International Society of Nephrology

Advancing Worldwide Kidney Health

•CMV Infection in the Renal Transplant Recipient

Elham Ramezanzadeh

Assistant Professor Of Nephrology

GUMS

- Cytomegalovirus (CMV) is a **globally widespread** virus.

- Like other members of the herpesvirus family,
- latent infection after the resolution of
- acute (or primary) infection. ..
- reactivates frequently ..Patients who are CMV seropositive have latent infection.

- Secondary, symptomatic disease may present later, reflecting either reactivation of latent CMV or, less commonly, reinfection with a novel exogenous strain.

- **INFECTION VERSUS DISEASE** :
- CMV infection

- CMV disease

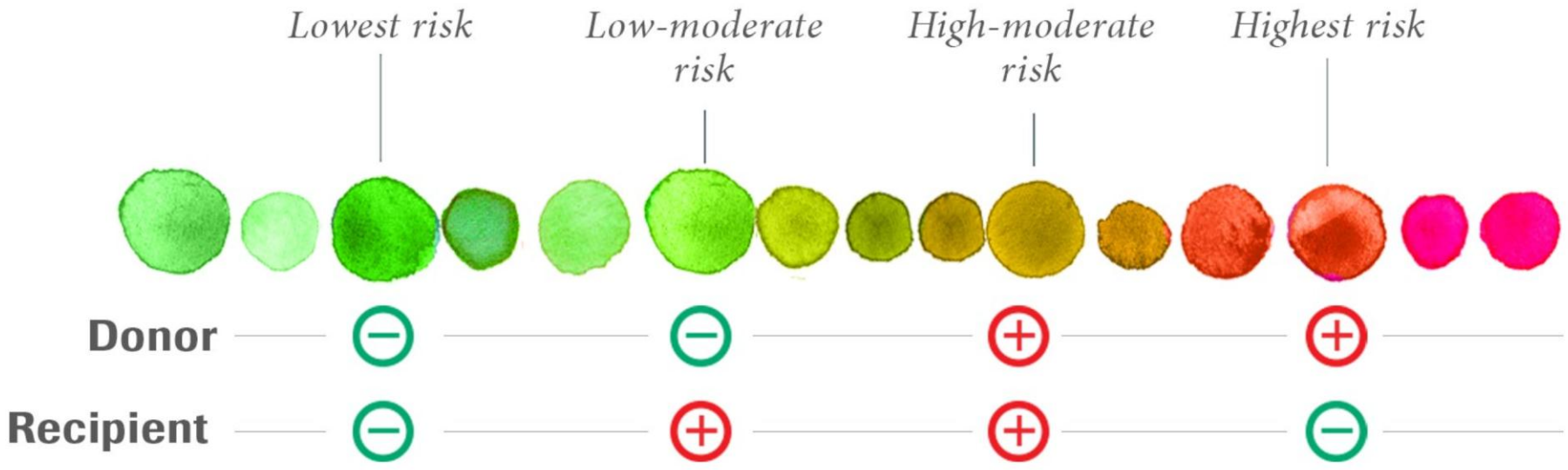
The risk of CMV reactivation is highest in the setting of systemic immunosuppression.

CMV can present in kidney transplant recipients

allograft failure and death;

