MAYO CLINIC LABORATORIES

Test Definition: CMVC8

Cytomegalovirus (CMV) CD8 T-Cell Immune Competence, Quantitative Assessment by Flow Cytometry, Blood

Overview

Useful For

Assessing cytomegalovirus (CMV)-specific immune competence in allo-hematopoietic stem cell transplantation patients who are at risk for developing late CMV disease (beyond day 100 after transplant)

Assessing CMV-specific immune competence in solid organ transplant patients who are at high risk for CMV reactivation posttransplant

Monitoring immune competence in patients post-primary CMV infection after transplant who are at risk for CMV reactivation after the cessation of antiviral prophylaxis

Identifying individuals who are likely to be protected from posttransplant CMV infection and those who are at higher risk of CMV reactivation

The global CD8 T cell immune competence assay is useful for determining over immunosuppression within the CD8 T cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

Special Instructions

- Quantitative CMV Immune Competence Assay Patient Information

Method Name

Flow Cytometry

NY State Available

No

Specimen

Specimen Type

WB Sodium Heparin

Ordering Guidance

Patient must be cytomegalovirus seropositive and have 1 or more of the 5 major histocompatibility complex alleles: HLA A1, A2, B7, B8, or B35 to utilize this assay.

Additional Testing Requirements

It is important to ascertain the patient's and the donor's cytomegalovirus serostatus, as well as the patient's major histocompatibility complex class I HLA haplotype, before ordering this assay; see 1DIS / Human Leukocyte Antigens (HLA) A-B-C Disease Association Typing Low Resolution, Blood.

Shipping Instructions

Testing is performed Monday through Friday. The test may be canceled if specimens are not received in the laboratory by Friday at 5 p.m. Central time.

Samples arriving on weekends and observed holidays may be canceled.

Collect and package specimen as close to shipping time as possible. Ship specimen overnight in an Ambient Shipping Box-Critical Specimens Only (T668) following the instructions in the box. It is recommended that specimens arrive within 24 hours of collection.

Necessary Information

Ordering healthcare professional name and phone number are required.

Specimen Required

Supplies: Ambient Shipping Box-Critical Specimens Only (T668)
Container/Tube: Green top (sodium heparin)
Specimen Volume: 20 mL
Collection Instructions: Send whole blood specimen in original tube. **Do not aliquot.**
Additional Information: For serial monitoring, it is recommended that specimens are collected at the same time of day.

Forms

Quantitative CMV Immune Competence Assay Patient Information (T592)

Specimen Minimum Volume

10 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
WB Sodium Heparin	Ambient	48 hours	GREEN TOP/HEP

Clinical & Interpretive

Clinical Information

Cytomegalovirus (CMV), a double-stranded DNA virus, belongs to the Herpesviridae family of viruses and is structurally similar to other herpes viruses. Although many human strains of CMV exist, there is little genetic homology between human CMV and CMV of other species. The reported seroprevalence rates of CMV range from 40% to 100% in the general population. In the urban United States, the seroprevalence of CMV has been reported to be 60% to 70%.(1) However, data from Mayo Clinic's laboratory indicate that the seroprevalence in the Midwestern US population is closer to 30% (unpublished observations).

Once CMV infection occurs, the virus spreads hematogenously to almost every organ. After acute infection, the virus enters a latent phase. Activation from this phase can be seen after acute illness, immunosuppression in allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplantation, or use of chemotherapy agents. CMV infection or reactivation has been implicated in allograft rejection in renal (2) and cardiac transplantation.(1) In cardiac transplants, CMV infection has been shown to contribute to accelerated development of transplant atherosclerosis (cardiac allograft vasculopathy). CMV remains a significant cause of morbidity and mortality after HSCT. Of allogeneic HSCT patients who are CMV-seropositive, 60% to 70% will experience reactivation and, without ganciclovir or other preemptive therapy, 20% to 30% will develop end-organ disease.(3)

