Herpes Simplex Virus Pneumonia in Patients with Hematologic Malignancies

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Contents

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24.1 Introduction

Herpes simplex virus (HSV) is known to cause mucocutaneous disease in patients with hematologic malignancies [11, 42]. HSV most commonly leads to orofacial, genital, and esophageal lesions, and less commonly can lead to hepatitis, meningitis, encephalitis, bone marrow suppression, and pneumonia [22, 38, 42]. HSV pneumonia is very rare and has been reported in about 3% of the patients with hematologic malignancies and in about 5% of patients who have undergone hematopoietic stem cell transplant (HSCT) (these patients will be referred to as 'HSCT patients' in the chapter) without prophylaxis [56]. After acyclovir prophylaxis was implemented in patients with a HSCT, the incidence of HSV excretion dropped to 2.5% [49], while HSV pneumonia has been reported in less than 1% of all pneumonias developing after HSCT [16].

Cytomegalovirus (CMV) has been implicated as the most common agent in nonbacterial pneumonias in patients with hematologic malignancies and in patients who have undergone HSCT [33, 46]. However, HSV has been demonstrated as the most common pathogen in bronchial samples of patients with severe respiratory distress who have been treated with assisted ventilation [54]. Before the 1990s, cases of HSV pneumonia were characterized as "idiopathic pneumonia" because of insufficient diagnostic testing or simply lack of awareness of HSV as a causative agent in lower respiratory tract disease [46].

HSV pneumonia is diagnosed most frequently in the setting of severe immunosuppression [14, 16, 17, 27, 60, 64]. Studies involving HSV pneumonia have been conducted frequently in patients who have undergone HSCT and less frequently in other types of immunocompromised patients, such as those with

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hematologic malignancies, solid tumors, burns, critical illnesses, or acquired immune deficiency syndrome (AIDS) [3, 8, 12, 17, 42, 54]. Respiratory involvement is seen most commonly with herpes simplex virus-1 (HSV-1) [40, 43, 56], but some cases of herpes simplex virus-2 (HSV-2) have been reported [13, 25].

In this chapter, we will focus on incidence and transmission, pathogenesis, risk factors, clinical features, diagnosis, and management for HSV pneumonia in patients with hematologic malignancies and HSCT patients as well as outcome and prognosis. Table 24.1 summarizes the outcomes in studies and

Table 24.1 Studies and case reports on HSV pneumonia

No.	Author, year	No. of cases	Type of immunocompromised population	Management	Outcome
1	Meyers 1982 [46]	10 Nonbacterial pneumonia.	10 weeks s/p HSCT, GVHD	Not enough information available.	All patients died.
2	Ramsey 1982 [56]	20 Autopsy cases	HM, 2 months s/p HSCT, nonHM; on chemotherapy, radiotherapy	None were on prophylaxis. No treatment given.	All patients died of respiratory failure. Pneumonia to death within 24 days (mean)
3	Ljungman 1990 [40]	3 Acyclovir-resistant HSV-1 pneumonia	Early HSCT period, GVHD	Case 1: Px: ACV 250 mg/m^2 Q12h × 30 days post-HSCT; Rx: ACV 500 mg/m^2 Q12h + IV Vidarabine 10 mg/kg	Patient 1: Died on day 70.
				Case 2: Px: ACV 250 mg/m^2 Q8h × 29 days; Rx: ACV × 250 mg/m^2 Q8h	Patient 2: Died on day 100.
				Case 3: Px-ACV 500 mg/m^2 Q8h × 25 days; Rx- Ganciclovir 5 mg/kg Q8h × 19 days, ACV 250 mg/m^2 Q8h × 39 days	Patient 3: Died on day 131.
5	Schuller 1993 [60]	15 HSV-1 pneumonia	Lymphoma, solid organ transplants, AIDS, SLE	Px- N/A Rx-ACV × 17 days (mean)	33% Died (n = 5) from sepsis (2), respiratory failure (2), dehiscence of tracheal anastomosis after lung transplant (1).
9	Ferrari 2005 [23]	1	B-cell ALL on chemotherapy	Px-None Rx-ACV 10 mg/kg Q8h on day 31; later Px- Valacyclovir	Noninvasive ventilation needed→ infection resolved by day 42.
10	Gasparetto 2005 [25]	3 HSV-2 pneumonia	HSCT (two early-phase, one late-phase)	Px- 1 pt on ACV 200 mg Q12h; Rx- ACV 500 mg Q8h	Two patients improved, one died of respiratory failure in 2 weeks
11	Frangoul 2007 [24]	2 ACV-resistant HSV-1 pneumonia	HSCT, GVHD	Px- PO ACV 600 mg/m^2 Q12h or IV ACV 250 mg/m^2 Q12h; Rx- IV ACV 250 mg/m^2 Q8h; Foscarnet 60 mg/kg Q12h – then 90 mg/kg Q12h	Died on day 110 from respiratory failure.
12	Aisenberg 2009 [3]	45 HSV pneumonia (6: proven, 25: probable, 14: possible)	Solid tumors on steroids and radiotherapy	Px-None Rx-ACV (n = 17), Valacyclovir (n = 7), Famciclovir (n = 1) × 13 days (mean)	Ten (22%) died: four treated, six untreated).

