Review Article

Cytomegalovirus infection in non-immunosuppressed critically ill patients

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Abstract
Cytomegalovirus (CMV) is an important and common cause of mortality and morbidity in immunocompromised patients such as those with HIV/AIDS, transplant recipients on immunosuppressive therapy, and malignant hematological disease. After primary infection with CMV the virus becomes latent in multiple organs and can later be reactivated during severe dysregulation of the immune system. A large population carry dormant virus and are thus at risk for reactivation.
However, reactivation of CMV has been reported in "non-immunosuppressed patients" such as severe trauma, sepsis, shock, burns, cirrhosis and other critically ill patients lying in the intensive care units. Therefore, the intensivists are increasingly facing a dilemma of identifying such patients to treat and there is a debate if there is a scientific justification for prophylaxis in such immunocompetent patients.

Introduction

Cytomegalovirus (CMV) is an important and common cause of mortality and morbidity in immunocompromised patients such as those with HIV/AIDS, transplant recipients on immunosuppressive therapy, and malignant hematological disease. After primary infection with CMV the virus becomes latent in multiple organs and can later be reactivated during severe dysregulation of the immune system. A large population carry dormant virus and are thus at risk for reactivation.

However, reactivation of CMV has been reported in "non-immunosuppressed patients" such as severe trauma, sepsis, shock, burns, cirrhosis and other critically ill patients lying in the intensive care units. Therefore, the intensivists are increasingly facing a dilemma of identifying such patients to treat and there is a debate if there is a scientific justification for prophylaxis in such immunocompetent patients

Review of literature

Cytomegalovirus (CMV) is the prototype member of Betaherpesvirinae in the subfamily Herpesviridae. The structure of CMV is similar to other members of Herpesviridae. It is an enveloped virus with icosahedral symmetry containing a large genome of double stranded DNA. CMV has the largest genome of around 235 kb encoding for over 200 genes [1].

CMV has a longer replication cycle and it encodes for a diverse array of gene products, many of which play an immunomodulatory role in the host. Its genome codes sequentially for three genes, which encode for immediate early, early and late proteins respectively. The immediate early (IE) proteins are regulatory and the late proteins are structural. Many late proteins such as pp65 antigen have antigenic properties which can be used for diagnosis of CMV infection.

Pathogenesis and immunological basis

Primary CMV infection is not a problem in these critically ill immunocompetent patients. The most common mechanism proposed for CMV infection or disease in such critically ill patients is as a result of reactivation of CMV virus and not primarily due to primary infection. CMV has the ability to establish latency in various different types of cells unlike other herpes viruses which largely remain localized [2,3]. Monocytes, CD 34+ haematopoietic progenitor cells, and endothelial cells are the major sites where latent CMV is present.

There are diverse mechanisms by which CMV is able to avoid immunosurveillance and establish

persistence in host cells. T cells and NK cells play a central role in controlling CMV infection and hence reactivation of CMV in immunocompetent persons is rare. CMV possesses a series of genes by which it escapes the defense immunity. Genes expressed in the unique short (US) region of CMV inhibit the expression of human leucocyte antigen (HLA) class I molecules and interfere with the antigen presentation in the infected cells. Thus the viral antigens are not recognized and they escape the cytotoxic CD 8 + T cells. Decreased expression of HLA makes the cells susceptible to lysis by NK cells and this is prevented by expression of proteins in the unique long region of CMV.

CMV has also devised mechanisms to avoid immunosurveillance by CD4+ T cells. It is seen that expression of HLA Class II is impaired in CMV infected cells. Though this is an oversimplified explanation, these escape mechanisms devised by CMV help it to maintain latency without being eliminated by the immune mechanisms [2,3]. Immunosuppression in the host for any reasons leads to replication of the virus which was kept in check by the immune mechanisms.

There is a high level of complexity between the virus and the host. The exact mechanisms of its reactivation are still not clear and many other mechanisms besides immune mediated have been implicated in the reactivation of CMV [4,5].

