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PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

# Challenges and Clinical Implications of the Diagnosis of Cytomegalovirus Lung Infection in Children

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## Abstract

**Purpose of Review** Pulmonary cytomegalovirus (CMV) infection is a potential lethal disease in children, but it remains a diagnostic challenge. The differentiation between latent CMV infections with viral shedding and active infections is difficult and may lead to false positives in bronchoalvolar lavage (BAL) PCR detection. This review summarizes current diagnostic approaches for CMV lung infection in children including progress in the identification of underlying immune defects linked to this condition.

**Recent Findings** There is increasing literature supporting that the combined assessment of host risk factors and lung disease pattern is essential for the diagnosis of pulmonary CMV infection in children. The most important host risk factor is an immunecompromised state that has expanded from primary or acquired immunodeficiency (e.g., HIV) to include a myriad of immune-dysregulation syndromes (e.g., CTLA4, PIK3 defects). Newborns, paricularly those born premature, are also a high-risk group. At the pulmonary level, active CMV infection is typically characterized by alveolar compromise leading to hypoxemia, ground-glass opacities, and intra-alveolar infiltrates with CMV inclusions in lung biopsy. The identification of active CMV lung infection should trigger additional evaluation of immune defects (primary or secondary) impairing T and NK cell function or innate antiviral responses as well as other immune dysregulation disorders.

**Summary** Lung CMV infections in children are more prevalent in immunocompromised hosts and premature newborns. Lung CMV infections should prompt further investigation into conditions altering immune mechanisms usually in place to contain CMV infections. Common clinical and radiological patterns such as hypoxemia and ground-glass pulmonary opacities may allow early identification and treatment of CMV lung infection and underlying causes in the pediatric population.

**Keywords** CMV · Lung infection · Pneumonitis · Immunodeficiencies · Immune-dysregulation syndromes · Children

## Introduction

Human cytomegalovirus (CMV), a betaherpesvirus [1], is an important cause of human respiratory infections worldwide, and its presence in populations is characterized by an age-dependent rise in seropositivity. After primary infection, CMV remains in the host cells in latent form, potentially reactivating in immunocompromised hosts [2]. Approximately 50 to 90% of the world population are CMV seropositive, although this figure varies with age and geographic location [3]. A minority of primary CMV infections in immunocompetent patients will result in symptoms. In such cases, a mononucleosis-like picture is seen with a variable degree of constitutional and organ-specific manifestations. In the general population, more severe tissue-invasive disease is almost always limited to patients with critical illness or comorbidities conferring relative immunosuppression [4]. The diagnosis of a lung CMV infection requires a combination of

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respiratory symptoms along with compatible radiologic findings and detection of the virus [5]. However, in spite of the knowledge and diagnostic tools available to date, the diagnosis of pulmonary CMV infections remain a diagnostic challenge, and the thresholds to initiate treatment in affected individuals remain a matter of controversy [6, 7]. Accordingly, to address these gaps, we present a literature review of pediatric lung CMV infections and key aspects of their clinical presentation, diagnosis, as well as special features of these infections in young children in order to provide a useful tools to health professionals who approach these patients.

## The Clinical Spectrum of Pediatric Lung Cytomegalovirus Infections

Primary CMV lung infection in immunocompetent individuals rarely causes serious illness [8] and usually manifests as a mononucleosis syndrome indistinguishable from primary Epstein–Barr virus (EBV) infections. The characteristic presentation includes persistent fever, myalgia, and lymphadenopathy. Less-frequent manifestations of primary infection include arthritis, arthralgia, colitis with ulcers, pneumonitis, hepatitis, encephalitis, and miocarditis [9]. The primary infection has been related to Guillain–Barré syndrome [9, 10] also associated with the development of bronchiolitis obliterans [11]. Although mostly uncomplicated, the lack of detection or delay in the diagnosis of these infections make these patients a source of infection to previously uninfected contacts and immunocompromised patients, a vulnerable group susceptible to severe infections. CMV infections in immunocompromised individuals are described to often affect multiple systems and manifest as with systemic symptoms such as prolonged fever or symptoms of target organs including pneumonia, hepatitis, encephalitis, myelitis, colitis, uveitis, retinitis, and neuropathy [12, 13].