ACV Acyclovir, *ALL* acute lymphocytic leukemia, *GVHD* graft-versus-host-disease, *HM* hematologic malignancy, *IV* intravenous, *N/A* not available, *PO* oral, *Px* prophylaxis, *Q8h* every 8 hourly, *Q12h* every 12 hourly, *Rx* treatment, *s/p HSCT* status post-hematopoietic stem cell transplant

case reports of patients with HSV pneumonia who have hematologic malignancies and HSCT patients.

24.2 Incidence and Transmission

HSV belongs to the *Herpesviridae* family, which comprises HSV-1, HSV-2, varicella zoster virus, CMV, Epstein-Barr virus, human herpes viruses 6 and 7, and Kaposi's sarcoma-associated herpesvirus (type 8) [37, 66]. HSV (types 1 and 2) belongs to the subfamily *Alphaherpesvirinae* [37, 66].

HSV-1 and -2 are ubiquitous and contagious, and they are transmitted horizontally during close contact with an infected person who is shedding the virus from the skin, saliva, or secretions from the genitals [22, 38]. Asymptomatic viral shedding and transmission are known to occur, especially in HSV-2 infections [38]. HSV-1 is usually acquired orally during childhood, but may also be transmitted sexually [38]. HSV-2 is transmitted primarily by sexual contact [38].

The virus is reactivated secondary to triggers such as psychological stress; fatigue; exposure to heat, cold, or sunlight; menstruation; sexual intercourse; fever; immunosuppression; corticosteroid administration; laser surgery; local tissue trauma; nerve damage; and change in antiviral activity of the saliva [22].

About 80% of adult patients with hematologic malignancies are HSV seropositive [62]. HSV reactivates in about 70–80% of seropositive patients [29]. The incidence of mucocutaneous lesions among seropositive patients with leukemia has been reported to range from 15% (among CLL patients treated with fludarabine) to 90% (in patients with acute leukemia or HSCT) [5, 11, 42, 57, 58]. HSCT patients more commonly show HSV reactivations, especially within the first 4 weeks of the transplant, while primary infections are unusual [45].

24.3 Pathogenesis

24.3.1 Pathogenesis in Humans

HSV is a double-stranded deoxyribonucleic acid (DNA) virus that measures approximately 200 nm in diameter and contains a linear, double-stranded DNA core enclosed within an icosahedral protein capsid, covered by a tegument and a glycoprotein-containing envelope [37, 44, 50, 66, 68].

Initial exposure to herpesviruses often leads to viral invasion of epithelial cells and intracellular replication at the site of primary exposure [50, 66, 68]. Following primary infection, the virus ascends in a retrograde manner through the periaxonal sheath of sensory nerves to the trigeminal, cervical, lumbosacral, or autonomic ganglia of the host's nervous system [50, 66, 68]. The virus replicates and remains dormant for life. The trigeminal and sacral ganglia are the most common locations for HSV-1 and HSV-2 latency, respectively [22].

Pulmonary involvement in patients with hematologic malignancies may be focal or diffuse [56]. Focal disease may begin as mucocutaneous/ororpharyngeal disease and continue down to the lower respiratory tract (contiguous spread), whereas diffuse pneumonia is associated with hematogenous dissemination [56]. Concomitant/preceding HSV in pharynx, urine, liver, or genitals has been reported [27, 52, 56]. HSV-1 pneumonia occurs through aspiration or contiguous spread, and HSV-2 pneumonia is caused by hematogenous spread [44]. HSV pneumonia is an intrabronchial process [27]. Focal or diffuse ulcers in the tracheobronchial epithelium can lead to necrotizing herpetic tracheitis, as was found in autopsy specimens of patients with hematologic malignancies [56].