CD8 T cells play a critical role in viral immunity, and CD8 T-cell effector functions include cytotoxicity and cytokine production. Cytotoxicity occurs after CD8 T-cell activation, causing target cell apoptosis. Cytotoxic T-cell responses mediate killing of target cells via 2 major pathways, granule-dependent (perforin and granzymes) and granule-independent (Fas and Fas ligand [FasL]) mechanisms. The granule-dependent pathway does not require the *de novo* synthesis of proteins by effector CD8 T cells, but rather it utilizes preformed lytic granules located within the cytoplasm. Among the proteins in these preformed lytic granules are the lysosomal-associated membrane proteins (LAMP), including LAMP-1 (CD107a) and LAMP-2 (CD107b). These proteins are not normally found on the surface of T cells. Degranulation of activated CD8 T cells occurs rapidly after T-cell receptor (TCR) stimulation, exposing CD107a and CD107b. The cytokines produced by activated T cells include interferon-gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), macrophage inflammatory protein 1 alpha (MIP-1 alpha), macrophage inflammatory protein 1 beta (MIP-1 beta), and interleukin-2 (IL-2). Several studies have shown the importance of cytotoxic T-cell responses to CMV in conferring protection from subsequent CMV disease.

Antiviral drugs have helped reduce the incidence of early CMV infection, and acyclovir and ganciclovir have been the mainstay of antiviral treatment for a number of years, although these drugs have poor bioavailability.(4) The development of the new antiviral drugs valacyclovir and valganciclovir (by the addition of a valine ester) has increased the bioavailability of these drugs by 10-fold.(4) There is some data to suggest valganciclovir prophylaxis may be considered for HSCT patients who are at high risk for infection and disease, though there is a need for further study in this area.(5)

Two main strategies have been used for the prevention of early CMV infection and disease in CMV-seropositive patients and in seronegative recipients who receive a seropositive graft-preemptive therapy:
-Patient monitoring for CMV infection and treatment only when CMV viremia is present.
-Prophylactic management-where all patients receive treatment after transplantation with the goal of preventing CMV disease.(5) The disadvantage of prophylactic therapy is that it requires monitoring for myelosuppression and infections-side effects of antiviral drug therapy. Despite this disadvantage, there are several reasons to consider

prophylaxis, including the fact that the incidence of recurrent infections after treatment is 30% to 40%,(5) patients receiving preemptive therapy have a 5% CMV disease break-through, and prophylaxis reduces the risk of viral reactivation.

Late CMV infection occurs 3 months after transplantation and is now recognized as a significant cause of morbidity after allogeneic HSCT.(6) These complications usually occur in the setting of continued immunosuppression for chronic graft-versus-host disease (GVHD). The clinical manifestations of late CMV disease differ slightly from those seen early after transplantation. Within the first 100 days after HSCT, almost all patients with CMV disease have CMV pneumonia or gastrointestinal disease. In late CMV disease, the more unusual manifestations of CMV infection (eg, CMV retinitis, CMV-associated bone marrow failure, or CMV encephalitis) tend to occur.(7) These late manifestations occur in a setting of continued CMV-specific T-cell immunodeficiency. Therefore, it is necessary to monitor CMV-specific CD8 T-cell responses, in addition to viral load, to effectively identify patients at higher risk of CMV disease.

It has been shown that ganciclovir may delay the recovery of the protective CMV-specific T-cell response, which may contribute to the occurrence of late CMV disease.(8) The use of ganciclovir as early treatment after detection of CMV in blood or other body fluid and as a prophylaxis for CMV infection in bone marrow transplant (BMT) and heart transplant recipients has dramatically reduced the incidence of CMV in these immunocompromised hosts. Yet, early treatment and prophylaxis have not been uniformly successful, with up to 15% of BMT recipients developing CMV disease after discontinuation of antiviral therapy. Similarly, patients undergoing lung transplantation have been shown to be only transiently protected with antiviral agents. These data suggest that the CMV-specific responses necessary for protection may not recover during the time the host is receiving antiviral therapy.

Ganciclovir exerts its antiviral effects at the stage of viral DNA replication and, therefore, in the presence of the drug, infected cells may express some of the immediate early and early gene products, but not the full complement of CMV genes required for replication and virion formation. In latently infected CMV-seropositive individuals, the human leukocyte antigen (HLA) class I-restricted cytotoxic T lymphocyte response to CMV is predominantly specific for epitopes derived from structural virion proteins. Therefore, in patients receiving ganciclovir, the viral antigens may be inadequate to activate host T-cell responses, resulting in the failure to reconstitute CMV-specific immunity. In fact, a prospective, randomized placebo-controlled study of ganciclovir prophylaxis revealed that when ganciclovir therapy is discontinued, a larger fraction of patients (who received the drug) are deficient in CMV-specific T-cell immunity at day 100 than in the placebo group.(8) That study also showed that bone marrow donor serology has an important influence on the early detection of virus-specific T-cell responses.(8) Not all medical centers use ganciclovir for prophylaxis; some use acyclovir and the same findings may apply in this case as well.

