Hey Clinical Problem Solvers! My name's T.J. La, a 6th year MD/JD/LLM student at Baylor College of Medicine and the University of Houston Law Center, and I am so excited to share with you more about cytomegalovirus, or CMV for short.

CMV is part of the *Herpesviridae* family and is known as human herpesvirus 5 (HHV-5). As herpesviruses are known to establish lifelong latency in their hosts after the primary infection, reactivation of CMV infection can cause disease in an immunocompromised host. CMV reinfection can also be seen in patients by being infected with a different strain of CMV.

The virus spreads through sexual and nonsexual contact with infected bodily fluids including saliva and urine (especially from babies and young children), mucus in the cervix, semen, stool, and breast milk to nursing infants. Contaminated surfaces can also serve as a vector for transmission.

Risk factors for contracting the virus include being immunocompromised (eg, solid organ or stem cell transplant recipients, HIV/AIDS, taking immunosuppressants like steroids), CMV serostatus of donor and recipient in transplant patients, and exposure to children most commonly in a daycare setting. Children typically have a less severe infection than adults.

Most people with CMV infection are asymptomatic and are not aware that they've been infected.

However, infection in heathy people, **called CMV mononucleosis**, can lead to mild illness including symptoms of fever, fatigue, sore throat, swollen glands, swollen tonsils and even a rash in about 1/3rd of patients.

- The nonspecific rash is often described as maculopapular and is a result of an immunologic response to the virus. Classically, this hypersensitivity drug rash associated with amoxicillin therapy given to patients with CMV mononucleosis can also be seen in EBV mononucleosis.

In those that are immunocompromised, CMV can have indirect immunomodulatory effects, higher rates of invasive bacterial and fungal infections, and transplant rejection. Organ specific manifestations include:

- the GI tract with CMV colitis, gastritis, hepatitis, and esophagitis.
- the CNS with meningoencephalitis, Guillain-Barré syndrome, transverse myelitis, and cranial nerve palsy.
- the lungs with pneumonitis.
- the eyes with chorioretinitis.

It is also important **to distinguish CMV mononucleosis from EBV mononucleosis** since both present with many of the same signs, symptoms and lab findings. In comparison to EBV, CMV is less likely to cause lymphadenopathy, tonsillopharyngitis, or splenomegaly, while patients may have more systemic symptoms/signs such as fevers and hepatitis. The prevalence of CMV mononucleosis increases with age in comparison to EBV. If a patient screens negative for EBV mononucleosis as indicated by a negative heterophil antibody test, then consider the possibility of an acute CMV infection especially since CMV infection rarely causes a false-positive

heterophil antibody test. The other acute mononucleosis syndromes to be aware of are acute Toxoplasmosis and acute HIV infection.

Labs will often show absolute lymphocytosis and atypical lymphocytes. Sometimes, you can see decreased Hgb, platelets, and haptoglobin. A positive ANA, RF, presence of cold agglutinins, and gammopathies can also be a clue for CMV infection, though not always present.

- As well, CMV mononucleosis can also cause subclinical hepatitis without signs of jaundice. Abnormal liver chemistry tests can be seen including a small increase in serum total bilirubin and serum alkaline phosphatase, and concurrent elevation of ALT and AST not exceeding five times the normal value.

For diagnosis, it is first important to have a compatible syndrome and then use your diagnostic tests. Serology should be used in the diagnosis of primary infection only in immunocompetent hosts. CMV IgM antibodies can be positive in patients during the symptomatic phase of the illness. Though, IgM antibody levels may not peak until 4-7 weeks after onset of the infection, and IgM antibodies produced in response to CMV infection may stay elevated for up to a year or longer in some patients which can make it hard to rule out CMV as the cause of a fever. An elevated CMV IgM may also be a false positive or cross-react with other viruses like EBV, making its use in the clinical setting difficult at times.

- On the flipside, CMV IgG antibody levels typically increase at least fourfold during an acute infection and thus monitoring IgG antibody is the best way to see if CMV is the cause of fever, though this is time consuming and won't lead to a definitive answer in the short term.

Detecting serum CMV PCR can also be helpful because an elevated CMV viral load can be suggestive of invasive disease. Sometimes, the serum CMV PCR can be negative despite significant organ disease. In times of uncertainty, a biopsy is needed to prove tissue-invasive disease of certain organs, such as the GI tract.

With respect to treatment, CMV infections in immunocompetent hosts are usually self-limiting and no specific antiviral therapy is needed.

For treatment of serious disease in immunocompromised patients, consider systemic antivirals (eg, ganciclovir, foscarnet, cidofovir). If a transplant patient is at risk of CMV infection, prophylactic antivirals such as valganciclovir may be needed.

Overall, 60-90% of adults have been infected with CMV. With primary infection in immunocompetent hosts, most are asymptomatic but some can develop CMV mononucleosis with symptoms of fever, fatigue, sore throat, and sometimes a rash. In immunocompromised patients, CMV can cause severe disease involving the GI tract, CNS, lungs or retina that require antiviral treatment.

We hoped you enjoyed this schema!