HSV has been shown to be less replicative than CMV is in alveolar macrophages, thus suggesting the role of altered macrophage function in the development of HSV pneumonia [20]. However, an age-dependent protective role against disseminated HSV disease has also been demonstrated [47].

24.3.2 Animal Models

Studies in animal models have attempted to elucidate the pathogenesis of HSV pneumonia [1, 2, 19]. Reactive oxygen/nitrogen species (RONS) has been implicated in the development of viral pneumonitis [19]. Intranasal infection of mice with HSV-1 resulted in rapid development of pneumonia and decreased lung compliance, and was associated with elevated expression of inducible nitrogen oxide synthase (iNOS) protein and increased nitrotyrosine adduct formation

in the lungs of infected mice. When these mice were treated with a NOS inhibitor, pneumonitis was almost completely suppressed, recovery of inflammatory cells from bronchoalveolar lavage fluid was decreased, and both lung compliance and survival were improved [1].

Animal models have also demonstrated that graft-versus-host disease (GVHD) is an important factor in the development of HSV pneumonitis. Allogeneic transplant mice with GVHD developed more severe pneumonitis after intranasal HSV-1 infection than did control mice without GVHD. The former group also showed an enhanced transforming growth factor-1 (TGF-1) production, which was implicated as a more important factor than the pulmonary viral load [2].

24.4 Risk Factors

Several risk factors have been identified that increase the risk of HSV pneumonia in patients with hematologic malignancies. HSV pneumonia is generally a result of reactivation of a latent HSV infection [42, 50, 56, 68]. Several triggers, such as stress, corticosteroid administration, and immunosuppression, may cause reactivation of the virus [22]. HSV affects squamous epithelial cells, and factors promoting squamous metaplasia such as smoking, trauma, burns, and tracheal trauma from intubation may predispose a patient to develop HSV pneumonia [27, 51, 52, 56, 60]. Intubation of a patient with oral herpes can trigger reactivation or cause a lower respiratory tract infection through direct inoculation or aspiration [8, 56]. Thus, intubated patients who fail to be weaned off the ventilator should be evaluated for HSV pneumonia, as it is an often under-recognized cause of nonbacterial pneumonia [46].

Patients with hematologic malignancies who are undergoing aggressive chemotherapy and treatment with corticosteroids are at increased risk of HSV, as impairment of cellular immunity is a risk factor for HSV infections and reactivations [57]. Persistent and severe T-cell depletion is seen after aggressive chemotherapy and after administration of monoclonal antibodies (e.g., anti-CD52 antibody, alemtuzumab) [32, 55] and has been identified as a predictor for HSV infections [15, 17, 64].

HSCT patients are at greater risk of developing HSV infections, as chemotherapy and radiotherapy used before HSCT may damage the normal upper respiratory mucosa and predispose the patient to direct spread of the virus to the lower respiratory tract [56]. These agents may also trigger reactivation of the virus [34]. The use of cyclophosphamide, busulfan, carmustine, and total body irradiation in conditioning regimens has been seen in patients with HSV pneumonia [24, 46]. HSV reactivation occurs most commonly in the first month after HSCT; however, late-onset HSV-associated pneumonia has also been reported [35].

Additionally, patients with hematologic malignancies are often neutropenic [absolute neutrophil count (ANC) <500/mL] secondary to the chemotherapy. Neutropenia has also been observed in patients with hematologic malignancies who have HSV pneumonia [56]. GVHD as a risk factor for HSV disease in HSCT patients and severity of GVHD as a predictor of nonresponsiveness to antiviral therapy has also been reported [16]. In some studies, the immunosuppressive effect of multiple blood transfusions has also been implicated in the development of HSV pneumonia [64]. Patients undergoing solid organ transplant (SOT) are at risk of developing HSV pneumonia. The incidence of HSV pneumonia in SOT patients is about 5%, while mortality of up to 100% has been reported, especially in liver transplant recipients [4, 31, 39].

24.5 Clinical Features

24.5.1 Clinical Manifestations

The clinical manifestations of HSV pneumonia are nonspecific [3, 18, 40, 56]. In HSCT patients, symptomatic disease occurs 2–3 weeks after transplant when mucosal damage is maximal from radiotherapy and chemotherapy [23]. HSV infections can manifest with nonrespiratory symptoms before showing signs of pulmonary involvement [23, 54]. Nonrespiratory manifestations of HSV reactivation infrequently include oral mucocutaneous lesions. Esophagitis and rarely, genital lesions may also precede lower respiratory involvement [54, 56]. Respiratory symptoms of HSV pneumonia include low-grade fever, cough, dyspnea, rales, hypoxemia, tachypnea, intractable wheezing, or chest pain [56]. Hemoptysis may also be present, secondary to tracheitis [63].