Reactivation is a multifactorial and multistep process. The activation of the IE region is seen as the first crucial step for reactivation of CMV. These IE enhancer/promoter sequences contain various nuclear factor kappa B (NF-κB) consensus sequences which are normally inactive [5].

It is thus postulated that any mediator or signal activating NF-κB is capable of triggering CMV reactivation. There are diverse stimuli which can activate NF-κB and in turn activate CMV. These include proinflammatory cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors which are released during sepsis, burns, surgery, trauma, multiple organ failure syndrome, allogeneic blood transfusions, or organ and bone marrow transplants [5,6,7,8]. It was seen that the proinflammatory cytokine TNF-α induces activation of protein kinase C and nuclear factor κB. These changes in turn result in expression of the IE gene thus initiating the replication cycle of CMV [5,7].

CMV lies latent in monocytes in which no viral gene is expressed. When these monocytes are differentiated into macrophages, as occurs during inflammatory conditions such as sepsis, burns, trauma and surgery, the viral genes are expressed and viral replication is initiated [5,7,8]. Thus theoretically in patients critically ill as a result of sepsis, trauma, burns and other conditions, CMV gets reactivated bypassing the immune mechanisms.

In addition to the direct harmful effects of CMV, many indirect effects have been recognized in the host cell [9]. Replication of CMV causes tissue injury. This leads to release of proinflammatory cytokines which causes low-grade chronic inflammatory changes or even exacerbation of certain preexisting diseases such as inflammatory bowel disease in the host.

CMV leads to a direct procoagulant activity in the host tissue because of its ability to directly invade vascular endothelial cells. It also causes activation of vascular cells which in turn increases expression of adhesion molecules. These adhesion molecules then react with platelets and leucocytes to cause a hypercoagulable state. These effects lead to thrombotic complications in the host. The virus also causes inhibition of progenitor haematopoietic cells and thus suppresses haematopoiesis in the host [10].

CMV infection can itself accelerate immune responses thus exacerbating graft versus host reactions. In experimental animal models it was observed that there was enhanced rejection of allogeneic transplants as a result of accelerated immune response by CMV infection [11].

Epidemiology

CMV is endemic in most areas of the world. The seroprevalence of CMV varies in different geographical areas and it ranges from 30-100% [1,9]. CMV infection is usually asymptomatic in immunocompetent persons. Reactivation of CMV has been of concern in immunosuppressed individuals as it is associated with adverse clinical outcomes. CMV reactivation in apparently immunocompetent individuals with critical illness is becoming an area of emerging clinical significance. It has been observed that CMV infection occurs in critically sick patients admitted in ICUs and the prevalence ranges from 0-35% [12-17]. This wide variation observed in different studies is due to different study designs, limited sample size, lack of standardized diagnostic criteria, inclusion of only selected types of ICU patients, different inclusion and exclusion criteria, and/or failure to include comprehensive and rigorous statistical analysis.

Table 1. Diagnosis of CMV end organ disease [18]

Site	Clinical Sample	Preferred diagnostic test
Lung	BAL, Lung biopsy from patient having signs and symptoms of pulmonary disease	Viral culture, IHC, histopathology, in situ hybridization
Gastro intestinal tract(GIT)	Biopsy from GIT in a patient having signs and symptoms of G.I disease along with mucosal lesions on endoscopy	Viral culture, IHC, histopathology, in situ hybridization
Liver	Liver biopsy in a patient with deranged liver function test and other apparent causes of hepatitis have been ruled out	Viral culture, IHC, histopathology, in situ hybridization
Pancreas	Pancreatic biopsy	Histopathologically s/o CMV infection and Viral culture, IHC, in situ hybridization
Central nervous system	• CSF • Brain biopsy (In patient having signs and symptoms of CNS disease)	• Viral culture or PCR • Viral culture, IHC, histopathology, in situ hybridization
Retina	Ophthalmologically features typical of CMV retinitis	
Kidneys	Kidney biopsy in a patient having abnormal renal function test	Histopathology s/o CMV infection and Viral culture, IHC, in situ hybridization
Heart	Biopsy from patient with myocarditis	Histopathology s/o CMV infection and Viral culture, IHC, in situ hybridization
Other categories	Biopsy with signs and symptoms related to organ of involvement with other causes ruled out	Histopathology s/o CMV infection and Viral culture, IHC, in situ hybridization

