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CYTOMEGALOVIRUS PNEUMONIA IN HEMATOPOIETIC STEM CELL RECIPIENTS

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Abstract

Cytomegalovirus (CMV) is a frequently encountered infection following hematopoietic cell transplantation, and tissue invasive pneumonia is a dreaded complication of the virus in this population. In this review of CMV pneumonia, we address epidemiology, pathogenesis, diagnostics, current therapy and strategies to prevent the development of CMV disease. We also review emerging treatment and prevention options for this challenging disease.

Keywords

Cytomegalovirus; CMV pneumonia; hematopoietic cell transplant; antiviral; prevention

INTRODUCTION

Cytomegalovirus (CMV) continues to be a major cause of morbidity in hematopoietic cell transplant (HCT) recipients[1,2], but of all CMV complications pneumonia is the most associated with significant mortality.[3] Prevention strategies aimed at limiting latent reactivation and viral replication have been successful in reducing the incidence of CMV pneumonia to approximately 4% in high-risk seropositive recipients[4,5], but changes in transplant practices such as the expanded use of high-risk unrelated and cord blood donor grafts, have also defined new populations more likely to develop CMV invasive disease.[6] Unfortunately, even with potent antiviral therapy and advanced critical care management, death from CMV pneumonia remains unacceptably high.[3,7]

In this review we address the epidemiology, pathogenesis, diagnostics, and review up-to-date treatment and prevention strategies for CMV pneumonia in HCT patients. We also discuss ongoing research focused on novel treatment and prevention options, including antivirals in development. With the continued expansion of transplant programs throughout

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the world, an increased number of critical care physicians will have exposure to and responsibilities for diagnosing and treating this major post-transplant infectious complication. We hope that this review will serve as a state-of-the-art update on this infrequent yet important HCT complication for those with experience in transplantation and provide a foundation for those new to this unique immunocompromised population.

Epidemiology

Incidence—The incidence of CMV pneumonia in the early years of HCT, prior to the introduction of CMV prevention strategies, was around 10–35% after allogeneic transplantation and 1–6% in autologous transplant recipients.[8] The institution of preemptive strategies used at most centers in the US (see prevention section below) have decreased the overall incidence of CMV disease in HCT recipients to around 5–8%.[3–5] The burden of disease has also shifted, as gastrointestinal (GI) disease is now considered the most common form of CMV disease in HCT; pneumonia is estimated to make up about 1/3 of disease cases.[5,9] The majority of cases of CMV pneumonia still occur in the early post-transplant period (≤ day +100), but the number of those occurring in the late period (after day 100) have increased.[3,10] Late CMV disease occurs more frequently in subjects who experienced CMV reactivation within the first 3 months after HCT (27), had graft-versus-host disease (GVHD), have persistent lymphopenia at day 100 (or low CD4 count) and in those seropositive recipients who received of a CMV-seronegative donor graft (28).[9–12]

Outcomes—Outcomes in patients who develop CMV pneumonia are generally very poor, even with the use of potent antiviral agents and aggressive critical care management. Rates of mortality associated with CMV pneumonia in the pre-treatment era were nearly 100%[13], but with the advent of ganciclovir (GCV) and other antiviral therapy options, rates of death have fallen to approximately 30–50%.[1,3,14,15] The need for respiratory and critical care support is strongly associated with increased mortality.[16] Interestingly, in some retrospective studies rare patients with proven CMV pneumonia survive even without antiviral therapy[1], suggesting different host factors may help determine survival post-infection.

Pre and Post-Transplant Risk Factors (Table 1)

Serologic status (Donor and Recipient): The most prominent risk factor for CMV pneumonia is the transplant recipient's CMV serologic status prior to transplantation (Table 1). Patients who are known to be seropositive (R+) are at the greatest risk for reactivation of latent virus through the transplant process and have the highest rates of subsequent CMV disease.[3,17–20] The relationship of donor serostatus in R+ recipients remains controversial.[21–23] In contrast to their high-risk counterparts, seronegative patients (R−) who receive a positive donor graft (D+) have a much lower risk of CMV infection (12–19%) and CMV disease (3–5%).[20,24] Less than half of the D+/R− patients that are found to have invasive disease have pneumonia and overall CMV pneumonia is an uncommon complication occurring in only about 1% of patients with preemptive therapy.[20] Patients who are CMV D−/R− rarely develop evidence of CMV infection and rates of CMV disease are very low (<1%).[3,25]