Preventive therapy decreases reactivation

- **EPIDEMIOLOGY :**



International Society of Nephrology
Advancing Worldwide Kidney Health

- **CLINICAL MANIFESTATIONS :**

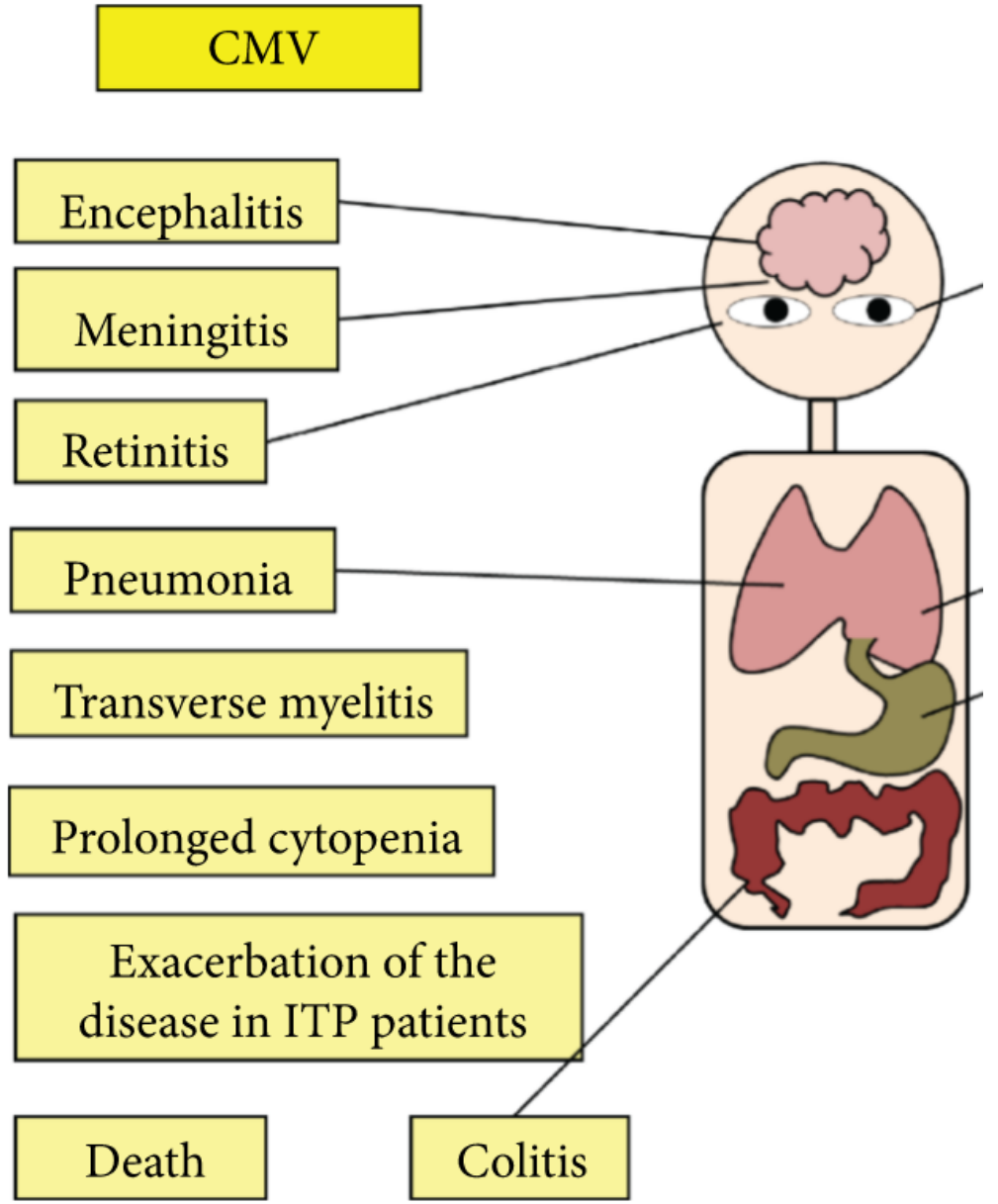
1-CMV syndrome

2-tissue-invasive CMV disease

The **most common 0f tissue-invasive CMV disease** in **kidney transplant** recipients is **gastrointestinal disease** .

tissue-invasive CMV disease :

- **Enteritis and/or colitis –**
- **Hepatitis –**
- **Pancreatitis –**
- **Pneumonitis –**
- **Meningoencephalitis –**
- **Retinitis –**
- **Nephritis –**



- **DIAGNOSIS:**

- The diagnosis of CMV should be suspected among transplant recipients who present with **signs or symptoms compatible** with CMV syndrome or disease.

- However, the clinical manifestations of CMV are **nonspecific** and **overlap** with many infectious and noninfectious illnesses.

- Thus, among **all transplant** recipients, **laboratory confirmation** is required to establish the diagnosis.
- Occasionally, a biopsy with histopathologic examination of tissue is necessary to diagnose tissue-invasive CMV disease .
-

- Among transplant recipients, we **confirm** the diagnosis of CMV infection or disease with nucleic acid testing (NAT). **NAT using the PCR** for the detection of CMV DNA is the diagnostic modality of **choice** for **most t**ransplant clinicians.

- PCR has broad linear range, low limits of detection, and low risk of contamination .

- PCR is primarily used to evaluate **blood, CSF**, or, among patients who have a funduscopic exam that is compatible with CMV retinitis, **ocular or vitreal fluid** .
- /

- Many commercial and laboratory-developed PCRs for CMV are used.Their results are not interchangeable, given differences in sample preparation, nucleic acid extraction, primers, targets, and PCR protocol .
- Efforts to standardize test results ..enabled by the release of an international reference standard by the WHO .
- Standardized assay results are reported as international units/mL, whereas non standardized assay results are reported as copies/mL.
- In general, there are no widely accepted PCR thresholds that differentiate among latent infection, low-level active infection, and CMV disease.
- Clinical judgment must be used when evaluating PCR results.
- In general, viral loads are highest among patients with tissue-invasive CMV disease.

.

- **Qualitative CMV PCR assays** are very sensitive **but cannot distinguish between latent DNA** and **actively replicating virus**. Given these limitations, **qualitative P**CR has a **limited role** for the **diagnosis or management** of patients with CMV infection.

