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RECURRENT FEVER IN A 5 MONTHS OLD MALE

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J.G is a 5 month old male from Antipolo admitted for the first time at PCMC because of fever.

He was apparently well until 4 months prior to admission (at 1 month of age) when he developed intermittent low grade fever accompanied by eye discharge. Consultation was done and was advised observation. The eye discharge resolved spontaneously but the fever persisted.

After 2 weeks, or 3 1/2 months PTA, J.G. still had occasional episodes of low grade fever. On consult with another physician, CBC was done which revealed leukocytosis. He was confined at Unciano Hospital in Antipolo for five days and was diagnosed to have bronchopneumonia. Gentamicin IV and 2 other unrecalled antibiotics were given. Patient was discharged improved and remained a febrile for 1 1/2 months.

Two months prior to admission (at three months of age) fever recurred this time accompanied with cough, and audible wheezes. He was active with good suck. On consult, he was given amoxicillin and salbutamol nebulization. There was no relief after one week of treatment. Medications were shifted to cephalexin and prednisone which were taken for four days, affording temporary relief of the cough.

One and a half months PTA, still with symptoms of recurrent fever, occasional cough and colds, J.G. was admitted at Antipolo Doctors Hospital. Initial CBC showed leukocytosis and chest x-ray showed bronchopneumonia. He was given ceftriaxone for three days which was shifted to ampicilin-sulbactam for the next 7 days. On the 10th hospital day, with lysis of fever and normal WBC count, he was discharged and remained afebrile.

Two weeks PTA, low grade fever recurred, again accompanied by non productive cough and occasional wheezing. He was given amoxicillin for 7 days but without improvement. He was then referred to Philippine Children's Medical Center and was subsequently admitted.

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REVIEW OF SYSTEMS

Three was no weight loss or jaundice

BIRTH / MATERNAL HISTORY

J.G. was born full term to a 29 year old primigravid via. Caesarian section because of shoulder malpresentation. He had good cry and activity with a birth weight of 3.2 kilograms. He stayed in the hospital for four days. Jaundice noted on the third day of life which spontaneously resolved after 7 days.

JG's mother had regular prenatal check-up since 1 1/2 months gestation. At 7 months of gestation she had cough and colds later follwed by vaginal spotting and hypogastric pain. she was admitted at maternity clinic for 5 days and was diagnosed to have chronic endocervicitis. She was treated with co-amoxiclav, isoxsuprine, terbutaline for a week and advised complete bed rest.

NUTRITIONAL HISTORY

Breastfed for 1/12 months then given feeding with S26 consuming five ounces every 3 hours supplemental feeds given at 4 months.

GROWTH AND DEVELOPEMENT

At par with age

PAST MEDICAL HISTORY:

No history of blood transfusion.

No history of skin infections.

FAMILY HISTORY

J.G. was the only child. His father is a free-lance agent and his mother is a grade school teacher.

On admission, he was awake, alert, not in cadiorespiratory distress with the following vital signs. Anthropometric measurements were at par with age. Physical examination centered on the chest which revealed symmetrical chest expansion, no retractions harsh breath sounds, with rhonchi and wheezes on both lung fields. There was no organomegaly.

Neurological examination was normal

The admitting impression was Bronchopneumonia

Initial laboratory exams included a CBC which showed leukocytosis and thrombocytosis and toxic granulation on peripheral smear. Chest x-ray showed prominent densities on both inner lung zones. Blood culture was done. Ampicillin was started and salbutamol nebulization was given.

On the 5th HD, JG remained febrile. Repeat CBC showed slight decrease in WBC with *predominance* of segmenters. Intravenous antibiotics were then shifted to ceftazidime, oxacillin and amikacin.

On the 6th hospital day, diarrhea, ensued with four bouts of watery, yellowish, mucoid, nonblood streaked stools occuring daily. Stool examination was normal. Blood, stool and urine cultures showed no growth. Lumbar tap showed normal results.

On the 9th HD, JG's diarrhea persisted and he remained highly febrile. Chest x-ray *showed no improvement*. Atypical *pneumonia* was then considered and erythromycin was started. J.G. was noted to be jaundiced with hepatomegaly, the liver edge was sharp and palpable 3 cm below the right costal margin (liver span=9 cm). Bilirubin determination showed direct hyperbilirubinemia. SGPT was elevated more than 3.5x the normal. Urine CMV, serum EBV as well as immunoglobulin titers were determined.