Stem Cell Source: Multiple transplant associated risk factors are linked to the development of CMV disease (see table 1). When considering donor graft source, peripheral blood cells are thought to be associated with a lower risk of CMV reactivation and pneumonia than bone marrow grafts [26], but umbilical cord blood transplant recipients appear to be at even higher risk for CMV disease due to significant delays in immune reconstitution.[6,19,27,28] Patients receiving unrelated and mismatched donors are at higher risk of CMV disease, although this increased risk appears to be associated with the development of late disease.[14,29–32]

Conditioning Regimen: Multiple transplant conditioning regimens have also been associated with the development of CMV disease. Earlier studies suggested CMV complications were delayed in those undergoing non-myeloablative conditioning when compared to myeloablative regimens[14], but this has not been confirmed in larger cohort studies.[4,31] T cell depletion delays anti-CMV T-cell reconstitution [33] and has been associated with a higher risk of CMV complications in multiple populations.[15,18,34–38]

Post-transplant complications: Post-transplant complications are also known risk factors for the development of CMV disease. The development of acute and chronic graft GVHD are associated with the development of CMV disease.[3,10,39–43] Immunosuppressive strategies for acute and chronic GVHD prophylaxis have been related to higher risk of CMV infection.[44] T-cell therapies and mycophenolate mofetil (MMF) delay CMV specific T-cell responses and lead to more frequent CMV complications. [45–47] Interestingly, not all immunosuppressive therapy may have a negative effect on CMV, as sirolimus may have a protective role in CMV infection.[48]

CMV detection in blood: It is important to note that not all patients who have detectable CMV in their blood develop CMV disease, but that nearly all patients with CMV pneumonia will have evidence of CMV reactivation.[49] Determining the risk factors for progression from viral replication in blood to development of tissue invasive disease are challenging in this population, as most risk factors associated with CMV disease are also associated with CMV reactivation. Rates of progression from reactivation to CMV pneumonia have however been associated with leukopenia/lymphopenia at the time of reactivation and the development of a high viral load during preemptive therapy.[50,51] Viral kinetics of CMV post-HCT, particularly initial viral load and expansion kinetics, also appear to be strong predictors for the development of CMV disease.[51]

PATHOPHYSIOLOGY

Following primary infection, CMV becomes latent in the human host avoiding immune detection through multiplicative and diverse mechanisms.[52] Data suggests that bone marrow-derived hematopoietic cells, granulocyte-macrophage progenitors, and peripheral blood monocytes serve as reservoirs for reactivation during immunosuppression.[20,53–58] In addition, murine models and human studies have demonstrated latency in lung alveolar macrophages and pulmonary epithelial cells.[59–61] The allogeneic process likely facilitates reactivation of CMV[62], and major alterations in adaptive and innate immunity following transplantation lead to viral escape, replication and eventual tissue invasion. CMV

replication is linked to the degree of immunosuppression, and CMV pneumonia is more frequent and severe in HCT recipients than in most other immunosuppressed populations.[7] Pathogenesis of CMV pneumonia has been reviewed by others in detail[63–65], but the mechanisms by which CMV invades the lung are unclear. In fact,

Immunopathology hypothesis

The immunopathology hypothesis suggests that immune responses to CMV lead to pulmonary complications.[63,64] Grundy and colleagues demonstrated that CMV proliferated extensively in the lung in athymic mice without development of pneumonitis, but that once their T-cell immunity had recovered pneumonitis rapidly developed.[64,66] This theory is also thought to be supported by the lack of CMV pneumonia events in syngeneic transplants and in HIV patients with more profound CD4 deficiency.[64,67]