Pulmonary involvement by CMV infections has been defined in adults [5, 14–16] as a set of signs and symptoms of pulmonary infection (fever, cough, dyspnea, costal retractions) in combination with serum CMV isolation (viral culture or CMV-DNA detection), demonstration of CMV in sputum or bronchoalveolar lavage PCR (BAL-PCR), or detection of cytomegalic inclusions in bronchoalveolar lavage cells, in lung tissue using immunohistochemical analysis or in situ hybridization. However, as found by Burgener et al. [6], in children, viral isolation in BAL does not always define the presence of acute CMV pulmonary disease. This pediatric case-series study reviewed the clinical, radiologic, and laboratory data of patients < 19 years old with a BAL specimen positive for CMV, half of which were in immunocompromised patients. Although respiratory failure was reported in 29% of the encounters, and in 44% of encounters patients required supplemental oxygen, the majority of patients were never treated for CMV and resolved their acute respiratory illness, suggesting that other respiratory diagnoses should be considered first, even if CMV is recovered in BAL [6].

Lung CMV infections have variable severity. Whereas mild lung infections may remain unnoticed or present as a self-resolved respiratory infections [17, 18], severe involvement is characterized by respiratory failure frequently requiring invasive ventilatory support [19]. CMV pneumonia should be suspected when degrees of hypoxemia do not correlate with the appearance and distribution of the infiltrates in chest radiographs. In some cases, CMV pneumonia can resemble non-infectious disorders such as pulmonary embolism, heart failure, drug reactions, alveolar hemorrhage, vasculitis, and pneumonitis in patients with preexisting lung disease [20]. These conditions should be first explored with a carefully directed history and physical examination and initial diagnostic studies. Chest images are often a valuable test in the diagnosis of CMV pneumonia. In particular, the presence of minimal symmetrical, bilateral, interstitial pulmonary opacities or absence of lung infiltrates in a patient with hypoxemia suggest an atypical infection [14, 21]. Once suspected, distinction of CMV pneumonia from other viral infections is important as it impacts diagnostic and treatment. Comparisons of clinical characteristics between CMV infections and other viral etiologies that may assist the clinician in their evaluation of suspected CMV infections have been described [14, 22]. However, as most symptoms are unspecific and clinical presentations vary, a high index of suspicion is required in order to properly pursue and detect lung CMV infections.

The definition as well as established guidelines for CMV pneumonia in pediatric patients have not been completely established leading heterogeneity in treatments and outcomes. For instance, in a study comparing the outcome among South African children with "probable CMV pneumonitis," [18, 23] defined as those with positive CMV DNA detection in non-bronchoscopic bronchoalveolar lavage fluid (NBBALF) and clinical and radiological signs of CMV infections treated with ganciclovir with a similar group with "pneumonia and detectable CMV DNA" who did not receive ganciclovir. The lower survival was found among patients in the group with CMV infection and pneumonitis and in those cases with higher viral loads in serum or NBBALF. The latter group also had a higher prevalence of human immunodeficiency virus (HIV) infection[18, 23]. Taken together, these findings highlight the heterogeneity in clinical presentation and the need for better defining the need for antiviral therapy [24]. Considering the potential for ganciclovir to cause neutropenia, anemia, and other effects, a judicious selection of patients to receive

treatment is needed [25]. Likewise, as there is no consensus in regard to the optimal treatment duration, additional studies are needed in this regard [23, 26, 27].