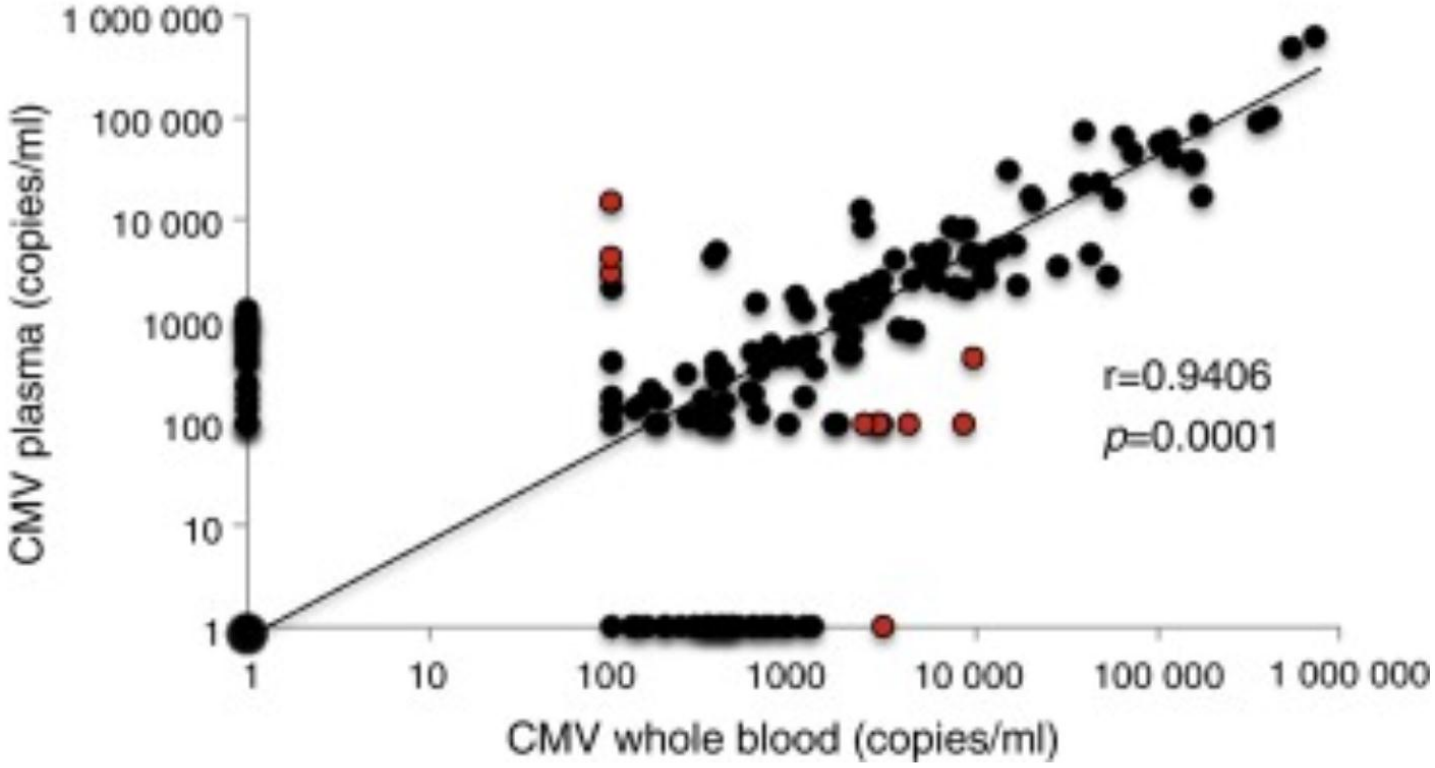
- **Quantitative CMV DNA** assays include:
- ●COBAS AmpliPrep/COBAS TaqMan CMV test –is a **real-time PCR test that targets the polymerase** gene and is **calibrated to** the **WHO international ..**reported range from **137 to 9,100,000 international units/mL** . approved by the FDA for serial testing to evaluate changes in CMV load in solid organ transplant recipients .

- ●COBAS CMV test –is a **real-time PCR** test that **targets the polymerase gene** and is calibrated to the WHO international standard to quantify the CMV load in plasma with a reported range from **34.5 to 10,000,000 international units/mL**. approved by the FDA as an aid in the management of CMV in solid organ transplant recipients and hematopoietic stem cell recipients.

- ●Artus CMV RGQ MDx test –**real-time PCR** test that targets the CMV **major immediate early gene** and is calibrated to the WHO international standard to quantify CMV DNA from plasma with a reported range of **159 to 7,940,000** international units/mL . approved by the FDA to use as an aid in the management of solid organ transplant patients **undergoing treatment** for CMV.