Cytopathological hypothesis

The alternate cytopathological hypothesis suggests that CD8+ T-cells are needed to protect against the development of CMV tissue invasion.[64,65] Studies have implicated deficiencies in class I MHC-restricted, CMV-specific CD8+ T-lymphocyte responses in the progression to invasive disease.[65] This theory has been supported by clinical observations of severe CMV pneumonia occurring in murine studies and in patients treated by T cell depleting agents.[15,68] Furthermore, it has been shown that neutralizing CD8+ T-cells in immunosuppressed CMV infected mice inhibited interstitial pulmonary involvement[69], and that adoptive immunotherapy has been shown to abrogate CMV complications.[70] In addition, studies have demonstrated that marked reductions in CD4/CD8+ CMV specific T-cells are associated with the development of late disease, and that low dose CMV reactivation and subsequent immune education may prevent this complication.[11]

Other factors

There are also emerging data that support a role for natural killer cells in CMV complications following HCT, specifically with activating killer immunoglobulin-like receptor (KIR) genotypes of donor cells.[71–73] The association between excess NK cells in BALs from immunocompromised patients who died from CMV pneumonia suggests a role in aberrant immune responses to CMV.[74] At the same time, herpesvirus infections are much more likely to occur in children who lack NK cells but possess an intact adaptive immune system.[75] The endothelium is also though to play a role in the pathophysiology of CMV lung involvement as infected endothelial cells upregulate adhesion molecules, allowing for leukocyte attachment and associated vascular damage.[76–78] It is unknown whether the driver of this associated endothelial injury is directly related to CMV, or if toxicity from the transplant process (e.g. total body irradiation) leads to such damage and subsequent CMV reactivation.

DIAGNOSIS

Signs and Symptoms

CMV pneumonia is defined by the presence of clinical signs and symptoms of pneumonia or pulmonary disease combined with the detection of CMV from the lung.[79] Patients with

CMV pneumonia present with findings consistent with pulmonary dysfunction including a non-productive cough, dyspnea and hypoxia; fever does not always have to be present.[80] Clinical examination may demonstrate prominent rales and tachypnea, but may initially be unremarkable. Nevertheless, none of these signs or symptoms are classically associated with CMV pneumonia, and nearly all are only indicative of an ongoing pulmonary process.

Non-Invasive testing

There are no typical laboratory findings that confirm the diagnosis of CMV pneumonia. Patients with CMV pneumonia may have low oxygen saturations on arterial blood gas evaluation, and some patients with may develop leucopenia or leukocytosis; these findings are not specific to CMV pneumonia. CMV detection in blood by CMV PCR or the pp65 antigenemia test can be helpful, but are not diagnostic even in the face of compatible symptoms. Although the majority of patients with CMV pneumonia will have CMV detected in blood, it can rarely occur with without detection in blood.[49]

Radiology

The most common radiological sign is bilateral interstitial infiltrates on chest x-ray (see Figure 1).[80] Focal radiographic signs may also be absent in patients with documented CMV pneumonia.[7,13,81] Moreover, neutropenic subjects are less likely to have abnormalities on conventional chest radiography may fail to detect lung infiltrates at an early stage, computed tomography (CT) scan has been shown to higher sensitivity and assist in the early detection of more subtle pulmonary infiltrates.[82] The most common findings on CT are bilateral asymmetric ground-glass, air-space opacities and small centrilobular nodules.[83] While often a diffuse interstitial process on CT, CMV can also present less frequently as nodules or pulmonary consolidations.[84,85] CMV may also present as a co-pathogen to other major infections, further limiting the specificity of radiologic findings.

Bronchoscopy/Bronchoalveolar Lavage

Bronchoalveolar lavage has become the most frequent mechanism for the detection of CMV during the clinical management of HCT recipients. A number of laboratory and pathologic analyses are available on BAL fluid, and any one of these tests (Figure 2)can be diagnostic of CMV pneumonia in the presence of appropriate clinical and radiologic findings; histopathology is not required.[79] Viral culture is performed by growing CMV in human fibroblastoid cell lines but slow growth may require up to 4 weeks for diagnosis. The required time, low reproducibility and low sensitivity of culture makes this technique impractical for prompt diagnoses. Cytopathologic evaluation for inclusion bodies from BAL fluid has a high specificity but low sensitivity for CMV pneumonia, but immunohistochemical staining with anti-CMV antibodies may enhance sensitivity of this method.[86]