On the 11th HD, JG's juandice deepened and his liver doubled in size with the spleen likewise palpable. Alkaline phosphatase was elevated. Hypoalbuminemia was noted so albumin was transfused.

On the 12th HD, abdominal CT Scan revealed mild hepatomegaly and moderate ascites. Mild to moderate bilateral effusion and bilateral segmental pneumonia were likewise evident. Severe anemia was noted so blood transfusion was given. Erythromycin was shifted to imipenem since repeat chest x-ray showed progression of bilateral pneumonia with right pleural effusion. He was reffered to a gastroenterologist. Hepatitis profile, BMA and liver biopsy were suggested. Prothrombin time and PTT were deranged thus Vitamin K and FFP were given. Urine CMV culture was positive. The mother was advised serological CMV testing but refused.

On the 15th HD, JG had episodes of squinting (non-purposeful blinking of both eyes) for a few minutes. Phenobarbital was given. He was referred to a neurologist who entertained a possible CNS infection. Serum eletrolytes were normal. Cranial ultrasound showed meningitic changes. A repeat lumbar puncture was deffered due to deranged bleeding parameters. Antibiotics were shifted to cefipime. The next day by BMA done revealed normal cellular marow but with note of unidentified marrow cells. Ganciclovir was started at 10 mkday every 11 hours. After only four doses of ganciclovir, JG's juandice resolved, his fever lysed and his liver decreased in size while liver function tests were almost normal.

On the 18th HD, on evaluation by an ophthalmologist, JG did not have chorioretinits but the optic dises were noted to be slightly pale, thus advised reevaluation after 2 weeks. CD4 CD8 and immunoglobulin titers (IgG, IgA and IgM) revealed normal results.

On the 27th HD, JG experienced episodes of low grade fever. Abscess was noted on the L foot from a previous IV site. Incision and drainage was done. Oxacillin was started but later shifted to vancomycin because the abcess did not resolved and JG still has fever. On the 35th HD blood culture showed coagulase-positive staphylococcus sensitive to vancomycin and oxacillin. After 14 days of antibiotics, fever lysed. After 20 days of ganciclovir, it was tapered from 10 to 6 mkd. However, increase in liver size was again noted thus original dose was resumed and tapered slowly.

On the 47th HD, JG was discharged improved to continue ganciclovir once a day 5x/week for one more weeks to complete 5 weeks on out-patient basis.

On follow-up, 4 days after discharge, he was noted to have pustules in the face. Culture of the pustule was done which revealed *Burkholderia* cepacia sensitive to cotrimoxazole so this was given. NBT was done which revealed below normal result. Repeat NBT done after 4 months still revealed below normal levels. He was then reffered to an immunologist who seggested to give interferon which was not given because of financial constraints. The pustules then resolved spontaneously.

CASE DISCUSSION

We are presented with the following salient features:

5 months old male
born full term
delivered thru CS
breastfed for 1 1/2 months
recurrent fever cough and colds since 1 month old
diarrhea
juandice
seizures

Physical Examination Revealed
Rhonchi
Wheezing

Hepatosplenomegaly noted on the 9th hospital day
Laboratory Exams Revealed
Leukocytosis
Toxic granules on peripheral smear
Brinchopneumonia on x-ray
Direct hyperbilirubinemia
Malarial smear
EBV anti VAC IgM (-)
Urine CMV culture (+)

Bronchopneumonia was the initial impression because of the respiratory symtoms and radiologic findings. However, JG was still febrile despite 5 days of ampicillin-sulbactam so it was shifted to ceftazidime, oxacillin and amikacin.

Atypical pneumonia was then considered because his pneumonia failed to respond to conventional antibiotics. Aside from cough, fever, and wheezes he had conjunctivitis at one month of age. Erythromycin was then started. However, JG still has high grade fever. The subsequent development of jaundice and note of hepatosplenomegaly later in the course of his illness could not be explained by pneumonia alone.

Sepsis could present a similar picture but blood culture was negative and despite adequate antibiotic coverage, no improvement was noted.

EBV mononucleosis was another consideration since fever abd hepatospenomegaly are prominent manifestations in children less than 4years old.