- ●**Real Time CMV test** –is a **real-time PCR** test that targets the **UL34 and UL80.5 genes** and is **calibrated t**o the **WHO international standard** to quantify the CMV load in plasma with a reported range from 50 to 156,000,000 international units/mL. The test has been approved by **the FDA** to use as an aid in the management of **hematopoietic stem cell** transplant recipients who are undergoing anti-CMV therapy.

- **Whole blood versus plasma** :



Comparison of the CMV viral load in plasma and whole blood. Pearson correlation coefficient (r) is shown for the comparison. Discordant measurements are shown in red in which the viral load was elevated in plasma, but not in whole blood or vice-versa. A 10-base logarithmic scale was used for the graph in order to better separate the data, although the Pearson correlation was calculated linearly.

CMV ANTIGENEMIA ASSAYS :

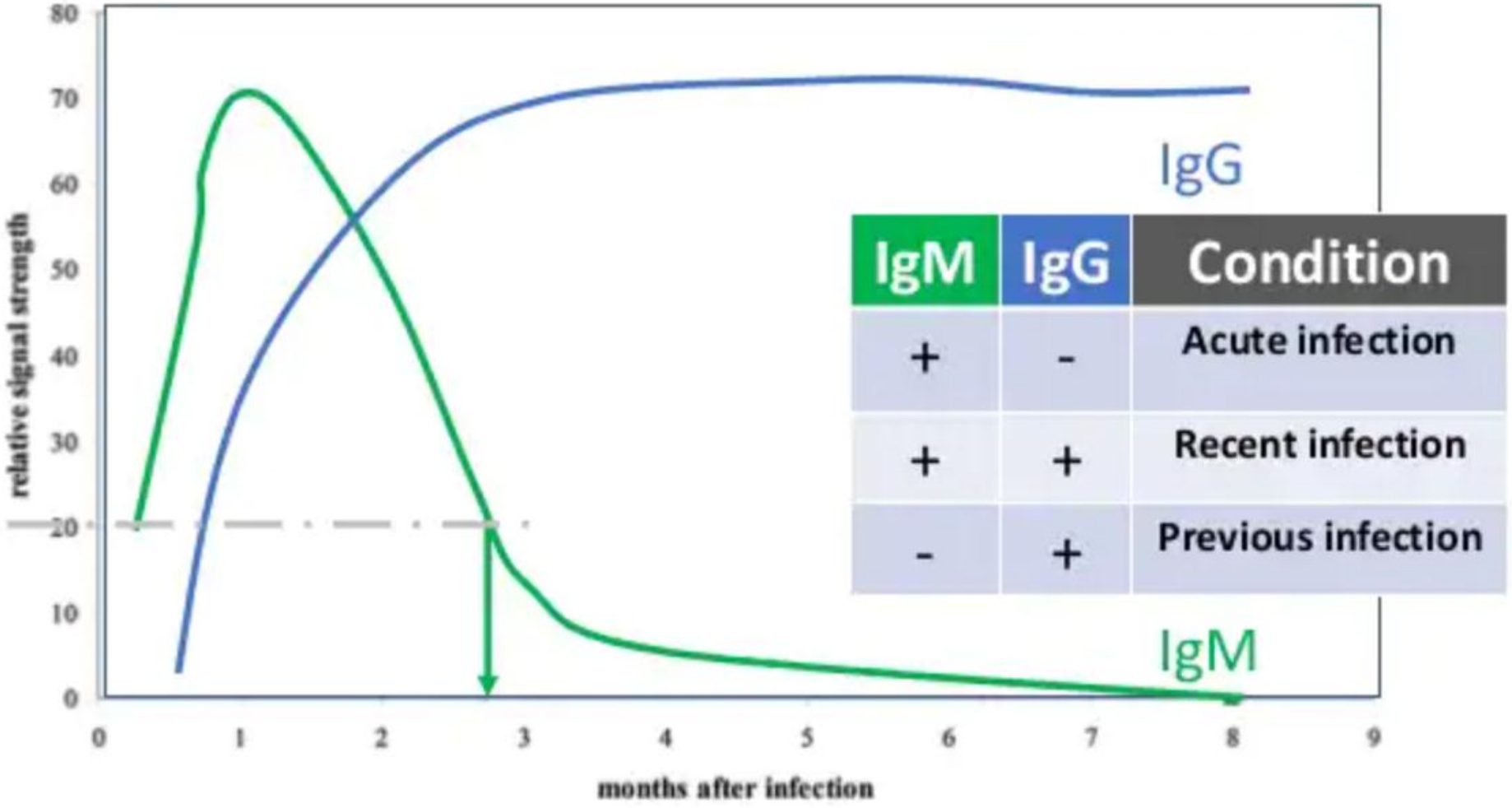
- CMV antigenemia assays permit the rapid and direct detection of CMV proteins (pp65) in peripheral blood PMN leukocytes.