In a more recent study, it was shown that impaired CD8 function was associated with the use of high-dose steroids, bone marrow as a source of stem cells, and CD8 T-cell lymphopenia.(3) In the absence of high-dose steroids, low-level subclinical CMV antigenemia was found to stimulate both CD4 and CD8 functional recovery in recipients of ganciclovir prophylaxis, suggesting that subclinical CMV reactivation while on antiviral therapy can be a potent stimulator of T-cell function.(3) Regardless of antiviral therapy, immunologic reconstitution remains the key element in protection from late-onset CMV disease.

This test assesses the number of CMV-specific CD8 T cells and their function (activation via production of the cytokine IFN-gamma and cytotoxic potential via CD107a and CD107b as markers of degranulation) using a panel of 5 major

histocompatibility complex (MHC) class I alleles (HLA A1, A2, B7, B8, and B35) along with their respective immunodominant CMV epitopes. This 3-part assay allows a comprehensive assessment of CMV-specific CD8 T cell immunity and, when combined with evaluation of viremia using molecular analyses, provides a more accurate picture of the nature of CMV reactivation and the corresponding immune response than evaluating viremia alone (9).

Assessment of Global CD8 T-Cell Function:
CD8 T cell activation occurs either through the TCR-peptide-MHC or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific.

Impairment of global CD8 T cell activation (due to inherent cellular immunodeficiency or as a consequence of immunosuppression by therapeutic agents) results in reduced production of interferon-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin.

The incorporation of global CD8 T cell function in this assay is helpful in determining if the lack of CMV-specific (antigen-specific) response is due to a global impairment in CD8 T cell function, due to immunosuppression or other causes, or whether the lack of CMV CD8 T cell immunity is unrelated to overall CD8 T cell function.

The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(10) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(11-13) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(11) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening(13), and during summer compared to winter.(14) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Reference Values

Total CD3 T cells: 884-5830 x 10(3)/mL
Total CD8 T cells: 168-1847 x 10(3)/mL
Total CMV CD8 T cells: 0-115 x 10(3)/mL

The adult reference values were determined for healthy adult controls ages 20 to 80 years (n=94), for HLA A1, A2, B7, B8, and B35 alleles.

Reference values for cytomegalovirus (CMV) specific T cells that are functional (interferon-gamma+, IFN-g+) and have cytotoxic activity (CD107a and CD107b expression, CD107 a/b+):
Total CMV CD8 T-cells IFN-g: 0.028-52.200 x 10(3)/mL
Total CMV CD8 T-cells CD107a/b: 0.252-50.760 x 10(3)/mL

The 95% confidence interval reference values were determined from 102 healthy adult donors:
Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%
CD107a/b expression (as % CD8 T cells): 8.5-49.1%

The reference values were developed for each of the following 4 major histocompatibility complex class I alleles: A1, A2, B7, and B8 (n=45). We were unable to develop ranges for the B35 allele due to a lack of matching donors. The data is expressed as the absolute number of CMV-specific CD8 T cells that are IFN-gamma+ or CD107a/b+.

Interpretation

For allogeneic hematopoietic stem cell transplantation (HSCT) and solid organ transplant patients who are cytomegalovirus (CMV)-seropositive and at risk for CMV reactivation, posttransplant results should be compared to pretransplant (preconditioning/baseline) results.

The report includes absolute CD3 and CD8 T-cell counts as well as a derived CMV-specific CD8 T-cell count (derived from CD3 and CD8 T-cell counts). The absolute count of CMV-CD8 T cells that are activated and have cytotoxic function in response to specific CMV peptide is also provided. The data from the 3 components of this assay should be interpreted together and not individually.(15)

In the setting of CMV viremia, frequent monitoring of CMV-immune competence helps define the evolution of the CMV-immune response. In this clinical context, CMV-immune competence should be measured as frequently as viral load to determine correlation between the 2 parameters. CMV-specific CD8 T-cell counts may show a decline in numbers over time in the absence of active infection or antigenemia.

The absence of CMV-specific CD8 T cells may be a risk factor in the immune-compromised or immune-incompetent transplant patient, who is at risk for CMV reactivation. The presence of CMV-specific CD8 T cells may not be protective in itself. If the CMV-specific CD8 T cells do not show appropriate cytotoxic function (due to the fact that they recognize CMV epitopes that do not effectively induce a cytotoxic response), these patients may be at higher risk of an inadequate immune response to CMV infection.