Pneumonia has been noted in association with primaryEBV infections. Other complications of EBV mononucleosis are neurologic (siezures) and hematologic (thrombocytopenia). Other manifestations such as lymphadenopathy, tonsillopharyngitis, rash and rhinitis common in EBV were not present. A typical lymphocytes usually seen in patients with EBV were also not noted. Moreover, EBV anti-VCA IgM was negative.

Presented with clinical manifestation of pneumonia, jaundice and hepatosplenomegaly and supported with positive urine CMV culture the diagnosis of Cytomegalovirus was considered.

CYTOMEGALOVIRUS is a ubiquitous agent that commonly infects persons of all ages from all parts of the world. It is the most common viral agent congenital infections in humansand probably the most important infective cause of mental retardation and nonhereditary sensorineural deafness in children. Infections is common and usually asymptomatic. The incidence does not appear to be seasonal. Prevalence of CMV IgG antibody is influenced by many factors including age, geographic location, cultural and socioeconomic status and child rearing practices of the group.Congenital infection occurs in 1% of all births in developed countries and in an even higher percentage in developing nations.

In the Philippines, Ignacio and Leeciones tested 107 mothers wherein 83were positive for CMV. There was a total of 86 infants since 3 were twins.Out of 86 infants born to seropositive women, there were 11 with congenital CMV (those with CMV viruria) a high rate or 12.8%. This is definitely higher than the worldwide estimate of neonatal transplacental infection of approximately 1% and correlates with the more than 3% of congenital infection rate observed in the developing countries.

Close contact is required for CMV transmission. It can be acquired thorugh: saliva, tears, urine, respiratory secretions. cervical secretions semen or breast milk. It can be transmitted through a number of ways:

1. Intrauterine/Congenital
2. Perinatal or natal
3. Postnatal

A. CONGENITAL INFECTIONS

One percent of all new borns congenitally infected with CMV. Maternal CMV infection that is eithe primary or recurrent during pregnancy can result in an infant who is infected congenitally with CMV. The rate of intauterine infection with recurrent infection in the mother is less than 1% whereas transmission in the fetus occurs in 40-50% of mother who primarily are infected with CMV.

Stagno et al noted that 10% have severe classic "cytomegalic inclusion disease" characterized by IUGR, juandice, hepatosplenomegaly, thrombocutopenia, petechia, purpura, pneumonia, severe CNS damage with microcephaly, intracerebral calcifications, chorioretinitis, and sensorineural hearing loss. JG did not have these manifestations at birth.

Five percent of congenital CMV has atypical involvement suchas ventriculomegaly, periventricular leukomalacia. periventricular cystic malformations with or without cacificaltions, strabismus, optic atrophy, long bone ostieitis, transient thrombocytopenia and petechiae, cutaneous vasculitis hemolytic anemia, ascites and chronic hepatitis. JG did not have these atypical manifestation at birth. 90 symptomatic at birth later have neurologic sequalae or deafness.

Up to 90% are a symptomatic at birth. The single most important abnormality in children born with congenital CMV is sensorineural hearing loss. The impairment is bilateral in one-half of the cases and is of sufficient magnitude (50-100bD) to produce serious difficulties on verbal communication and learning. In at least 25%, hearing impairments have either developed or become more severe after the first year of life. Brain stem auditory evoked response was alreadydone to JG wherein infact hearing was noted.

There is solid evidence from controled prospective studies that at least 5% and perhaps as many 15% of them are at risk of having developmental abnormalities such as microcephaly, motor defect, mental retardation, chorioretinitis and dental defects usually become apparent within the first 2 years of life. A present, JG is almost 2 years old and did not have any of these manifestations.

B. POSTNATAL ACQUISITION

Hanshaw et al did CMV culture to 200 children 8 months to 14 years old. Only 2 of them excreted CMV in urine. Both were clinically well: however, hepatomegaly and abnormal liver function test were noted.

A child may be infected by other children duringthe toddler or preschool years. Children who attent group day care facilities are especially likely to acquire CMV and this reservior of virus may be a risk to a pregnant women and her fetus.

The prevalence of CMV in day care centers in the US was first reported by Pass et al in 1982.The authors found that 51% of children attending day care participated in the horizontal transmission of CMV. Prevalence of CMV excretion vareid with age; 83% of children 13-24 months of age shed virus, compered with only 9% of those children younger than 1 year of age.