- This technique employs fluorescently labeled monoclonal antibodies specific to the pp65 lower matrix protein of CMV in PMN . Results are generally available within 24 hours.

- The antigenemia test is more sensitive than culture for the detection of CMV in blood.
- The limitations :
- lack of stability of the whole-blood specimen.
- insensitivity when the patient has a low neutrophil count (<1000 cells/microL), and
- more difficulty standardizing test results .
- most laboratories have **moved away from** antigenemia testing to quantitative molecular methods.

.

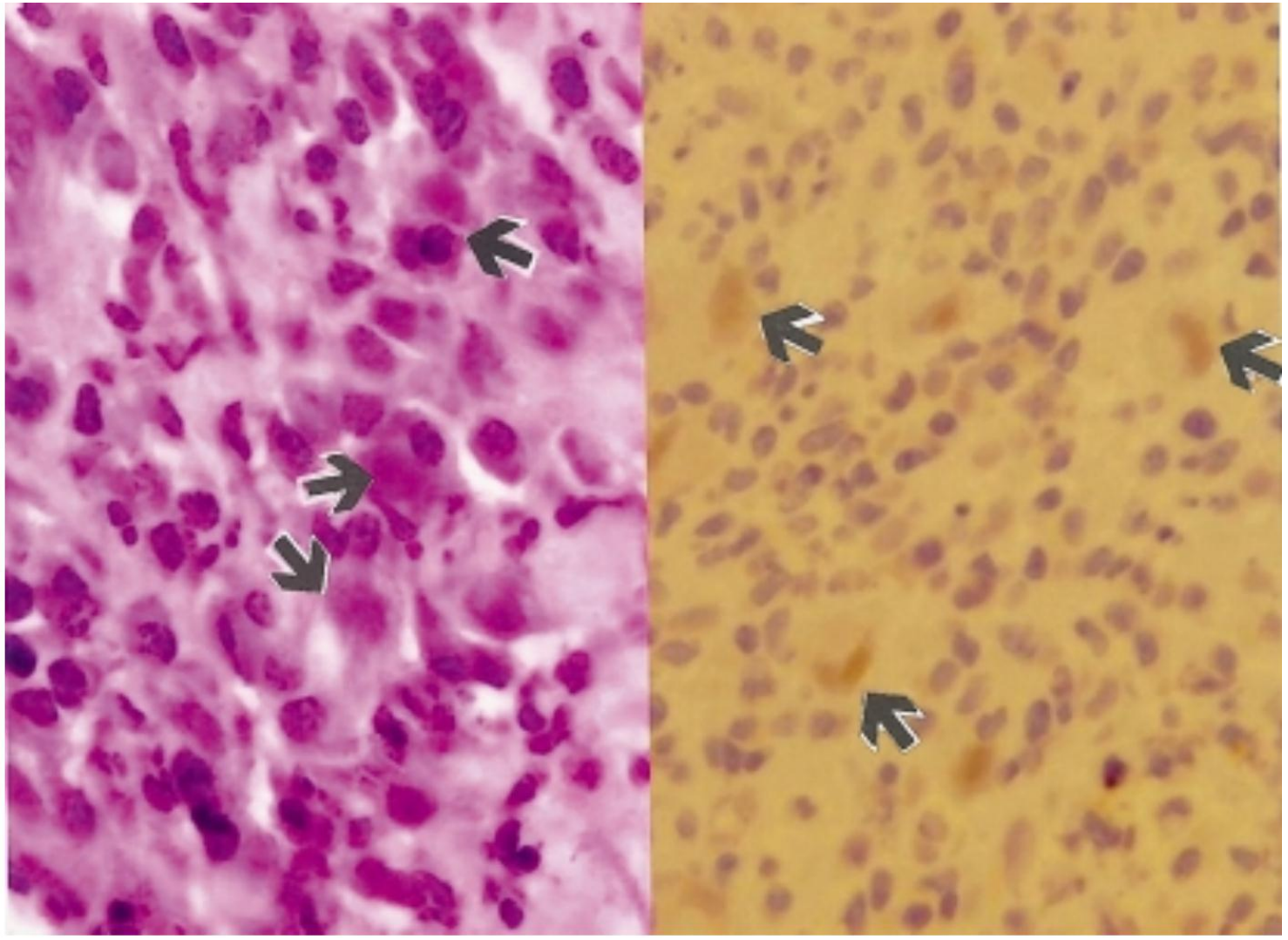
- **SEROLOGY**



IgM	IgG	Condition
+	-	Acute infection
+	+	Recent infection
-	+	Previous infection