While the reference values provide a guideline of CMV-specific CD8 T-cell numbers and function in a cohort of healthy individuals, baseline (pretransplant/preconditioning) assessments should be taken into consideration when determining CMV-specific immune competence posttransplant. Correlation between data from multiple post-transplant specimens (if available) and the presence or absence of viremia (or active CMV disease) also are useful in the interpretation of results.

CD8 T cell counts are elevated when the immune system is initially reconstituted post-HSCT, and the CD4 to CD8 ratio can be inverted for about 12 months post-HSCT.

Interferon-gamma (IFN-gamma) and CD107a/b expression below the defined reference range are consistent with a global impairment in CD8 T cell function, most likely due to over-immunosuppression. IFN-gamma and CD107a/b levels greater than the defined reference range are unlikely to have any clinical significance.

Cautions

The assay is specific for 5 major histocompatibility complex (MHC) class I alleles: HLA A1, A2, B7, B8, and B35, which cover about 70% of the White population and approximately 40% of the Asian population. It is important to ascertain the patient's and the donor's cytomegalovirus (CMV) serostatus, as well as the patient's MHC class I HLA haplotype, before ordering this assay; see 1DIS / Human Leukocyte Antigens (HLA) A-B-C Disease Association Typing Low Resolution, Blood.

Serial assessment of CMV-immune competence posttransplant in the setting of viremia is recommended to establish CMV-specific immune response trends. In the absence of viremia, CMV-immune competence assessment should include a day 100 or later posttransplant specimen or a specimen after the cessation of antiviral prophylaxis in solid organ transplantation patients.

A single measurement of CMV-immune competence is not sufficient to determine immune response to CMV; serial measurements are essential to proper interpretation of the results. Appropriate interpretation of results requires a pretransplant measurement of CMV-specific immunity to assess baseline immune competence.

Since healthy, asymptomatic individuals may not have detectable CMV-specific CD8 T cells, for these individuals, the absence of CMV-specific CD8 T cells alone may not be a risk factor.

The global CD8 T cell immune competence assessment is specific only for CD8 T cells; it does not provide information for overall T cell competence. Further studies are needed to determine if, within the reference range, certain levels of interferon-gamma and CD107a/b expression confer greater or lesser degrees of risk for infectious disease.

Timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. See data under Clinical Information.

Clinical Reference

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Performance

Method Description

Assessment of cytomegalovirus (CMV)-immune competence measures 3 different components of the immune response: 1) numerical analysis of the CMV-specific CD8 T-cell population (enumeration), which provides absolute counts of the antigen-specific CD8 T cells, 2) functional, and 3) cytotoxic analysis of the CMV-specific CD8 T cells (functionality and cytotoxic activity).

Enumeration:
Enumeration of CD8 T cells is performed on whole blood using Beckman Coulter MHC class I tetramers, specific for 5 major histocompatibility complex (MHC) class I alleles-A1, A2, B7, B8, and B35.

Panel I consists of whole blood stained with CD3, CD8, and CD4 fluorochrome conjugated antibodies followed by incubation at ambient temperature in the dark. The sample is then treated with a tetramer lyse reagent. The flow count bead solution is then thoroughly mixed and added at a volume exactly equal to the volume of whole blood added. After the addition of beads, the sample is analyzed on a flow cytometer.

In Panel II, whole blood is stained with CD3 and CD8 fluorochrome conjugated antibodies and incubated with the relevant MHC class I tetramer at ambient temperature in the dark. The sample is then treated with a tetramer lyse reagent and washed with wash buffer. The sample is then analyzed on a flow cytometer an the CMV-specific CD8 T cells are analyzed as a percentage of the total CD8+ T cells calculated in Panel I.

The final absolute counts for CD3 T cells, CD8 T cells, and CMV-specific CD8 T cells are expressed as cells/mL of whole

blood.