Furthermore, Hutto et al noted that CMV was isolated from plastic toys and hands of day care center workers. These studies utilized molecular fingerprinting techniques to show that infected children in contact with each shed strains of CMV with similar or identical restriction-enzyme banding patterns and that predominant strain of CMV appeared to circulatecover a given period in a given day care center.

Our patient was never sent to a daycare center and supposed he had his manifestation at 4 weeks of age during this time. no toy was offered to the patient, only the nursing bottle.Therefore the likelihood of postnatal acquisition is unlikely.

C. PERINATAL

Perinatal CMV infection refers to those naturally acquired during the course of delivery (natal) from exposure to infected maternal genital secretions, acquired during the postnatal period from ingestion of infected breastmilk or iatrogenically acquired as a result of blood transfusions. It occurs in 40-60% of infants who are breastfed by seropositive mother for more than 1 month and in 25-50% of infants exposed to CMV in the birth canal. Given the curent rates seropositivity of the mothers, the prevalence of CMV being excreted in the genital tract at delivery and the prevalence of breastfeeding in the United States 1-15% of infants become perinatally infected by 6 months of age. Incubation period of perinatal CMV infection ranges from 4-12 weeks. Although the quantity of virus excreted by infants with perinatal infection is less than that seen with intrauterine acquisitions is also chronic with shedding of virus persisting for year. Vast majority of infants with perinatal CMV infections remain asymptomatic. Up to 1/3 may have signs and symptoms of disease associated with CMV infection most often self limited lymphadenopathy, hepatosplenomegaly or pneumonitis. It can cause severe protracted pneumonitis and has been associated with the development of bronchopulmonary dysplasia in premature infants. It do not appear to cause neurodevelopmental sequelae or deafness just like in JG case.

JG was asymptomatic at birth; however developed respiratory symptoms since 1 month of age. The onset of clinical manifestations in patients with perinatal CMV infections is usually at 4-6 weeks of age.

If JG was born thru CS and not thru vaginal delivery, how then he aquire CMV infection?

Stagno et al studied breastmilk and risk of CMV infection. (Table 1).

Table 1. Maternal excretion of CMV from various sites and infection of the infant-(Stagno et al)

Only sit of maternal excretion	Infants infected exposed	
Breastmilk-Breast-fed infants	11/19	(58)
Bottle-fed infants	0/19	(0)
Cervix - 3rd trim & postpartum	8/14	(57)
3rd trimester	18/68	(26)
1st & 2nd trim	1/8	(12)
Urine	0/11	
Saliva	0/15	
Non-excreting women		
Bottle-fed	0/125	
Breast-fed	0/11	(0)

298 of the 396 women who recently gave birth were positive for CMV. 38 of the 278 women excreted CMV at least once into either colostrum or milk. The rates of isolation were 68% among women who had just delivered congenitally infected infants 16% among those excreting CMV from other sites late in gestation and 9% among seropositive women who did not excrete CMV . To define whether CMV could be transmitted by breastmilk, the infants of 28 women shedding CMV only in breastmilk were studied prospectively. 19 of them were breastfed and 9 were exclusively bottle fed. None of the infants had been infected in utero or received blood transfusions. Whereas none of the 9 bottle fed infants became infected. 11 of the 19 infants (58%) fed infected breastmilk acquired CMV infection. The infants became viruric between 4 weeks to 4 months of age except for one who became viruric at 9 months of age, 3 months after his mother had her first CMV positive milk specimen. Between the mother who did not transmit CMV to their infants, respectively there were no important differences in age, number of siblings in the household, race, duration of lactation, duration of CMV excretion in milk, presence of IgA specific antibody and the infectivity titers of CMV in milk. When fed, infected breastmilk or exposed to CMV in the genital tract during delivery the rate of infection in young infants was high and nearly the same 58% of them infected breast milk and 57% in those exposed to CMV during delivery.

Breastmilk could be a possible mode of CMV transmission in patients who are born thru CS like in JG case.