BAL: Bronchoalveolar lavage, IHC : Immuno histochemistry, CSF: Cerebrospinal fluid

It has further been observed that CMV infection is associated with adverse clinical outcomes in these critically ill patients. Many studies have shown the importance of CMV infection in such patients [12-17]. Presence of CMV infection in critically ill ICU patients led to increased length of ICU stay and increased duration of mechanical ventilation as compared to patients negative for CMV infections even when both the groups had similar disease severity [8,12,13] Nosocomial infections were also significantly higher in patients positive for CMV as compared to non CMV patients [15]. The rates of renal failure and steroid therapy were also higher in CMV positive groups [8,14]. CMV infected patients also had higher mortality as compared to CMV negative patients [12,15]. Thus many different studies have highlighted the importance of CMV infection in ICU patients [8,12-17].

Diagnosis

Diagnosis of CMV infection in such critically ill but immunocompetent cases is another area of controversy and there are no uniform guidelines available. An ideal diagnostic test should be able to detect active CMV infection and differentiate it from CMV disease. The test should be simple to perform and it should also give rapid and reliable test results. It should further be able to identify the CMV infection as early as possible and be useful in monitoring the progress of CMV disease.

There is still a diagnostic dilemma between active CMV infection and CMV disease; hence advanced diagnostic procedures are initiated to confirm active CMV disease. CMV infection is defined as isolation of CMV (viral culture) or detection of CMV proteins (pp65) or nucleic acid by polymerase chain reaction (PCR) from blood or other clinical samples [18].

CMV can cause end organ disease in various body organs/tissues. The disease is confirmed by clinical findings suggestive of the organ involvement plus demonstration of CMV by viral isolation, histopathologic testing, immunohistochemical analysis, or *in situ* hybridization from the relevant clinical sample obtained from the site of involvement. Detection of CMV by PCR alone is too

Table 2. Clinical manifestations of CMV in immunocompetent patients

Clinical disease	Comorbid condition	patients diagnosed with CMV /no. of patients reviewed (%)	Diagnostic test used	Reference
Mediastinitis	Cardiac surgery Blood transfusion	29/115 (25.2)	Viral culture of blood and urine	27
Pneumonia	Mechanical ventilation	25/86 (29)	Histopathology of lung tissue	28
Dyspepsia and other GI symptoms	None	14/33 (42%)	IHC against pp65	29
Colitis	Advanced age, post surgical interventions	Meta analysis and case reports	Histopathology of GIT tissue biopsy. +ve pp65 antigenemia +ve CMV serology	30,31
Thrombotic complication (portal vein thrombosis)	Prothrombotic disorder Cancer , cirrhosis, hepatitis	Case reports	+ve CMV serology(IgG and IgM), other apparent causes ruled out	32
Meningitis	None	Case report	CMV DNA in CSF	33
Pericardial effusion	Pericardial effusion Congenital heart disease	5/33 (15)	Viral Culture, +ve serology	34
Myopericarditis and hepatitis	None	Case reports	+ve CMV serology(IgG and IgM), other apparent causes ruled out In one report +ve pp65 Ag in PBL	35,36

sensitive and insufficient for confirming CMV disease [18].