## Host Immunity and Lung Cytomegalovirus Infections

A key factor to consider in the diagnosis of lung CMV infection is the host immunity. Indeed, the clinical presentation of lung CMV infections in children varies in severity ranging from only mild self-resolved respiratory symptoms to life-threatening disease and the interplay between viral and host factors at the local and systemic level seem to determine their clinical course [28–30]. On the one hand, CMV is known to deploy multiple mechanisms of immune evasion that interfere with the innate and adaptive arms of the human immune response [31]. During acute infections, CMV inhibits cell responses by targeting antigen presentation through interference with antigen loading and MHC downregulation [29, 32, 33], inhibition of T cell receptor co-stimulators, production of viral peptides that mimic inhibitory cytokines (e.g., IL10) or act as "traps" of cytokines involved in lymphocyte migration and activation [29, 34, 35]. Human CMV is also known to halt natural killer (NK) cell responses by downregulating NK activating ligands on infected cells or upregulating inhibitors of NK function [29, 36]. During latent infections, CMV produces immunosuppressive cytokines (e.g., IL10 and TGF-β), inhibits T cell cytotoxic functions, and has the ability to remain dormant in cell reservoirs such as CD34+ hematopoietic progenitor cells in the bone marrow [37] and T cells in the blood, lymphoid tissues, and the lungs [30]. On the other hand, the human host, although unable to clear the virus, is able to keep CMV from causing overt infections through innate immune responses (e.g., mast cells, dendritic natural killers, dendritic cells, and γδ T lymphocytes) [38–41] production of high-affinity neutralizing antibodies and specific CD4+ and CD8+ T cell immunity which limits viral replication and cell damage [29, 37, 41–43].

Individuals with conditions weakening cellular or innate antiviral immune responses are susceptible to severe CMV infections since the balance between viral virulence factors and immune pressure to control infections is altered [2, 29]. Clinically, individuals at high risk include patients with malignancies or posttransplant, those with primary or secondary immunodeficiencies, and patients with acutely debilitating events (e.g., burns, trauma, severe illness) or severe prematurity [2, 29, 37, 44, 45]. Induced causes of immunosuppression such as chemotherapy, immunomodulatory therapy with cytotoxic and antimetabolite immunosuppressants, systemic corticosteroids, or monoclonal antibodies (e.g., anti-CD52, anti-CD20, anti-CD25, or anti-TNF therapy) also facilitate severe infections [2, 46]. In children, the fetus is particularly vulnerable to in utero infections attributed to pregnancy-related changes of the fetal, placental, and maternal immune compartments [47].

## Early Life, Premature Birth, and Lung Cytomegalovirus Infections

Another important consideration of lung CMV infection is the host suceptibility during early life. Maternofetal infection with CMV is the most common congenital infection and a leading cause of mental retardation and sensorineural hearing loss [48]. Population-based studies indicate that the overal prevalence of congenital CMV ranges between 4 and 20 per 1000 live births [49, 50]. Transmission of CMV to the fetus occurs in approximately 40% of mothers and primary infections in the first trimester of pregnancy are associated with the highest risk of fetal harm [48]. Approximately 11% of infants born with congenital CMV infection are symptomatic, exhibiting clinical manifestations such as jaundice, hepatosplenomegaly, petechiae, central nervous system abnormalities (e.g., microcephaly, seizures, focal or generalized neurological deficits), intrauterine growth restriction or death [50]. Congenital CMV infection may cause severe long-term sequelae, including progressive sensorineural hearing loss and developmental delay in 40–58% of symptomatic neonates, and 14% of initially asymptomatic infected neonates [51, 52].

Studies in newborns have shown CMV accounting for about 6% of viral respiratory infections detected in babies hospitalized in neonatal intensive care units [53]. CMV pneumonitis, although infrequent in full-term neonates, may be common and severe in debilitated and preterm infants [50]. Lung CMV infections in the neonatal period result from congenital or perinatally acquired CMV infections. CMV pneumonitis is estimated to occur in less than 1% of infants with congenital CMV; however, it has been associated with decreased surfactant production, lung immaturity, and endothelial and vasculitic changes in small vessels in the lungs, altering pulmonary arterial resistances [21, 54]. After birth, congenital lung CMV infections are also known to persist for months and are associated with the development of severe bacterial infections and lung fibrosis [21].

Perinatally acquired lung CMV infections are more common than those acquired transplacentally. These postnatal CMV infections are defined as the detection of CMV in blood, urine, cerebrospinal fluid, or respiratory secretions on or after day of life 21 [55], and are usually transmitted by aspiration of infected cervical secretions during delivery, infected breastmilk, or transfusion with CMV-positive blood [21, 50, 56]. Premature infants, especially very-low birth weight (VLBW) babies (< 1500 g) are particulalry vulnerable to postnatal CMV infections