JG presented with recurrent pneumonia. Recent reports indicate that CMV infection may be temporally associated with respiratory involvement. Smith et al reported pulmonary involvement with cytomegalovirus in 18 children. 12 were under 2 years old and the remaining were 7&9 years old. 14 had interstitial pneumonitis while the 4 had respiratory symptoms but without classical radiograpic evidence of interstitial pneumonitis. He noted that 3 patients who had coexisting pulmonary pathology developed persistent pneumonia or pulmonary fibrosis. 7 patients had respiratory symptoms of less than 4 weeks. The remaining 12 patients without underlying disease all except 2 had relatively mild respiratory symptoms. The x-ray evidence resolved in less than 8 weeks. CMV infection was seen in a group of patients who had normal immunological functions but had suffered a significant pulmonary insult during the newborn period or had an associated chronic respiratory problem. He concluded that the role of CMV in these processes is difficult to determine however what may contribute to the persistent infection and delayed resolution of infiltrates is the damage to the local defense mechanism in the lungs.

PATHOLOGY

CMV infection causes characteristic type A Cowdry intranuclear inclusions and massive enlargement of the affected cells. It is this property of "cytomegaly" from which CMV acquired its name. These large cells represent productive virus infection and cells may also be infected latently. These cells may express virus-specific antigen and contain viral nucleic acid without producing typical cytomegaly or cytophatic effect. With severe disseminated CMV disease involvement can be seen in virtually all organs.

IMMUNITY

Viral strain differences, to date have not been shown to influence pathogenicity. However, immune responses, including maturity of the immune response, appear to be a major factor exhibiting control over virulence because CMV disease occurs more frequently in fetuses, premature neonates, transplant recipient, and patients with AIDS than in older healthy infants, children, and adults with acquired CMV infection.

The cell-mediated immune response, both specific and nonspecific is thought to be important in the host defense of CMV. Nonspecific immune mechanisms of natural killer cells and interferon production occur early after CMV infection when early antigens are being produce and before infectious virus is released from the cell. The generation of cytotoxic T cells against CMV early antigens probably is the most important specific host immune response to CMV.

Humoral immunity, on the other hand, does not appear to be a key factor in host's defense against CMV infection. A fetus can be infected by intrauterine transmission through a reactivated CMV infection in women who are CMV-seropositive prior to pregnancy, and infants commonly are infected perinatally from infected cervicovaginal secretions or breastmilk in the pressence of passive maternal antibody. The presence of antibody, therefore, should be considered a marker of previous or current infection with the virus rather than a measure of immunity. Although humoral immunity does not appear to prevent infection with CMV, it does appear to lessen the severity of symptoms associated with the infection. Infants congenitally

infected with CMV as a result of reactivation in their mother almost always are asymptomatic, and perinatally infected infants rarely have significant symptoms.

A growing body of clinical and experimental evidence indicates that CMV is itself immunosuppressive. Patients with mononucleosis have depressed in vitro cell-mediated immune responses to mitogens and other antigens. The virus also depresses natural killer cell activity and T-cell proliferation in vitro.

The laboratory diagnosis of CMV is established by isolation of the virus or by serology.

Detection of the Infectious Agent:

1. CMV can be isolated in tissue culture using fibroblast cell lines, such as human foreskin fibroblasts and human embryonic lung fibroblasts..

   Specimens that contain a high titer of virus, such as those specimens from congenitally infected infants, may grow in 24 hours.

   Some specimens, such as those specimens from persons with aquired asymptomatic infections, may require up to 6 weeks to grow, but most cultures grow in 1 to 2 weeks.

   CMV has been isolated from variety of specimens, including urine, saliva, nasopharyngeal fluid, white blood cells, amniotic fluid, bronchial lavage samples, and tissue from biopsy or autopsy specimens.
2. An adaptation of tissue culture that is now popular in viral diagnostic laboratories is the low-speed centrifugation enhancement, monoclonal-antibody culture technique, also called shell vial assay.

   In this procedure, the clinical specimen is centrifuged onto fibrolast-coated shell vials. After an incubation of approximately 16 to 18 hours, monoclonal antibodies specific to the 72-kDA major immediate-early (IE) CMV protein are used to detect IE antigen expression.