The conventional methods for the diagnosis of CMV infection/disease are viral isolation by viral culture, serology which includes CMV specific antigen and antibody detection, and molecular method for detection of viral DNA from blood and other clinical specimens. Viral isolation done by either tissue culture or shell vial culture is the most specific diagnostic test and until now was regarded as the gold standard, but it is labor intensive and the results are available after a minimum of one to two days. Hence other rapid methods such as detection of pp65 antigen from peripheral blood leucocytes and PCR from blood or peripheral blood leucocytes (PBL) for detection of CMV DNA are preferred for diagnosis.

CMV antigenemia has appeared as a major advancement in the diagnosis of both active CMV infection and CMV disease. It has a definite advantage over shell vial culture and is equally sensitive and specific compared to CMV DNA detection for diagnosis of CMV infection [19,20]. It

is a rapid test with the results being available in four to five hours of processing time [19]. A blood sample is treated to separate the polymorpho nuclear leucocyte (PMNL) fraction, which is then placed on a microscopy slide, incubated to facilitate cell adherence, then fixed with either acetone or fomalin and stained by indirect immunofluorescence to look for nuclear or perinuclear staining of the cells seen in case of CMV infection [19,20]. The limitations of the test, however, are that it is labor intensive, immediate processing is required, and the test results are dependent on the number of leucocytes evaluated. Furthermore, the interpretation of the test is subjective and a skilled microscopist is required to accurately interpret the results.

Molecular methods for the detection of CMV DNA from various samples are also being widely used. PCR is a highly sensitive method because of its ability to detect minute amounts of nucleic acid in various clinical samples. A study regarding the use of nested PCR using PBL resulted in a sensitivity and specificity of 100% for detection of CMV infection. [21]. The limitation of the assay is that it is not well standardized. Hence, for increasing

Figure 1. Systematic approach for diagnosing acute CMV infection
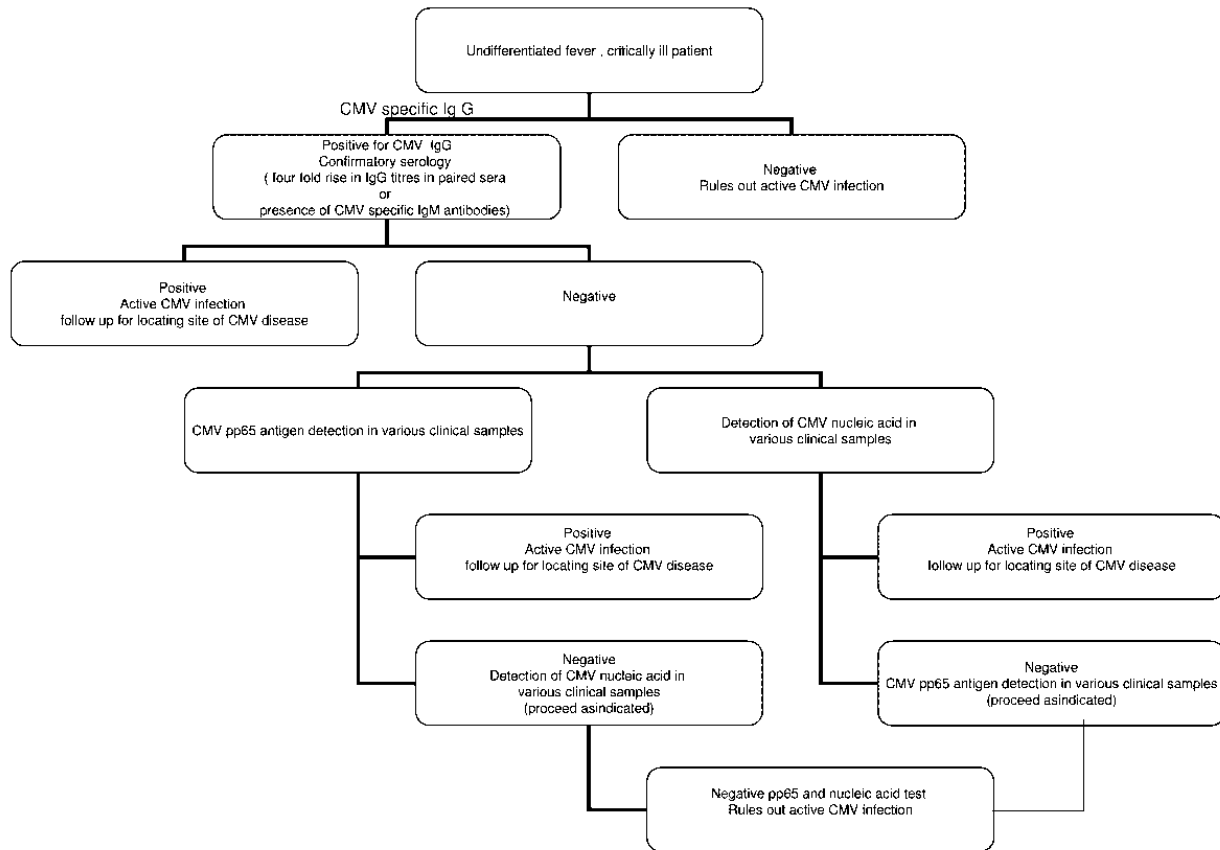
interlaboratory comparability of standard reference materials, commercially available systems must be used. These are costly and therefore not practical in basic laboratories [20,21,22]. The role of viral serology in diagnosing CMV infection in critically ill immunocompetent patients is significant as most CMV infections are as a result of reactivation of the virus and not primary infection. In most cases, therefore, CMV specific IgG antibodies would be present. The presence of CMV specific Ig M antibodies and four fold rise of Ig G titers in paired sera help to confirm active CMV infection.