Rapid detection of CMV can be performed by shell vial culture and/or direct fluorescent antigen testing (DFA). The shell vial method is a rapid culture technique that allows for identification of virus using monoclonal antibodies to immediate-early antigen within 24 hours and has been shown to be highly sensitive for the detection of CMV pneumonia.[87] This test however, is operator dependent which limits widespread use in all but the largest

centers. DFA is useful as a rapid test (within 1.5 hour), but lacks the sensitivity of other rapid tests.[88] Qualitative CMV polymerase chain reaction (PCR) from BAL fluid has been shown to have a good negative predictive value, but poor positive predictive value for the diagnosis of CMV pneumonia.[89,90] Quantitative PCR has been suggested to have a higher sensitivity but the absence of established viral load cut-off of CMV for defining CMV disease, limits the use of this technique. Furthermore, studies have demonstrated CMV DNA in BAL samples of asymptomatic HCT recipients, limiting interpretation of positive results.[91,92] Still many centers currently utilize CMV PCR as part of their diagnostic strategy although it is not currently considered criteria for CMV pneumonia.[79]

Lung Biopsy

Histopathological diagnosis of CMV pneumonia from lung biopsy demonstrates typical intranuclear inclusions; CMV within cells may also be detected by immunohistochemical staining or in-situ hybridization.[79] All lung biopsies and autopsy samples should also undergo routine shell viral testing for rapid diagnosis. Even though less likely to inform clinical care biopsy samples may also be held for CMV culture as a positive result can be important for epidemiologic studies. Unfortunately in severe cases, lung biopsy is not always feasible, as rapid onset of respiratory failure, mechanic ventilation or thrombocytopenia may limit access to this procedure.[93] The patchy nature of the disease suggests that fine needle aspiration and less invasive pathologic sampling may miss clinically relevant disease.[94]

DIFFERENTIAL DIAGNOSIS

Infectious

Signs and symptoms of CMV pneumonia are not pathognomonic, and clinical manifestations and interstitial lung involvement may be caused by a multitude of other pathogens. Further complicating the picture is the uncertain role of CMV as either pathogen or bystander, as it can be detected in BAL specimens of patients with other confirmed pathogens.[24] Bacteria such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or Legionella species can all have similar subacute presentations. Respiratory viral pathogens, including influenza, parainfluenza and respiratory syncytial virus, among others, can present with findings that are similar to CMV; these infections may not always be associated with upper respiratory symptoms.[95] Other herpesviruses, albeit less frequently, can also present with pulmonary complications following transplantation.[96,97] HHV6's role in pulmonary disease remains somewhat unclear, but it can be seen as a co-pathogen in some patients.[98–101] Adenovirus, another latent virus, has similar risk factors and can also present during the post-HCT period with similar radiographic and clinical findings.[102] The fungus *Pneumocystis jiroveci* can be challenging to distinguish from CMV pneumonia on clinical and radiographic findings alone, and although infrequent, CMV can also present with nodules or consolidation that resembles fungal pneumonia.[84,85]

Non-infectious

Non-infectious pulmonary complications can also present with signs and symptoms that may be similar to CMV. Idiopathic pneumonia syndrome presents with cough and tachypnea

often seen in CMV pneumonia, and has associated multilobular infiltrates on chest x-ray or CT.[103] As a subgroup of these patients, patients with diffuse alveolar hemorrhage (DAH) usually present more acutely.[103] Patients who develop non-infectious cryptogenic organizing pneumonia (COP) can also present with low grade fever, non-productive cough, and dyspnea similar to CMV pneumonia.[104] Radiologic manifestations can mimic viral pneumonia.[105] The development of pulmonary edema or patients who develop chemotherapy associated pulmonary complications can also mimic CMV pneumonia.[106] Other medications, such as Sirolimus, can lead to adverse pulmonary complications that may present with interstitial pneumonitis similar to CMV pneumonia or viral process.[107]

