportunistic infections", 2000 [E]).

Pre-emptive Approach

Solid Organ

Laboratory Evaluation and Pre-emptive Therapy

1. There is insufficient evidence to make recommendations for any specific preemptive screening or therapy in low risk solid organ transplant recipients. It is reasonable to consider an ongoing approach of assessment for clinical signs and symptoms of CMV disease (Local Expert Consensus [E]).

Blood & Marrow (see algorithm 2 in the original guideline document)

Laboratory Evaluation (see table 3 in the original guideline document)

2. It is recommended that pre-emptive screening for CMV infection be considered for all blood and marrow transplant recipients. Screening consists of a qualitative polymerase chain reaction (PCR), weekly from weeks 2 through 12-post transplant. This is then followed by monthly screening for at least 6 months (Local Expert Consensus [E]; Goodrich et al., 1991 [B]; Ljungman et al., 1996 [C]; Nichols & Boeckh, 2000 [S]).

   Note: The first qualitative CMV PCR obtained at week 2 may serve as the baseline for blood and marrow recipients. Laboratory evaluation for suspected disease or to follow up a positive qualitative PCR could include repeat qualitative PCR (Brennan et al., "Polymerase chain reaction-triggered," 1997 [B]) and/or any of the tests listed (see Table 3 in the original guideline document).

Pre-emptive Therapy (see table 6 in the original guideline document)

3. For blood and marrow transplant recipients with viremia or deoxyribonucleic acid (DNA) positivity detected by screening, (Locatelli et al., 1994 [C]; Manteiga et al., 1998 [C]) consider therapy with IV GCV at induction doses for 7 to 14 days (Boeckh, Myerson, & Bowden 1994 [S]; Boeckh et al., 1996 [B]; Schmidt et al., 1991 [B]) followed by IV GCV Monday through Friday until day +100 or for a minimum of three weeks, whichever occurs later (Goodrich et al., 1991 [B]; Schmidt et al., 1991 [B]; Boeckh et al., 1996 [B]; Canpolat et al., 1996 [C]; Centers for Disease Control and Prevention, 2000 [E]).

   Note: As shown in limited solid organ data (Pescovitz et al., 1997 [C]) oral ganciclovir, capsules or suspension, may be considered as an alternative to IV GCV following induction until day +100 or for a minimum of three weeks, whichever occurs later (Local Expert Consensus [E]).

4. If, while on maintenance dosing with ganciclovir, a positive qualitative PCR recurs and clinical symptoms are absent, researchers report restarting ganciclovir at induction doses for blood and marrow recipients (Boeckh et al.,1996 [B]).
5. If positive antigenemia (Moretti et al., 1998 [C]) or a positive qualitative PCR persists (Local Expert Consensus [E]) after four weeks of pre-emptive therapy with ganciclovir or if the level of antigenemia continues to rise after three weeks of ganciclovir, ganciclovir resistance may need to be considered.

Consultation with an infectious disease specialist may be appropriate in this situation.

6. It is recommended that absolute neutrophil counts (ANCs) be monitored at least twice weekly in blood and marrow recipients while receiving ganciclovir. Consider managing ganciclovir neutropenia by adding granulocyte colony-stimulating factor (G-CSF) or temporarily stopping ganciclovir for more than two days if the recipient's ANC is <1,000 (Przepiorka et al., 1994 [D]; Goodrich et al., 1993 [B]; Goodrich et al., 1991 [B]; Verdonck et al., 1997 [B]; Spector et al., 1996 [B]; Winston, "Ganciclovir prophylaxis," 1993 [B]; Canpolat et al., 1996 [C]). Ganciclovir may be restarted when the recipient's ANC is ≥1,000 for two consecutive days (Canpolat et al., 1996 [C]).

   Note 1: Foscarnet may also be considered if the ANC remains <1,000 for more than five days after ganciclovir has been discontinued (Moretti et al., 1998 [C]).

   Note 2: Both ganciclovir and foscarnet require dosage adjustments in patients with renal dysfunction (Taketomo, Hodding, & Kraus, 2000 [O]; Moretti et al., 1998 [C]) (see tables 7 thru 9 in the original guideline document).

   Note 3: Use of intravenous immunoglobulin or CMV-intravenous immunoglobulin has not consistently shown reduction of CMV disease (Bowden et al., 1991 [B]) but individually, case reports have suggested a decreased incidence (Winston et al., 1987 [B]; Messori et al., 1994 [M]).

Clinical Assessment

1. 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

Definitions:

Evidence Based Grading Scale:

A: Randomized controlled trial: large sample
B: Randomized controlled trial: small sample
C: Prospective trial or large case series
D: Retrospective analysis
E: Expert opinion or consensus
F: Basic laboratory research
S: Review article
M: Meta-analysis

Q: Decision analysis
L: Legal requirement
O: Other evidence
X: No evidence

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for:

- Solid Organ Transplant Prophylactic Approach
- Blood and Marrow Transplant Pre-emptive 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:

A: Randomized controlled trial: large sample
B: Randomized controlled trial: small sample
C: Prospective trial or large case series
D: Retrospective analysis
E: Expert opinion or consensus
F: Basic laboratory research
S: Review article
M: Meta-analysis
Q: Decision analysis
L: Legal requirement
O: Other evidence
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
- Decrease hospital stay
- Decrease hospital charges

POTENTIAL HARMS

Ganciclovir can induce neutropenia

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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

The implementation process for each Cincinnati Children's Hospital Medical Center (CCHMC) guideline is a phase in a larger process of Guideline Development. This process is utilized for every guideline but is not addressed in the content of every guideline.

At the start of each guideline, a projected implementation date is determined. Reservations for education are then made (Grand Rounds, Patient Services Inservices). When the guideline is complete and enters into the Approval Process, education planning begins. Changes created by the guideline are outlined as well as anticipated outcomes. The implementation date is confirmed. Education is provided. The guideline is implemented and pilot information collection started. The Guideline Coordinator makes daily rounds and eligible children are followed to document the use of the guideline. The implementation phase aids in finding areas for improvement or question. When issues identified are improved, the guideline progresses to the monitoring phase.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

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

DATE RELEASED

2001 Jun 7

GUIDELINE DEVELOPER(S)

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

SOURCE(S) OF FUNDING

Cincinnati Children's Hospital Medical Center

GUIDELINE COMMITTEE

Clinical Effectiveness Team for Cytomegalovirus Prophylaxis (CMV)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

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

None available

NGC STATUS

This NGC summary was completed by ECRI on March 11, 2004.

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