The relevant diagnostic test for identifying CMV infection in critically ill patients would be the presence of CMV specific Ig G antibodies and confirmatory serology or detection of CMV antigen (pp65) or DNA (by PCR) from blood and other clinical samples (Figure 1).

To confirm the presence of CMV disease clinical findings should be supplemented with diagnostic tests such as the demonstration of CMV from the suspected organ/site by histopathological evaluation (Table1). Cytomegalovirus produces typical cytopathic effects which include cytomegaly, *i.e.*, large cells around 25-35 μm containing basophilic intranuclear inclusions which are sometimes surrounded by a clear halo and are usually associated with clusters of intracytoplasmic inclusions [23].

Immunohistochemistry using monoclonal antibodies and *in situ* DNA hybridization on the biopsied tissue increases the sensitivity of histopathologic CMV diagnosis.

Determination of CMV viral load by quantitative methods should be done before starting therapy. This helps in monitoring the progress of CMV disease. Conventional assays for quantitating CMV include the traditional plaque assay, determination of 50% tissue culture infective dose (TCID 50), and modified tissue culture methods. These methods are time-consuming, laborious and are less sensitive. Hence

Table 3. Treatment options for CMV infection and disease [35,36,37]

Drug	MOA	Side effects	Beneficial role
Ganciclovir (GCV) and valganciclovir (VGCV)	Nucleoside analogue	Bone marrow suppression, neuropsychiatric disturbance	GCV :DOC for prophylaxis, preemptive therapy and treatment of CMV disease
Acyclovir (ACV) and Valacyclovir (VACV)	Nucleoside analogue	CNS side effects (tremors, hallucination, convulsion), allergic reactions	Not studied for preemptive therapy or treatment Can be used for Prophylaxis
Cidofovir	Nucleotide analogue	Nephrotoxic thrombocytopenia ophthalmological or neurological toxicity	Poor results for Preemptive therapy and treatment of CMV disease
Foscarnet	Pyrophosphate analogue	Nephrotoxic, paraesthesia, electrolyte disturbance	2nd line drug for preemptive therapy or treatment of CMV disease DOC in cases of neutropenia or resistance to GCV
Maribavir (investigational)	Benzimidazole riboside compound		Prophylaxis and treatment of CMV resistant to GCV
Carimune, Gamimune, Gammagard S/D, Gammar P, Polygam S/D	Random donor immunoglobulins		Immunomodulatory, can be used for prophylaxis or in treatment of CMV disease in combination with antivirals
CytoGam	CMV hyper immunoglobulin		Immunomodulatory, can be used for prophylaxis or in treatment of CMV disease in combination with antivirals
CD8+ CMV CTLs	Adoptive immunotherapy		Shown to be effective as prophylaxis or preemptive therapy