   This technique detects over 90% of specimens that will ultimately be shown to be CMV-culture-positive. This rapid viral diagnostic technique especially is reliable in urine and bronchoalveolar lavage specimens and has been applied with results in blood and tissue specimens. However, maximum sensitivity and specificity are obtained when shell vials are used as an adjunct to, and not in place of, routine tissue culture.
3. CMV infected cells can also be detected by direct immunoflourescence of exfoliated cells in bronchoalveolar lavage specimens or in frozen tissue specimens. This however, requires laboratory experience in direct immunoflourescence technique.
4. Viral nucleic acid can be detected in clinical specimens by using cloned subgenomic probes that are either radioactively or enzymatically labeled. A variety of DNA hybridization techniques, including dot-blot, Southern blot, and in-situ hybridization, have been applied to the clinical diagnosis of CMV infection.
5. Newer technology using primer-mediated DNA amplication techniques (such as polymerase chain reaction) achieves new levels of sensitivity in viral detection and should be useful for clinical diagnosis and for investigation of CMV pathogenes and laboratory has been applied to the diagnosis of CMV infections in newborns, patients with AIDS, and recipients of transplants. If primer selection and amplication and product detection conditions are chosen carefully, PCR can give results comparable with, and often more sensitive and rapid than, standard tissue culture or clone probe technique. However, the exquisite sensitivity of PCR also is a major disadvantage. This extreme sensitivity makes the test vulnerable to false-positive results from contamination and low positive predictive values for CMV disease. Clinical utility of CMV DNA:

   In CSF in patients with AIDS or newborns
   In vitreous fluid in retinitis
   In WBC, plasma or serum in newborns and immunocompromised
   Patients correlate with disease severity and viral dissemination
6. CMV antigen also may be detected in the white blood cells of patients with CMV infection and disease, and this CMV antigenemia may be quantified to monitor response to antiviral therapy.
7. Exfoliated cells in urine or bronchoalveolar lavage specimens or cells in tissue obtained by biopsy can be examine for histologic evidence of CMV infection. Cells that are infected productively with CMV are enlarged, have type-A Cowdry intranuclear inclusions, and occasionally have perinuclear inclusion. The appearance of these cells is characteristic and has been called owl's eyes. The presence of these cells correlates with the presence of active CMV disease and may be useful clinically.

SEROLOGY

CMV seropositivity ranges from 30%-100%. CMV Ag generally if detectable within a few weeks of onset of viral shedding in primary infection.

Standard serologic techniques also can be applied to the diagnosis of CMV infections:

CMV antibody can be determined by several different methods, including complement fixation, hemaagglutination inhibition, indirect flourescent-antibody assay, anticomplement immunoflourescence assay, enzyme linked immunosorbent assay, later agglutination and neutralization test. ELISA and LATE Agglutination are accurate and efficient for screening donors and recipient and determining susceptibility to primary infection.

CMV-IgG (–) in a single serum implies that the patient at some time has been infected with CMV. CMV-IgG (-) good evidence against current or past CMV infection because CMV antibody usually is present at the time of infection and persists for life. a primary infection with CMV is documented best by a clear seroconversion from negative to positive CMV-IgG antibody. Presence of CMV-IgM antibody implies a current or recent primary CMV infection. In healthy adults, CMV-IgM antibody usually persists for 6 weeks and may persist for 3-6 months after the primary infection occurs. In immunocompromised adults experiencing clinically significant infection with CMV. CMV-IgM antibody may be detected for prolonged periods

General guidelines for the diagnosis of congenital infections:

In suspected congenitally infected infants, serologic testing should be done on maternal and infant sera collected at the same time for appropriate interpretation of the antibody titer in the infant.

Transplacental transmission of IgG antibodies occurs; these maternal antibodies normally decrease and disappear within 3-6 months. Therefore, an antibody titer in the infant during the first month of life that is less than or equal to the maternal antibody titer usually represents passive transfer of maternal antibodies. A titer in the infant that is fourfold higher or more than the maternal titer suggests active infection.

In neonatal infections, the early immune response includes the production by the infant of IgM antibodies. Since placental transfer of IgM antibodies from the mother does not occur, determination of IgM antibodies in the infant can be useful in the diagnosis of congenital CMV.