Functionality (Intracellular Interferon-gamma: IFN-gamma) and Cytotoxic Activity (Surface CD107a/b):
Peripheral blood mononuclear cells (PBMC) are isolated from the same sample of whole blood used for enumeration. PBMC are stimulated with human leukocyte antigen (HLA) allele-specific CMV peptides and costimulatory molecules (CD28/CD49d) in a polypropylene tube. Antihuman CD107a/b conjugated with fluorochrome is added along with the peptides to capture the transient expression of the CD107a and CD107b, which are markers for cytotoxic activity. A mixture of Brefeldin A (BFA) and monensin is also added during the stimulation to facilitate the intracellular accumulation of IFN-gamma, which is detected using an antihuman IFN-gamma antibody conjugated with fluorochrome. A similar tube is prepared for the patient sample with the absence of exogenous CMV peptide and this tube serves as the unstimulated control (back-ground stimulation). Thus, there are 2 tubes for every HLA allele. After peptide stimulation, EDTA is added to the sample to arrest activation and to remove adherent cells from the activation tube. Antihuman CD8 antibody and the relevant MCH-class I tetramer are added and incubated at ambient temperature in the dark. This step is followed by a simultaneous lysis and fixation of the cells to prepare them for permeabilization. Cells are then washed and permeabilized with BD FACS Permeabilizing Solution 2. The antihuman IFN-gamma antibody is added, and the sample is incubated at ambient temperature in the dark. Finally, the cells are washed and analyzed by flow cytometry. The delta percent (stimulation in the presence of CMV-specific peptide stimulation in the absence of specific peptide) CMV-specific CD8 T cells expressing IFN-gamma and CD107a/b is used to calculate the absolute count of activated and functionally cytotoxic CMV-specific CD8 T cells.(Functionality: IFN-gamma assay, Unpublished Mayo method; Cytotoxic Activity: Betts MR, Brenchley JM, Price DA, et al. Sensitive and viable identification of antigen-specific CD8+ T cells by a flow cytometric assay for degranulation. J Immunol Methods. 2003;281 (102):65-78; Betts MR, Price DA, Brenchley JM, et al. The functional profile of primary human antiviral CD8 T cell effector activity is dictated by cognate peptide concentration. J Immunol. 2004;172(10):6407-6417)

Global CD8 T-Cell Immune Competence:
Peripheral blood mononuclear cells (PBMC), which contain CD8 T cells, are stimulated with a mixture of phorbol myristate acetate (PMA) and ionomycin, and with stimulatory signals derived using antibodies against the costimulatory molecules CD28/CD49d. The cells are simultaneously treated with a mixture of BFA and monensin, which blocks extracellular secretion of IFN-gamma, enabling intracellular retention and detection of the protein. PBMCs that have not been stimulated are used as a control to determine the background levels of IFN-gamma and CD107a and CD107b. The cells are analyzed on a flow cytometer and analysis involves gating (defining) of the CD8 T cells using an antihuman CD8 antibody. Specific IFN-gamma and CD107a and CD107b signals are determined within the "gated" CD8 T cell population. Global CD8 T cell immune competence is measured by the amount of IFN-gamma produced (CD8 T-cell functional activity) and surface expression of CD107a/b (cytotoxicity assessment) relative to the unstimulated control and is interpreted on the basis of the reference range determined from healthy adult donors.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available

3 to 6 days

Specimen Retention Time
PBMC: 7 days

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed using an analyte specific reagent. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
86356 x 6
86359
86352

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CMVC8	CMV CD8 T-Cell QN by Flow Cytometry	95184-8

Result ID	Test Result Name	Result LOINC® Value
28157	CMV CD8 T cells CD107 A1	95191-3
28158	CMV CD8 T cells CD107 A2	95190-5
28159	CMV CD8 T cells CD107 B7	95189-7
28160	CMV CD8 T cells CD107 B8	95188-9
28161	CMV CD8 T cells CD107 B35	95187-1
30694	CD107a/b expression	95203-6
28155	CMV CD8 T cells IFN-g B35	95193-9
28151	CMV CD8 T cells IFN-g A1	95197-0
28152	CMV CD8 T cells IFN-g A2	95196-2

28153	CMV CD8 T cells IFN-g B7	95195-4
28154	CMV CD8 T cells IFN-g B8	95194-7
30693	IFN-gamma expression	95204-4
28162	Total CMV CD8 T cells CD107a/b	95186-3
28156	Total CMV CD8 T cells IFN-g	95192-1
28163	Interpretation	69052-9
28145	CMV CD8 T cells A1	95185-5
28146	CMV CD8 T cells A2	95202-8
28147	CMV CD8 T cells B7	95201-0
28148	CMV CD8 T cells B8	95200-2
28149	CMV CD8 T cells B35	95199-6
28150	Total CMV CD8 T cells	95198-8
28143	Total CD3 T cells	8122-4
28144	Total CD8 T cells	14135-8