CTL: cytotoxic lymphocytes

newer methods such as quantitative antigen detection assays and molecular methods can be used to quantitate CMV in various clinical samples. These are relatively simpler and more sensitive methods [24,25].

Clinical manifestation

Clinical spectrum of CMV disease ranges from a mild mononucleosis-like syndrome to very severe multivisceral involvement. All types of visceral involvement have been observed even in immunocompetent persons. The clinical syndromes observed in such patients include interstitial pneumonitis, hematological disorders, hepatitis, gastroenteritis, colitis, myocarditis, meningoencephalitis, uveitis, retinitis and others. Such severe manifestations of CMV are rare in immunocompetent hosts without any identifiable risk

factors. Critically ill patients admitted in ICUs are at increased risk for such multivisceral involvement as there is usually an identifiable risk factor which is present in such patients. The common risk factors present would include presence of mechanical ventilation, sepsis, burns, recipients of blood transfusion, trauma, post surgical patients, chronic renal failure, steroid therapy, and extremes of age.

Contrary to the traditional belief that CMV infection in immunocompetent but critically ill patients follows a self-limited course, are considerable investigations that report increased morbidity and mortality as a result of CMV in such cases [12-17].

CMV is ubiquitously present in the body [26]. CMV establishes latency in various organs; thus any site is susceptible for reactivation of the disease (Table2). The type of organ system affected by CMV

is different in different patient groups. Lungs act as reservoir in cases of latent CMV infection and thus act as the most consistent site for its reactivation. Domart *et al*. diagnosed CMV infection in 29 patients with mediastinitis among 115 immunocompetent patients after cardiac surgery. The peri-operative blood transfusion of non leukocyte depleted blood was considered to be responsible for CMV seroconversion [27].

Papazian *et al*. reviewed 2,785 patients admitted to ICUs during the years 1989-1994. Sixty autopsies and 26 open lung biopsies were performed in non-immunosuppressed patients with acute respiratory failure and ventilator associated pneumonia. CMV as a causative agent of pneumonia was demonstrated in 25 of them and all these patients had a more severe hypoxemia as compared to others [28].

Clinically significant gastrointestinal manifestations are seen as a result of CMV in critically ill immunocompetent patients. Halme *et al*. demonstrated that CMV was detected in 71% of the patients with liver transplants who had gastrointestinal symptoms, 45% with chronic liver disease, 20% with acute liver disease, and 45% of otherwise immunocompetent patients with dyspepsia. CMV was detected by immunohistochemistry technique using monoclonal antibodies against pp65 antigen of CMV on gastric biopsies [29].

Although CMV colitis is not a common clinical presentation, it has been detected in otherwise immunocompetent patients. These patients usually experience diarrhoea as a result of colitis. It is more common in extremes of age, presence of immunomodulating conditions such as diabetes mellitus, renal failure, malignancies, and patients who have had post surgical interventions [30,31].

Thrombotic complications have also been associated with CMV infection in immunocompetent individuals. Some viral infections are known to cause hemostatic abnormalities which could be as severe as disseminated intravascular coagulation. CMV mediated portal venous thrombosis has been reported probably as a consequence of acute hepatitis. Liver function abnormalities are comparatively common in symptomatic individuals as CMV is a hepatotropic virus. Though CMV commonly causes hepatitis it can be proved only if virus is detected on liver biopsies by detection of inclusion bodies or by immunohistochemical staining [32].