International Society of Nephrology
Advancing Worldwide Kidney Health

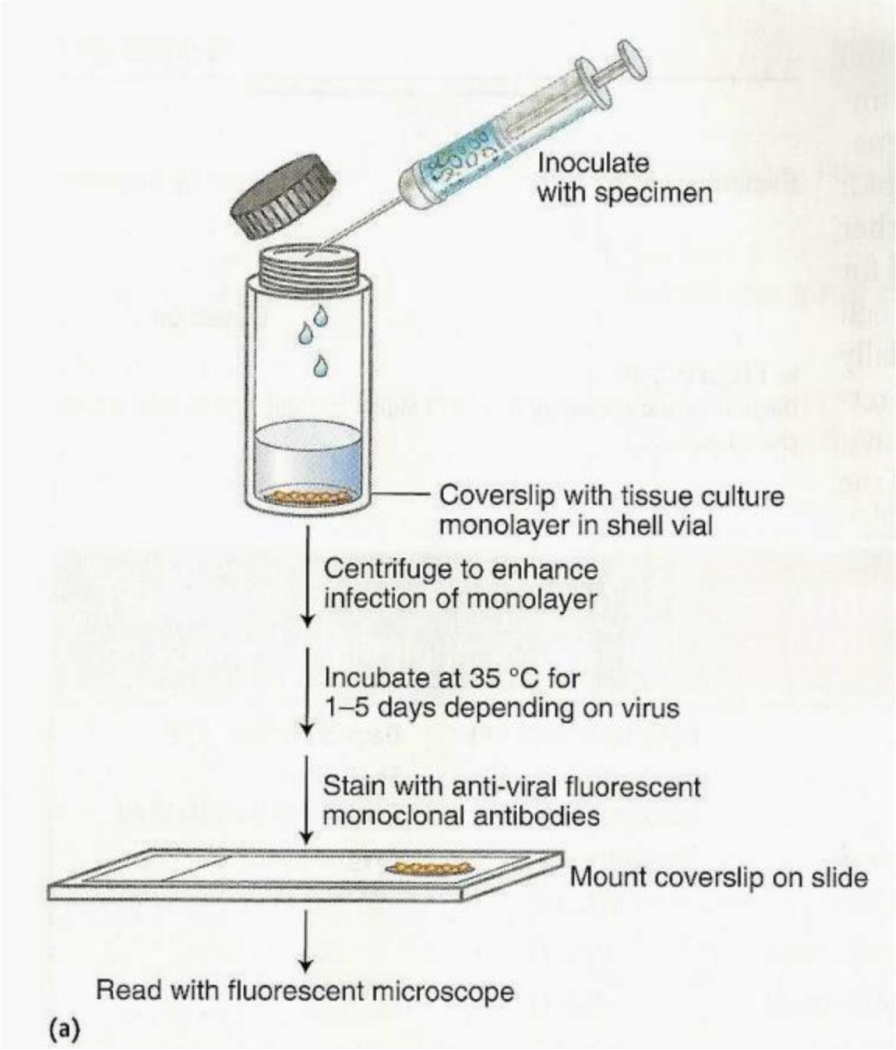
- **HISTOPATHOLOGY** :

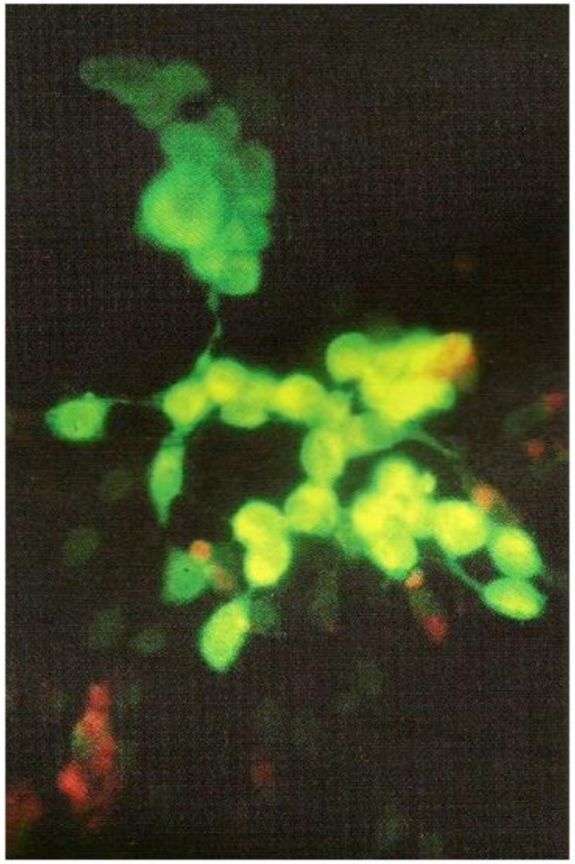


Intranuclear inclusion body of cytomegalovirus (CMV) in the gastrointestinal tract. (A) Hematoxylin and eosin-stained sample (arrow, original magnification, 400x). (B) Immunohistochemical staining with anti-CMV monoclonal antibody (arrow, original magnification, 100x).