developing pneumonitis and sepsis-like symptoms in up to 15% of cases [55, 57]. Common symptoms of postnatal CMV infections include apnea, bradycardia, pneumonia, hepatitis, gastrointestinal tract symptoms, and hematological signs (thrombocytopenia, neutropenia, and lymphocytosis) [57, 58]. Diffuse severe interstitial pneumonitis may develop in premature or immunocompromised infants (e.g., children with primary immunodeficiencies), and it is potentially life-threatening [21]. Severe respiratory involvement can also be seen in systemic infections in the abscence of pneumonitis. Indeed, respiratory deterioration and thrombocytopenia were the findings most commonly associated with CMV infection in a study of 2142 VLBW newborns [59]. Notably, CMV-infected infants had significantly more exposure to mechanical ventilation and longer duration of hospitalization [59]. Pre- and postnatal CMV infections in premature infants have also been associated with adverse chronic respiratory outcomes including bronchopulmonary displasia (BPD), cystic lung disease, and persistent pulmonary hypertension of the newborn (PPHN) [21, 59–62]. Indeed, in the study by Mukhopadhyay et al., [59] after adjusting for multiple predictors of respiratory morbidity, the odds of BPD were significantly higher among infants diagnosed with postnatal CMV infection (odds ratio 4.0, 95% confidence interval 1.3–12.4, $p = 0.02$) when compared with uninfected children. In a larger retrospective cohort study of 101,111 hospitalized VLBW infants by Kelly et al., patients with postnatal CMV infection had a increased risk for BPD (risk ratio 1.33; 95% confidence interval 1.19–1.50) when compared with matched non-infected babies [55].

Full-term newborns who acquire CMV infections through breastmilk are almost always asymptomatic, in contrast to infants born < 30 weeks gestational age and < 1500 g who may develop a late-onset sepsis-like syndrome. [55, 57] The benign course of these infections in term babies seems to be related to the transfer of maternal antibodies during the thrid trimester and the fact that preterm infants have additional nosocomial exposures to infectious agents and exhibit overall enhanced inflammatory responses [21, 60]. In addition, as gestational age increases, infants are equipped with more robust and specific immune responses to pathogens [53] and the risk of developing chronic respiratory disease decreases. In summary, although lung CMV infections are mild or asymptomatic in immunocompetent full-term newborns in most cases, they represent a significant cause of respiratory morbidity and superimposed lung injury for prematures, immunocompromised and debilitated infants. In these settings, lung CMV infections can contribute to lung damage by direct effects, as a result of tissue inflammation, predisposition to additional infections, and secondarily through the exposure to mechanical ventilation and supplemental oxygen, highlighting the importance of prevention efforts, prompt diagnosis and proper management strategies of prenatal and perinatal lung CMV infections in these vulnerable groups. [58, 63–65]

## Approach to the Diagnosis of Pediatric Lung Cytomegalovirus Infections

Human CMV is a ubiquitous pathogen highly prevalent in children, estimated to affect more than one third of school age children and adolescents in the USA [66, 67] with higher rates in certain areas worldwide and among certain populations [3, 27, 67, 68]. CMV lung infections can be diagnosed by detecting the presence of virus in serum and/or respiratory samples, obtained by bronchoscopy or tracheal aspiration, being the virus detection directly in the respiratory tract more predictive of CMV pneumonitis [69]. In regard to viral detection in the circulation, among the techniques available, PCR detection has been proven more sensitive for the detection of CMV and preferred over others such as the measurement of the viral phosphoprotein 65 (pp65), a marker of active viral replication, in blood and CMV blood cultures [70].

Nonetheless, because of its ubiquitous presence and high prevalence of asymptomatic infections in pediatric patients, especially at early age, the diagnosis of pediatric lung CMV disease in poses especial challenges. First, as children have high viremia and urinary CMV shedding even during latent and asymptomatic infections, and the lungs are a known viral reservoir [71], no definite threshold viral load levels in serum, urine, or respiratory secretions have been established to distinguish asymptomatic infections from those clinically relevant [26]. Second, the clinical presentation of lung CMV and symptoms may overlap with other common viral lung infections. Also, although tests for viral detection are available clinically, other than the detection of cytomegalic inclusions by lung biopsy, there is no confirmatory test in patients with potential respiratory CMV involvement [72].