Laboratory diagnosis of congenital cytomegalovirus infection:

The best method of diagnosis is isolating the virus from a urine culture on the first 1-2 weeks of life. Most congenitally infected infants shed extremely high titer of virus in the urine. Urine culture obtained after 2 weeks of age sould be interpreted with caution because perinatally aquired infections can be detected after this time period. The presence of CMV-IgM antibody in an infant within 2 weeks of birth is highly suggestive of CMV infection[2]. The authors compared the results of CMV cultures, single sera IgM ELISA, IgG acute to convalescent paired sera and IgM/IgG passive latex agglutination and came up with the recommendations for CMV testing:

Clinical Status	Test(Gold Standard)
Congenital CMV(vertical transmission)	Culture positivity at birth or within 1-2 weeks
Perinatal CMV(horizontal transmission)	Culture change from negative to positive at >4 weeks
Immunocompetent(pregnancy, CMV Mononucleosis in adolescents	Serology: presence of IgM, IgG seroconversion
Immunocompromised (transplant, HIV, etc)	Tissue biopsy, Possible antigen test (CMV pp65 protein)

TREATMENT

Currently, there are 6 FDA approved treatment for CMV retinitis

1. Intravenous Ganciclovir (Cytovene)
2. Oral Ganciclovir (Cytovene)
3. Intravenous Foscarnet (Foscavir)
4. Intravenous cidovir (Vistide)
5. Ganciclovir implant (Vitrasert)
6. Fomivirsen (Vitravene)

Induction/Maintenance Approach to therapy

The first 2 therapies available were Ganciclovir in 1989 and in 1991, Foscarnet was approved. Induction

phase using one of these 2 drugs, attempts to render the disease inactive with high dose medication while the maintenance phase, keeps the retinitis under control.

Ganciclovir

It has been licensed specifically for the treatment of life-threatening and sight-threatening infections with CMV. It is a synthetic acyclic nucleotide analog of guanine, structurally similar to acyclovir and appears to have in vitro activity against all the human herpes viruses. Its mechanism of action includes entering a CMV-infected cell wherein it is converted by cellular enzymes to ganciclovir-5'-triphosphate which has a primary antiviral effect against CMV.

Ganciclovir is virostatic suppressing active CMV infection but does not produce a cure. Viral replication resumes when the drug is removed. It is excreted largely unmetabolized by kidneys. CSF concentration is 25-70% of plasma concentration. It penetrates ocular fluid well. Oral bioavailability is less than 10%.

It is indicated for the treatment of CMV retinitis in immunocompromised patients and for life threatening complications of CMV. It may also be effective against CMV colitis, esophagitis,hepatitis and meningoencephalitis. Likewise, in the treatment of pneumonia in patients with AIDS.

In the **induction phase**, 5mg/kg bid (5-7 mg/kg) for 2-3 weeks is given. While on treatment, hematologic monitoring must be done twice weekly and if necessary transfusion of G-CSF and PRBC are done. Expected outcome after treatment is cessation of retinal lesion and advancement and resolution of acute inflammation within 4 weeks.

In the **maintenance phase**, 5-10 mg/kg daily is given with indefinite duration. Hematologic monitoring is likewise done weekly. Expected outcome are short term control of retinitis and disease relapse is inevitable usually within 2-4 months unless immune recovery is achieved.

Laboratory Monitoring During Treatment

Blood and urine culture for CMV should be obtained and repeated at least weekly during induction and early maintenance therapy to monitor for antiviral effect. CMV DNA antigenemia tests or detection of CMV DNA (PCR) may be used to monitor response in selected patients. It may be detectable in the blood for weeks or months after apparently successful antiviral treatment.

Weekly ophthalmologic examinations with retinal photographs documenting regression or progression of CMV retinitis should be done.

Renal function should be likewise monitored while on treatment. In patients with renal insufficiency, dosage adjustment according to creatinine clearance must be done.

CBC and platelet count monitoring daily or every other day is recommended. If values decreased to 50% of the baseline count, (ANC 500 or platelet count <25,000) treatment should be suspended. Ganciclovir induced neutropenia usually is reversible, and recovery commonly occurs within 5-7 days of temporary discontinuation of the drug.

Combination with IV immunoglobulins in bone marrow transplant recipients with CMV peritonitis may increase survival.

Adverse Effect of Ganciclovir include neutropenia with ANC < 750cells/cumm in 15-40%. This can be managed by giving G-CSF 300mcg daily to titrate 2-3x each week to keep ANC >1000. Other adverse effects are thrombocytopenia(5-10%), nausea, vomiting, elevated lever enzymes, confusion, dizziness and headache. Seizure is a rare adverse effect.