CNS manifestations are very common in immunocompromised patients but there have been reports of meningitis and other CNS manifestations as a result of CMV even in immunocompetent patients[33]. Cardiac involvement, though rare, has also been observed in immunocompetent adults. In a study of 57 patients with pericardial effusion, Campbell *et al*. found five patients with CMV pericardial disease. In three of these patients underlying risk factors were present [34]. There have also been case reports of CMV associated myocarditis and hepatitis [35,36].

The list is not exhaustive and there are still other case reports and case series of CMV mediated disease. The purpose of mentioning these case reports was to highlight the fact that CMV can virtually affect any organ even in otherwise immunocompetent individuals. Hence it should be kept in mind as a differential diagnosis in critically ill ICU patients presenting with fever.

Treatment

The use of antiviral treatment for CMV has proven to be of benefit in immunosuppressed individuals, but there is a scientific debate over the issues of treating CMV infection in cases of immunocompetent individuals. The major therapeutic strategies used by clinicians are prophylactic or preemptive therapy. The goal is to prevent the development of end stage organ disease. The first step is to start the therapy universally (prophylactic therapy) and the next is to give antivirals to specific high-risk patients (preemptive therapy). The basic principle of preemptive therapy is to initiate antivirals for patients displaying viremia early in the clinical course to halt the progression to end organ disease [37].

The drugs available for treating CMV include ganciclovir (GCV) and valganciclovir (VGCV), acyclovir (ACV) and valacylovir (VACV), Mirabivir, foscarnet and cidofovir Table 3). Most of the studies involving these treatments have been performed in immunocompromised patients and transplant recipients [37,38,39]. There is a need to perform multicentre experimental studies using these antivirals in a large number of critically ill immunocompetent patients to come to a conclusion regarding their beneficial role in such cases.

One experimental study demonstrated that ganciclovir prevented murine CMV reactivation and the development of pulmonary fibrosis in immunocompetent mice with sepsis [40]. The improvement seen in some patients in a few other studies could also be due to the self-limiting nature of

CMV disease and therefore the credit cannot be given to antivirals with certainty.

Resistance to these drugs has been documented on prolonged usage, as seen in HIV patients. Antivirals have to be used only for a limited duration in immunocompetent patients to tide over the acute phase. In such circumstances resistance to these antivirals is not usually a problem. Targeting antivirals in all critically ill patients in the ICU might be impractical as these antivirals frequently have bone marrow suppression as one of their major side effects. There has been no consensus regarding the therapeutic protocol to be used in such patients. Many clinicians believe that CMV is self-limiting in immunocompetent patients and the critically ill patients should not be exposed to the adverse effects associated with these antivirals. But there have been considerable reports of adverse clinical outcomes in such critically ill immunocompetent patients who have associated risk factors. Hence the correct approach would be to treat critically ill patients who are at higher risk of developing CMV disease.

Conclusion

CMV reactivation in critically ill non-immunosuppressed patients leads to increased mortality and morbidity in terms of increased ICU stay, longer duration of mechanical ventilation, and higher rates of nosocomial infections. Though CMV can virtually affect any organ system, lungs appear to be the most common organ of involvement. There are no overt signs and symptoms of active CMV disease and most episodes start with fever. The intensivists should thus be aware of the possibility of CMV reactivation in otherwise immunocompetent patients admitted in the ICU who have associated risk factors such as mechanical ventilation, severe sepsis, or blood transfusion. Advanced diagnostic procedures should be initiated to identify active CMV infection and disease as early as possible. No definitive conclusions can be made regarding the beneficial effect of antiviral therapy in immunocompetent individuals as there are very few experiences and further clinical trials are required to reach definitive conclusions. The decision to initiate antivirals should be based on clinical assessment. Patients who have associated risk factors should preferably be given antiviral treatment.

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