THERAPY

Antiviral therapy

The foundation for CMV pneumonia treatment is the early institution of antiviral therapy. CMV pneumonia following HCT, before the availability of current antivirals, was associated with a high mortality rate (nearly 100%). HCT recipients who receive early antiviral intervention may have improved outcome from CMV pneumonia.[108] Early treatment is thought to help control viral replication which may help to limit immune-related lung damage, thereby reducing additional morbidities, such as the development of secondary infections, need for mechanical ventilation and aggressive intensive care management. Still, antiviral therapy will not change the outcome in all patients, as even with active antiviral therapy, death from CMV pneumonia remains an unavoidable outcome in many patients.[7,16,109]

Therapy is focused on an induction phase (twice daily dosing) and a maintenance phase (once daily dosing) of treatment. At our center patients with CMV pneumonia receive a minimum 3 weeks of induction therapy and at least 2 weeks of maintenance, but patients with more severe disease or slower responses to therapy may need prolonged therapy. First line therapy of CMV pneumonia is intravenous (IV) ganciclovir (GCV). GCV is nucleoside analogue of 2'-deosygaunosine, that undergoes initial phosphorylation by viral kinases encoded by CMV UL97 open reading frame (ORF).[110] The active form of the drug, triphosphorylated GCV, competitively inhibits DNA synthesis catalyzed by CMV DNA polymerase (encoded by the UL 54 ORF).[110] The use of GCV is limited by hematologic side effects, primarily by neutropenia, which restrict its use in the pre-engraftment phase of transplantation. IV GCV is recommended therapy for CMV pneumonia, although valganciclovir (the L-valyl ester of GCV) is available for oral dosing, it is not typically recommended for HCT patients with CMV pneumonia. Valgancyclovir can be considered for maintenance therapy in lower risk patients who have demonstrated clinical response to therapy.

An alternate to GCV, foscarnet acts by inhibition of CMV viral polymerase.[110] Nephrotoxicity is the major adverse side effect of the drug, and can lead to acute renal failure, as well as mineral and electrolyte abnormalities. Because of these serious side effects, foscarnet is considered the second line therapy but is preferred in subjects with myelosuppression and for patients with known resistance to GCV. Cidofovir acts as a competitive inhibitor of DNA polymerase that has been shown to be effective in CMV

ocular disease.[110,111] Many consider cidofovir a third line agent, due to its significant renal and hematologic toxicities. Combination therapy is sometimes considered in patients with evidence of drug resistance (reviewed in detail elsewhere[112]) or in those with refractory disease.

Novel antiviral options have generally been studied in the context of CMV prophylaxis, so data on their efficacy in treatment of disease are inadequate to support the use of any of these agents as primary therapy. Maribavir (MBV), is an orally bioavailable drug that interferes with DNA synthesis of CMV, and is also felt to inhibit viral encapsidation and nuclear egress of viral particles by binding to UL97 viral protein kinases.[113] MBV has been used as salvage therapy for patients with proven CMV disease under individual emergency investigational new drug applications and the drug was effective at clearing CMV from the blood, but in this study one patient with CMV pneumonia following HCT died from progressive disease despite viral clearance.[114] A phase II treatment trial for refractory infections is currently underway.[115] Lipid-complex cidofovir (CMX-001) has shown promise against CMV[116], but data on its use in CMV pneumonia are not currently available. Letermovir (AIC246), a novel anti-CMV drug that inhibits CMV replication through a mechanism that involves the viral terminase[117], has been reported to lead to successful treatment in a patient with disseminated CMV disease.[118] Leflunomide, an agent approved for use in rheumatoid arthritis, has CMV activity[119] and has also been attempted with mixed success in refractory cases.[120,121] None of these agents are currently FDA approved for treatment of CMV or CMV pneumonia.