Virus Cell Culture - Shell Vial

- **CULTURE :**
- **Conventional culture**
- **Shell vial culture :**





- **Diagnosis in Tissue-invasive disease** :

- The gold standard : CMV inclusions or positive CMV-specific IHC staining on histopathology.

- A positive culture from a biopsy specimen is also considered consistent with CMV disease, but, tissue may be contaminated.

- since PCR results are often available prior to the biopsy results and may influence the decision to initiate antiviral therapy.

- establish the baseline ,,to monitor response to therapy.

- A negative plasma or whole-blood PCR does not exclude tissue-invasive CMV disease,
- The absence of CMV inclusions on histopathology also does not exclude tissue-invasive disease Culture of urine specimens should be avoided
- .

International Society of Nephrology

Advancing Worldwide Kidney Health

- **Pneumonitis:**

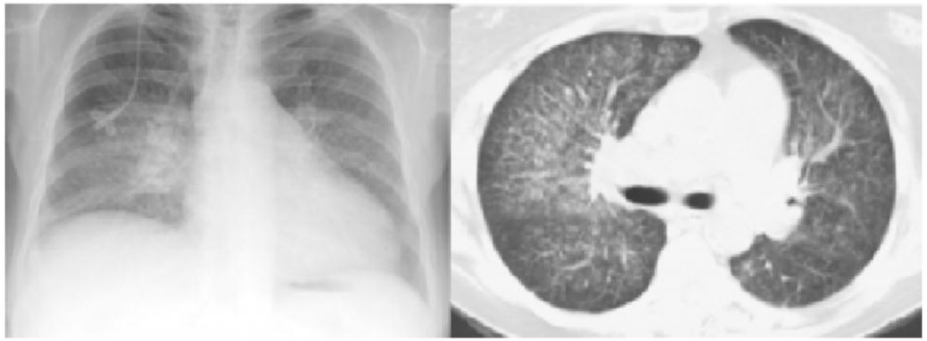


Figure 1 Figure 1: Chest radiograph and CT scan of chest showing bilateral fine nodular infiltrates

Published in 2004

CMV Pneumonia in a Renal-Transplant Recipient: Diagnosis and Treatment

- **Gastrointestinal disease:**
- the diagnosis relies upon culture and histopathology of a tissue biopsy.
- Gastrointestinal disease may be focal and patchy, so multiple biopsies may be needed to confirm.
- CMV gastrointestinal disease cannot be excluded based on a negative plasma or whole-blood PCR result.
- CMV culture of stool specimens has no role for the diagnosis of CMV colitis.

- **Central nervous system disease:**
- For the diagnosis of CMV encephalitis, myelitis, or polyradiculopathy, viral-load testing of CSF has become the standard of care.
- CMV culture of CSF specimens has poor sensitivity.

- CNS disease in solid organ transplant recipients is very rare.

• CLINICAL SIGNIFICANCE in renal allograft:

- CMV increases mortality and graft loss.
- CMV has both direct and indirect effects on kidney transplant outcomes:
- Direct effects : cytopathic effects on kidney allograft cells that can lead to nephropathy and allograft loss ..
- Indirect effects : upregulation of human leukocyte antigens (HLAs) and adhesion molecules.

- **RISK FACTORS** —
- The primary risk factor for CMV infection or disease is the CMV serostatus of the donor/recipient pair:
- **Other risk factors** for CMV disease relate to increased net states of immunosuppression and include:
- Use of **lymphocyte-depleting agents** (eg, antithymocyte globulin [**ATG]**) for **induction** immunosuppression
- Use of **mycophenolate for maintenance** immunosuppression.
- Administration of lymphocyte-depleting therapy or **high-dose glucocorticoids** to treat **acute cellular rejection**
- **Lymphopenia pretransplant or posttransplant** .
- **Multiple organ transplantation, such as combined kidney-pancreas** transplantation, also appears to increase the risk of developing CMV infection or disease .

- **PREVENTION :**
- Optimization of immunosuppression

- Indications for a preventive strategy :
- It is important to prevent CMV infection in high-risk patients.

use CMV prophylaxis in CMV (D+/R-) and CMV R+ kidney transplant recipients.

- do not give CMV prophylaxis to CMV D-/R- patients beyond administering acyclovir to prevent HSV infections given their very low risk of CMV infection and disease .

- the risk of active CMV infection or disease occurs in fewer than 5 percent of such patients.