Available tests for the evaluation of suspected lung CMV infections include the detection of viral DNA by PCR in bronchoalvolar lavage (BAL CMV-PCR), which has emerged as the most accepted approach for viral isolation in the lungs due to its high sensitivity [64]. Viral cultures can be performed in blood, urine, BAL, and other fluids, and although very specific, they require the presence of the virus directly in the tested specimens; hence, their sensitivity is variable [64]. Additional approaches, such as the evaluation of viral microRNAs (miRs) during latency and reactivation, have been attempted to differentiate CMV latency from reactivation but remain at the experimental level. In summary, in addition to diagnostic tests for viral isolation, therapeutic decisions in children with suspected respiratory CMV involvement continue to rely on a combination of clinical and radiological laboratory and pathology findings.

## Chest Imaging and Pathology in Pediatric Lung Cytomegalovirus Infections

Lung CMV infections are associated with radiological findings that often provide helpful information when assessing children with suggestive clinical presentation. As previously described by us and others [28, 73, 74], the most consistent findings in up to 80% of patients are the development of ground glass and airspace opacities (Fig. 1), indicating various degrees of lung parenchymal (alveolar) involvement [69, 73]. Additional findings include volume loss [75], the presence of pulmonary nodules in almost one third of patients, and interstitial infiltrates in about half of affected children [69, 76, 77]. The above changes are often seen in chest radiographs; however, they may be subtle or may not be visualized, requiring confirmation by chest computed tomography, often performed to assist further diagnostic and therapeutic decisions.

In terms of pathology findings, lung biopsy is still considered the gold standard for the diagnosis of pulmonary CMV infections [78]. The presence of cytomegalovirus inclusions (Fig. 2a), is confirmatory of lung infection [79–81]. Other non-confirmatory but suggestive findings include diffuse alveolar damage (DAD) with findings such as hyaline membranes, detached swollen pneumocytes, intra-alveolar exudation, and alveolar wall edema, intermixed pattern of DAD and interstitial inflamation/fibrosis and predominantly interstitial inflamation/fibrosis pattern (Fig. 2b) which have been associated with the virus predominant intrapulmonary tropism for pneumocytes or stromal cells and the characteristics of the host immune response [82]. The virus can also be detected by immunostaining of viral antigens [64]. Of note, the diagnostic yield of lung biopsy for the diagnosis of lung CMV infections is highly variable as inclusions are not always visualized, [81] it may affected by the underlying disease (e.g., HIV) [78], and certain patients with active lung CMV infections may have only minimal changes as represented in Fig. 2d.

In summary, the diagnosis of lung CMV infections in pediatric patients remains a challenge. Nonetheless, because of their life-threatening potential, a prompt detection and treatment of serious symptomatic infections is critical. Based on our previous work and the current review, we have updated a previously proposed set of clinical features that may assist clinicians with their diagnostic (e.g., bronchoscopy) and therapeutic decisions (e.g., empiric antiviral therapy) when approaching patients with possible lung CMV infections (Table 1).

## Implication of the Diagnosis of Pediatric Lung Cytomegalovirus Infections

The clinical assessment of patients with lung and other systemic or tissue-invasive CMV infections should include the evaluation of factors facilitating severe disease. Secondary causes of immunodeficiency should be excluded if not revealed by clinical history (e.g., HIV). Screening for primary immunodeficiencies when no additional underlying causes are identified is also indicated as susceptibility to CMV infections has been described in a number of primary immune defects (Table 1). Specifically, early-onset postnatal, severe CMV infections should prompt investigation for severe combined immunodeficiency (SCID) and other complex immune defects [83–86]. Any patient with a primary T cell defect is at risk for CMV infection or reactivation [86–88]. Severe CMV infections may also ocurr in patients with NK cell deficiencies and multiple combined immune defects [84, 88–90]. Susceptibility to CMV infections is also described in defects in interferon production or signaling [84, 91], familial forms of hemophagocytic lymphohistiocytosis (HLH) [84, 88], class-swicthing defects (e.g., CD40 ligand deficiency) [90, 92],