Immunoglobulins

The use of both CMV-specific and non specific intravenous immunoglobulin (IVIG), are an additional component to consider during therapy. A number of clinical trials have assessed the role of IVIG in the treatment of CMV pneumonia.[122] Although early studies did not show effectiveness of IVIG as a stand-alone therapy, studies in the in late 1980's evaluating combination therapy with antivirals and various IVIG formulations demonstrated improved outcomes in patients with CMV pneumonia when compared with historical controls[123,124], or to GCV or IVIG alone.[125] The small sample size of these early studies and recent evaluations under current preemptive strategies, however, suggest that combination therapy may provide minimal if any additional benefits to standard antiviral treatment.[16,108,126,127] The high mortality seen in these patients, the limited side effects of IVIG treatment, and the lack of a randomized clinical trial comparing combination therapy versus antiviral therapy alone, has led most to err on the side of caution and continue the routine use of combined antiviral and immunoglobulin therapy in the treatment of CMV pneumonia. For those centers that choose to use IVIG, it does appear that more costly CMV-specific IVIG may be no better than standard pooled IVIG preparations.[128]

Adoptive immunotherapy

Newer laboratory techniques to treat severe viral infections include the development of ex-vivo T-cells that are specific for individual and multiple viruses.[70,129–131] These therapies have been used to treat patients with severe infections.[132] Limited availability, the need for significant preparatory time and high cost of these procedures, limits their use to only major

medical centers. The development of novel “off the shelf” methods for improving access and speed of delivery of these therapies should allow for future clinical trials.

PREVENTION

There are numerous reviews that discuss the advantages and disadvantages of different strategies to prevent CMV disease.[9,25] In general prevention falls under two principles, primary prophylaxis and preemptive therapy, and both have strengths and weaknesses.

Antiviral prophylaxis

Antiviral prophylaxis has also been evaluated in a number of important clinical trials. GCV prophylaxis has been shown to decrease the risk of early CMV disease, but patients in these trials also had associated increases in neutropenia and subsequent risk for bacterial and fungal infections.[133–136] Prolonged antiviral exposure can also lead to selection of resistant CMV,[112] and may increase the risk of late disease events by delaying CMV immune recovery.[137] Prophylactic strategies among CMV-seropositive allogeneic transplant recipients lowered the incidence of CMV disease to 6% within the first 100 days after HCT but increased late complications (day +100 to 1 year) from 4% to 15% after the end of prophylaxis.[138] Acyclovir/Valacyclovir, which have less systemic toxicity, can be used as an alternate to CMV-specific antiviral agents. Use of high-dose valacyclovir reduces the risk of CMV infection[139], and in a randomized clinical trial was as effective as GCV as chemoprophylaxis[140]; others have shown benefits for disease prevention in high-risk populations when combined with preemptive therapy and other more aggressive prevention strategies.[6]

Newer antiviral agents described in prior sections, may have more tolerable side effect profiles and have been evaluated as options for chemoprophylaxis. Low dose MBV appeared to be beneficial in a phase II trial[141], but was ultimately shown to be ineffective as a prophylactic agent in a large multinational trial in HCT.[142] CMX001 and Letermovir, appear promising, as both agents have shown reductions in CMV complications in high-risk seropositive allogeneic HCT patients.[143,144] Side effects of Letermovir were minimal, while CMX001 had notable GI side effects at high doses; neither drug had adverse effects on hematologic recovery. Although these data are encouraging, future phase III studies are needed to confirm these findings.

Preemptive therapy strategies

Most centers in the US and worldwide use a preemptive approach[145], by which patients are screened weekly for CMV in blood and “preemptively” treated with CMV-specific antiviral therapy to prevent the development of disease. This approach has been shown to be effective at decreasing the risk CMV disease (particularly pneumonia) using either a pp65 or CMV PCR based strategies.[5,146] Specific cutoffs for institution of preemptive therapy depend on the type of laboratory screening method (pp65 vs. serum PCR vs. whole blood PVR) used at individual centers. Since not all patients who have CMV detected will develop disease[20,147], institutions should develop specific thresholds for starting therapy. Once the threshold of detection has been met patients are typically started on preemptive therapy with GCV or

foscarnet until they clear CMV from their blood. For example, at our center patients are monitored week by CMV PCR through day 100, and started on therapy if they develop ≥ 500 copies copies/ml plasma. If patients are at high risk (T-cell depleted or on ≥ 1 mg/kg of steroids) they are started at 100 copies[31], all cord blood transplant recipients are tested twice weekly and started at any positive value.[6] Upon detection patients are started on induction with GCV or foscarnet for at minimum two weeks, followed with at least one week of maintenance. Patients are continued on induction until they have improvement in the viral copy numbers, and therapy is discontinued only after viral clearance. Continued surveillance is recommended in some patients at high-risk for CMV complications after day 100, including those who develop early CMV reactivation and those on high-dose steroids for GVHD.[31]

Immunoprophylaxis

Immunoprophylaxis has been evaluated in recent metanalysis, which found no benefit to either polyvalent or CMV-specific IVIG in the prevention of CMV pneumonia.[148] Since this strategy is both costly and with uncertain benefit, it is not recommended for CMV prevention in this population.