- **Preventive strategies** :
- **prophylactic doses**
- **preemptive therapy ….detection of active** CMV infection with weekly or biweekly CMV testing (ie, a preemptive approach) .

- **CMV prophylaxis** :
- **valganciclovir.**
- We start valganciclovir in the **immediate posttransplant** period.
- The dose and duration … CMV serotype combination and on the patient's eGFR:

- For CMV **D+/R-** patients, use **valganciclovir** at **900 mg orally once** daily for **six months**

- For CMV **R+** patients, use **valganciclovir at 900** mg orally once daily for **three months**

- **40 to 59 mL/min**, the correct dose of prophylactic **valganciclovir** is **450 mg once daily**.

- .

- *Available anti-CMV drugs include*:
- IV ganciclovir,
- oral valganciclovir,
- IV foscarnet,
- and IV cidofovir.
- These drugs interfere with viral replication by targeting **CMV DNA polymerase**.

selection of agent depends on:

. the severity of the clinical manifestations and

. the level of viremia and,

. among some patients, patterns of drug resistance.

- **Initial therapy :**
- **life-threatening** illness: (eg, pneumonitis, meningoencephalitis), high viral loads, or moderate to severe gastrointestinal disease (with either diarrhea or nausea and vomiting) with full treatment doses of antiviral therapy with **ganciclovir**, **5 mg/kg IV every 12 hours** (adjusted for kidney function) .
- **mild CMV disease** (ie, those with minimal signs and symptoms) who are expected to have good absorption of oral medications, we use full treatment doses of valganciclovir.
- Oral valganciclovir has **good oral bioavailability** and spares patients from the risks and cost of **central venous access**; however, the drug's absorption relies on enterocyte metabolism of the prodrug, which can be variable in people with **gastrointestinal tract disease**, resulting in low or variable levels.
- Patients who **do not respond** to reduction of immunosuppression and to antiviral therapy may require an alternative regimen, further reduction of immunosuppression, and/or adjunctive treatment with **cytomegalovirus immune globulin(CytoGam, CMV Ig) or intravenous immune globulin (IVIG).**

- **Active CMV infection management:**

- **repeat** the **PCR one week** after stopping the antimetabolite to assess response and add an antiviral if there is continued evidence of viremia. If the patient continues to have evidence of active viral replication, start antiviral treatment **even in the** absence of symptoms. PCR should be **checked weekly**.

- While we typically do not restart the antimetabolite upon resolution of viremia, we reintroduce it at a lower dose in patients who are at increased risk of rejection.

- We monitor the blood for CMV replication with PCR at weekly intervals for four weeks to ensure that CMV does not reactivate at the lower antimetabolite dose.

- **If** CMV infection **recurs, we discontinue** the antimetabolite indefinitely.

- **If** CMV reactivation does not occur, we continue the antimetabolite **at the reduced dose**.
- .

- **CMV disease** :
- **Reduction of immunosuppression** :
- depends on the:

1- severity of disease, as well as

2-the clinical and virologic response to treatment.

- one of the antiviral regimens at the full treatment doses described above **until:**
- **the clinical signs and symptoms** of CMV disease are **completely resolved** and
- there is no evidence of CMV viremia in **two blood PCRs** performed at least **one** week apart.
- The typical duration of therapy is **21 days** but can **range from 14 to 28 days or longer**.
- The **longer t**ime period is typically required in people with **GI tract disease**.
- **Adverse effects** :
- **Hematologic suppression**, in particular **leukopenia** (including **neutropenia**), appears to be the **most significant and common adverse e**vent associated with ganciclovir and valganciclovir.
- When leukopenia occurs, dose reduction of these agents **should be avoided,** given the risk of promoting **resistance .**
- Patients should be evaluated for other potential causes of leukopenia (eg, **mycophenolate**, **trimethoprim-sulfamet**hoxazole).
- It is also important to note that **CMV itself** can **cause leukopenia** and t**hrombocytopeni**a and that these abnormalities often improve with antiviral therapy.

- The addition of GCSF should be considered before discontinuing ganciclovir or valganciclovir. /
- **Resistance testing** :

- life-threatening disease despite antiviral agents and reduction of immunosuppression agents: cytomegalovirus immune globulin (CytoGam, CMV Ig) and IVIG irrespective of the mutation that is identified and even if no mutation is identified.

Two antiviral drugs are undergoing clinical development and may have roles in the treatment of multidrug-resistant CMV disease;

- Maribavir : oral drug that inhibits UL97 kinase. no evidence of myelosuppression or nephrotoxicity .

- Brincidofovir : orally bioavailable lipid conjugate of cidofovir that has not been associated with kidney or bone marrow toxicity .
- It has broad antiviral efficacy and inhibits DNA polymerase.

- .

Thanks for your attention