Drug resistance can occur in 8% of patients after 3 months of treatment or 38% of patients with (+) CMV urine culture. Sensitivity test must be done after 3 months of therapy.

Foscarnet

It is a trisodium phosphonoformate inhibiting DNA polymerase of the human herpes viruses including CMV. It is virostatic and viral replication will resume when the drug is removed. It is also active against HIV. It is excreted in the urine and up to 30% of each dose may be deposited in the bone. The drug rapidly distributes into the CSF.

It is an alternative for ganciclovir. In some patients on ganciclovir alone, retinitis appears to progress thus foscarnet can be given alone or in combination.For patients with AIDS and HIV, it may offer survival advantage over ganciclovir. However, it is less tolerated because of its nephrotoxicity. It is not myelosuppressive and appears to deposit in bones, teeth and cartilages which is an important consideration when treating pediatric patients.

For the **induction phase**, it is given at 90mg/kg bid for 2-3 weeks. Patients must be hydrated well with at least 1 liter saline IV or 2 liters orally bid. Neutrophil count, electrolytes, creatinine, calcium,

phosphate and magnesium level monitoring must be done. Adjust dose every 2 weeks if necessary based on creatinine clearance.

Expected outcome of treatment is cessation of retinal lesion advancement and resolution of acute inflammation within 4 weeks.

For the **maintenance phase** it is given at 90 mg/kg/day (90-120) with indefinite duration of treatment. Expected outcome is short term control of retinitis and disease relapse is inevitable usually in 2-4 months unless immune recovery is achieved. If the disease progress, another course of foscarnet induction possibly in combination with ganciclovir is recommended.

Clinical and virological monitoring is similar with ganciclovir. Foscarnet produces a variety of metabolic abnormalities because it binds divalent ions.

Adverse effects include elevated creatinine in 20-30%, decreased calcium, magnesium,and potassium. Calcium carbonate 500 mg tid and magnesium oxide 416 mg daily can be given as preventive measures. Nausea can occur in 25-40% of patients. Other adverse effects are tetany, perioral numbness, finger paresthesia, seizure, muscle tremor, agitation, confusion, weakness, anemia and dysuria. Intravenous or oral hydration is required to reduce adverse effects. Patients should be closely monitored for nephrotoxicity which is usually reversible over approximately 2-4 weeks.

Oral Ganciclovir

The use of ganciclovir for maintenance therapy for CMV retinitis was approved in 1995 to be given 1g 3x daily.

Cidovir

It is active against ganciclovir resistant CMV with mutations in UL97, suggesting that the CMV DNA polymerase is the target of the drug. It is eliminated primarily by glomerular filtration.

For the **induction phase**, it is given at 5 mg/kg IV once a week for 2 weeks. One liter NSS is infused before and after infusion of cidovir. Probenicid 2g is given 3 hours prior to infusion, half dose for patients <50 kg. Serum electrolytes, creatinine and urinalysis should be monitored prior to administration of each dose.

For the **maintenance phase**, it is given at 5 mg/kg once every 2 weeks for an indefinite duration. It is also given with NSS and probenecid. Conduct monthly ophthalmologic examination while on treatment.

Adverse effects include proteinuria in 20%, in which case the drug should be discontinued if with proteinuria of 2+ or more. Creatinine level of >2g/dl is partially reversible. Renal failure can also occur. Likewise, neutropenia in 15%. G-CSF 300meg 3x/week can be given if ANC <500. Eye complications include uveitis and ocular hypotony. The drug should be discontinued if red eye, photophobia or blurred vision develops. It has been established that the drug is toxic to the ciliary body which is the structure responsible for producing aqueous fluid that maintains the intraocular pressure. This can result to uveitis and ocular hypotony leading to permanent severe vision loss in some cases.

REFERENCES:

1. Serologic and DNC-based testing for congenital and perinatal infections c. Litwin MD and H. Hill MD, PIDJ 1997; 1166-75
2. Use of Viral Cultures and Serologic Tests for CMV infection Rational or Random? William E. Mangano, MD. Robert P. Gruninger, MD. American Journal Clinical Pathology 1996: 106; 180-184

(For other references, please contact the authors)