CMV Vaccines

Future options for prevention may include CMV vaccines which are currently in development. The CMV vaccine TransVax was shown to decrease the rates of significant CMV viremia (≥ 500 copies/ml) and the days free from viremia, but the rates of CMV disease did not differ between the vaccine and placebo groups.[149] A phase III trial evaluating this vaccine in allogeneic HCT patients is needed. A glycoprotein B vaccine has also been shown to be effective at decreasing the rate and severity of CMV viremia in other immunocompromised patients[150], but no current data exists in HCT recipients. A novel tetanus-CMV fusion peptide vaccine has demonstrated immunogenicity in immunocompotent patients, but has not been tested in immunocompromised populations to date.[151]

CONCLUSIONS

Improved prevention strategies have decreased the incidence of this dreaded transplant complication, but CMV pneumonia remains a problem in patients undergoing HCT. The frequency of CMV reactivation and respiratory complications following transplantation, the diversity of etiologies of pulmonary disease, and the negative side effects associated with CMV-specific antiviral therapy strengthen the argument for an aggressive diagnostic approach in HCT patients with respiratory symptoms and abnormalities on radiologic evaluation. Diagnosis of CMV pneumonia by standard techniques should be done as soon as possible. Future studies are needed to improve currently available diagnostics, including defining thresholds for CMV PCR from BAL, and to develop non-invasive methods of diagnosing CMV disease. There is also a need to develop improved strategies for prevention which are non-toxic, easily administered and effective. The development of the first new CMV antivirals in over 15 years, suggests new treatment options are on the horizon. These

novel antiviral agents and emerging CMV vaccines may also help provide improved methods for preventing this important complication.

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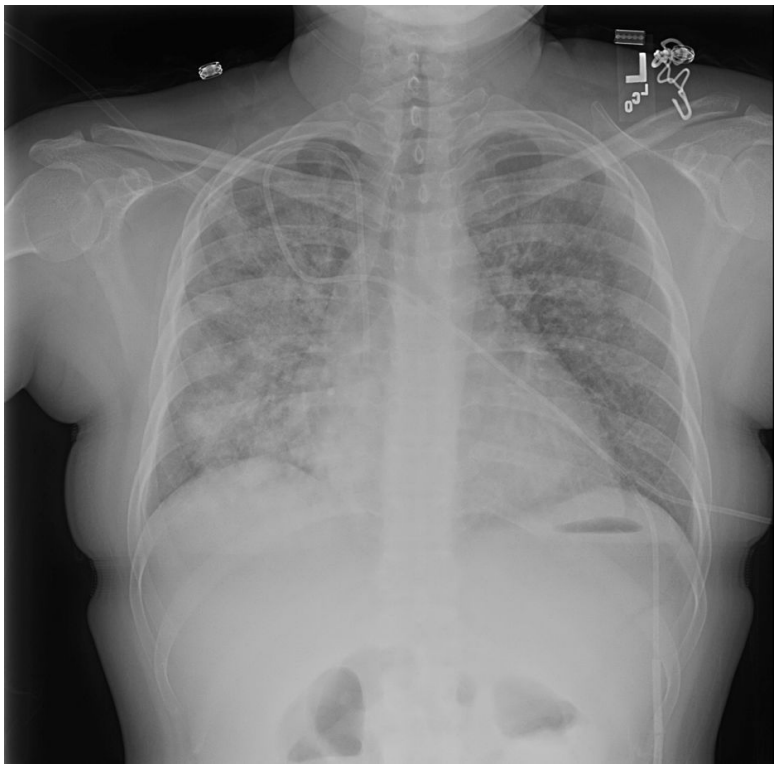

Figure 1. Methods Used to Diagnose CMV Pneumonia

In order to make a diagnosis of patients must have signs and/or symptoms of pulmonary disease combined with the detection of CMV in bronchoalveolar lavage fluid or lung tissue samples. Detection of CMV can be by any one of the methods described in this figure.[79] *A positive PCR test is not considered diagnostic by current guidelines[79], but is nonetheless used at many centers for diagnosis of CMV pneumonia.