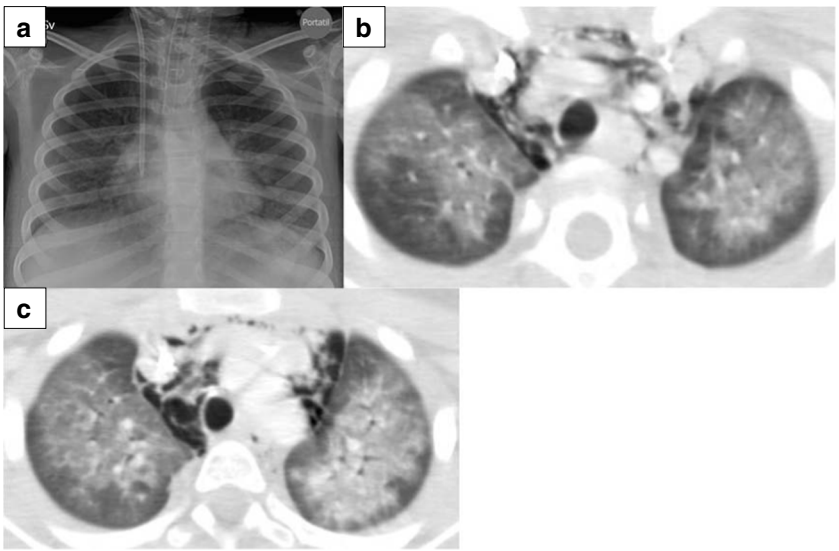


**Fig. 1** Chest images from a 12-year-old girl with active lung CMV infection and acute respiratory failure. The patient had a history of ALL and had received a hematopoietic stem cell transplant 5 months before. **a** Diffuse hazy opacities are seen in the chest radiograph. **b**, **c** Chest CT scan shows ground-glass opacities with areas of consolidation, emphysema and pneumomediastinum. BAL CMV-PCR detected abundant viral load above the maximum level of detection of the assay

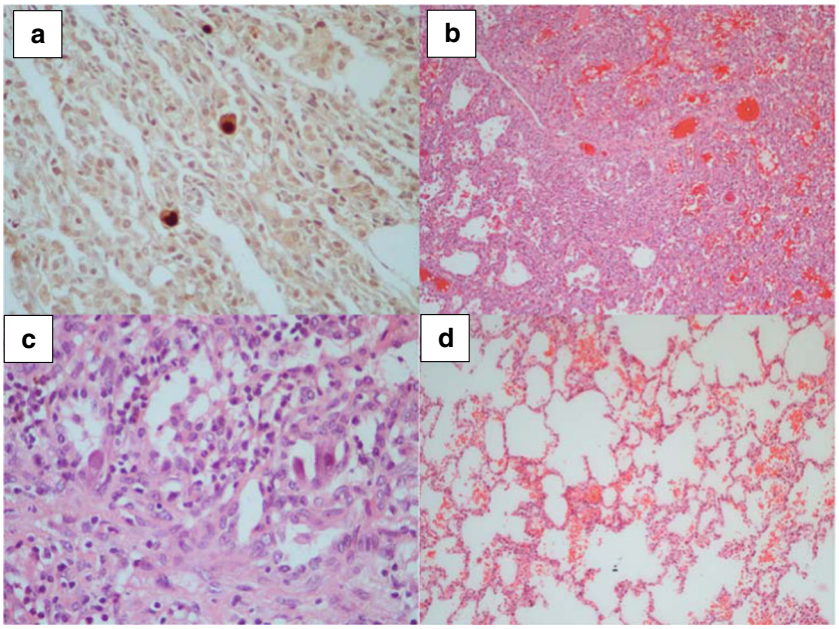


**Fig. 2** Lung biopsy findings in children with lung CMV infections. **a** Lung biopsy with cytomegalic inclusions stained by immunohistochemistry. **b** Interstitial inflammatory exudate with multiple inflammatory cells (predominantly monocytes and neutrophils). **c** Lung tissue displaying enlarged infected cells with intranuclear and cytoplasmic cytomegalic inclusions. (hematoxylin-eosin stain of lung tissue). **d** Lung biopsy with only minimal thinning of pulmonary septa