Abbreviations: CMV, cytomegalovirus; DFA, direct fluorescent antigen; PCR, polymerase chain reaction.

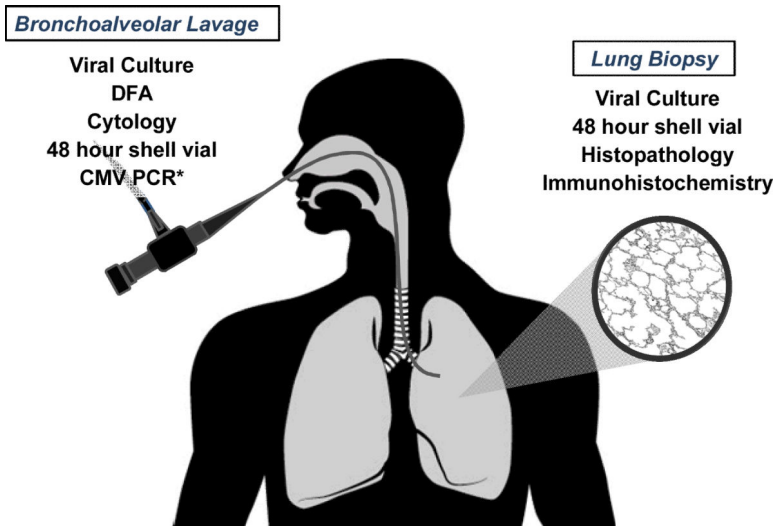

Figure 2. Radiographic Findings of CMV Pneumonia

A 45 y/o female 34 days post-hematopoietic cell transplantation with CMV pneumonia. Anterior posterior chest radiograph demonstrates a diffuse interstitial process consistent with viral pneumonia.

Table 1

Epidemiologic Risk-factors Associated with CMV Disease in Patients Undergoing Hematopoietic Cell Transplantation

Transplant Associated Risk Factors	Risk	Selected References
Pre-Transplant Risk Factors		
CMV Serostatus		
CMV R+ Status	⬆⬆⬆	3,17,25,152
- if CMV D- Donor Status	⬆	21,22,153
CMV R-/D+	⬆	20,24
Donor Graft		
PBMC vs. Bone Marrow	⇩	26
Umbilical Cord Blood	⬆⬆	6,19,27,28
Unrelated Donor	⬆	14,29,32,154
Donor Mismatch	⬆	154,155
Conditioning Regimen		
T-cell depletion	⬆⬆	15,18,34–37
Myeloablative vs. Non-myeloablative	⇳	4,30,156,157
Post-Transplant Risk Factors		
CMV detection in Blood*	⬆⬆⬆	multiple
High initial viral load	⬆⬆	50,51
Hematologic recovery		
Lymphopenia†	⬆⬆	11,12,50
GVHD		
Acute GVHD	⬆⬆	41–43,50,158
Chronic GVHD	⬆	10,39,159
GVHD prophylaxis and treatment		
Anti-T-cell therapy	⬆⬆	3,160 (see above)
Use of MMF	⬆	45 – 47
Use of Sirolimus	⇩	48
Steroids >1 mg/kg/day	⬆⬆	39,158

Abbreviations: CMV, Cytomegalovirus; R+, recipient serpositive; D−, Donor seronegative; R−, recipient seronegative; D+, Donor positive; PBMC, peripheral blood mononuclear cells; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil. Strength of association demonstrated by the number of arrows: ⬆ indicates increased rate; ⇩indicates decreased rate; ⇳ indicates conflicting data.

*Detection in blood increases the risk for the development for both early and late CMV disease.

†Likely related to all lymphocyte subsets, but CD4 and CD8 probably most important.