**Table 1** Risk factors and clinical features associated with lung CMV infection in children

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|---|
| Risk factors and associated conditions |
| • Prematurity and low birth weight |
| • Primary immunodeficiency and immune dysregulation disorders |
| - Severe combined immunodeficiency (SCID) |
| - Severe T cell and/or combined defects |
| - NK cell deficiencies |
| - Defects in interferon production or signaling |
| - Familial forms of hemophagocytic lymphohistiocytosis (HLH) |
| - Wiscott-Aldrich syndrome (WAS) |
| - Dedicator of cytokinesis 8 (DOCK 8) deficiency |
| - GATA2/GATA-binding factor 2 deficiency |
| - NEMO/nuclear factor-kappa B essential modulator deficiency |
| - CD40-ligand deficiency |
| - ICOS/inducible T cell co0stimulator deficiency |
| - TNFRSF13B/tumor necrosis receptor superfamily 13B |
| - CTLA4/cytotoxic T lymphocyte antigen-4 deficiency |
| - PIK3/phosphoinositide 3-kinase pathway defects |
| • Secondary immunodeficiency |
| - HIV |
| - Malnutrition |
| - Systemic steroids or other immunosupressants |
| • Hematologic malignancy |
| • Posttransplantation |
| Clinical |
| • Persistent cough |
| • Increased work of breathing |
| • Hypoxemia (espcially if disproportionate in relationship with radiologic findings) |
| • Diffuse adventitious lung sounds (e.g., rales) |
| Imaging |
| Ground-glass opacity/consolidation |
| Bronchoscopy |
| CMV PCR in BAL |

complex immunodeficiencies such as Wiscott-Aldrich syndrome (WAS) [85, 93], dedicator of cytokinesis 8 (DOCK 8) deficiency [94], GATA-binding factor 2 (GATA2) deficiency [95], and nuclear factor-kappa B essential modulator (NEMO) deficiency [84]. Lung and severe CMV infections may also occur in miscellaneous immune defects presenting clinically as hypogammaglobulinemia or common variable immunodeficiency (CVID) and other immune dysregulation disorders (e.g., ICOS/inducible T cell co-stimulator, TNFRSF13B/tumor necrosis receptor superfamily 13B, CTLA4/cytotoxic T lymphocyte antigen-4, PIK3/phosphoinositide 3-kinase defects). [84, 88, 89]

Although the diagnosis of pediatric lung CMC infection is challenging, the early identification of CMV lung infection in the pediatric population is essential for the prompt initiation of antiviral therapy and consequent better clinical outcomes. Available antiviral medications for the treatment of CMV infections such as gancyclovir, approved for the treatment of CMV retinitis and antiviral prophylaxis, is used off-label for the treatment of severe cases of CMV pneumonitis [96]. Gancyclovir is available in oral and intravenous forms; however, its oral availability is poor (< 10%), and its use is limited due to potential renal and bone marrow toxicity as well as antiviral resistance. Gancyclovir resistance is associated with mutations in the viral UL97 and UL54 genes which prevent the activation of the drug. Alternatives for the treatment of lung CMV also include foscarnet, maribavir, valgancyclovir, and cidofivir; nonetheless, significant renal toxicity may also occur with these medications. Adjuvant treatment with intravenous immunoglobulin or CMV hyperimmunoglobulin is recommended in immunocompromised patients and may be used in cases of severe CMV disease and hypogammaglobulinemia [7]. Newer strategies such as the use of antiviral adoptive T cell immunotherapy are being

attempted and may help to overcome some of the challenges in the treatment of CMV infections [97, 98].

## Conclusion

Lung CMV infections in children are prevalent in immunocompromised hosts and have a variable presentation. The severity of the disease is usually determined by viral factors as well as by the adequacy of the host's antiviral response immune response and severe lung CMV infections should prompt further investigation into underlying conditions altering the mechanisms usually in place to contain CMV infections. In children, the differentiation between latent infections with active viral shedding and active infections may be difficult especially at early ages. Clinical clues to symptomatic CMV lung infections include the presence of respiratory symptoms, hypoxemia, and diffuse lung abnormalities in the clinical exam. The initial diagnostic approach should include a chest X-ray that shows variable degrees of alveolar disease (e.g., ground-glass opacities, consolidations). These findings may be subtle and require confirmation by chest CT when suggested by symptoms and physical exam findings. If clinical and radiologic findings suggest lung CMV infection, bronchoscopy and CMV-PCR of BAL are indicated. These steps should be undertaken early in the evaluation of chidlren with suspected lung CMV as this infections can be life-threatening and antiviral treatment should be instituted promptly especially in vulnerable populations and the immunocopromised child.

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### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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