Patients with HSV pneumonia may typically either demonstrate worsening respiratory status that is unresponsive to prolonged antibacterial treatment and may require intubation or patients may already be intubated, and may worsen and fail to wean off the ventilator. Persistent low-grade fevers and unimpressive infiltrates on imaging with leukocytosis would indicate a nonbacterial cause. Interstitial lung involvement in HSV pneumonia is characterized by worsening oxygenation [evident from low pO_2 with a high fraction of inspired oxygen (FiO_2)], decrease in diffusing capacity of the lung for carbon monoxide (DLCO), and an increase in alveolar-arterial (A-a) gradient over 30 [18]. HSV pneumonia is often complicated by acute respiratory distress syndrome (ARDS) and respiratory failure, and mechanical ventilation is often needed, especially in untreated patients [56].

24.5.2 Coinfections

Pulmonary coinfections may often be present and may complicate the diagnosis of patients with HSV pneumonia. Up to 65% of the patients with HSV pneumonia may have copathogens, such as CMV, *Candida*, Aspergillus, *Pneumocystis jirovecii*, *mycobacterium avium intracellulare* (MAI), and other bacteria [3, 40, 56]. Patients are often treated preemptively for bacterial pneumonia before diagnosis of HSV has been confirmed, which may lead to a delay in initiation of HSV-specific treatment.

24.5.3 Differential Diagnosis

In an immunocompromised host, the most common infectious cause of pneumonia is bacterial, which presents with acute deterioration and significant hypoxemia. Subacute presentation suggests involvement of atypical bacterial, viral, or fungal organisms, while chronic presentation suggests fungal or mycobacterial infection. *Pneumocystis jirovecii,* CMV, respiratory syncytial virus, and influenza pneumonia are the most important organisms in the differential diagnosis of diffuse bilateral infiltrates, accompanied by significant oxygen defect (A-a gradient >30) [18]. Noninfectious causes may include drug toxicity, pulmonary hemorrhage, GVHD, and heart failure.

24.6 Diagnosis

HSV pneumonia should be suspected in immunocompromised patients who are not on acyclovir prophylaxis, who are intubated with worsening oxygenation, and who have not been weaned off a ventilator despite aggressive management [18, 23, 54].

There are no standardized diagnostic criteria for HSV pneumonia. The definitive diagnosis of HSV pneumonia can be made by isolating the virus from respiratory secretions, bronchoalveolar lavage samples, and lung tissue and by demonstrating viral cytopathic effects on histopathology [18, 42, 56].

24.6.1 Virus Isolation

Shell-vial culture for virus isolation and demonstration of cytopathic effects are methods commonly used to diagnose HSV. The sensitivity of these methods has been reported to be 57%, with a specificity of 100% [10]. The shell-vial culture yields results in 48 h [62].

Rapid antigen detection by direct immunofluorescence is also often employed for early detection of HSV, with sensitivity and specificity of about 80% and 100%, respectively [10].

24.6.2 Gene Amplification

Polymerase chain reaction (PCR) for HSV DNA is more rapid and more sensitive than conventional culture, shell-vial culture, and antigen-detection methods [61]. However, PCR is unable to distinguish between active disease and contamination from oral cavity [61].

Serology is useful for identifying patients with seropositive HSV before induction chemotherapy or before HSCT [62]. Detection of immunoglobulin M (IgM) antibody and demonstration of an increase in immunoglobulin G (IgG) titers can be useful in patients with an active infection [59]. However, it takes several weeks to mount a significant antibody response and depends on a functioning immune system. Thus, serology is less useful with HSV pneumonia when a rapid diagnosis is necessary [30, 59]. Additionally, a

fourfold increase in titers is helpful for diagnosing primary HSV infection; however, such an increase may not be observed in recurrent infections [30].

24.6.3 Lung Biopsy/Cytology

Nonspecific fibroproliferative pattern and tissue necrosis are demonstrated on lung biopsy in patients with HSV pneumonia [23]. However, lung biopsy is rarely performed in patients with cancer because of increased complications, inconsistent diagnosis, and questionable reliability [56, 64]. A few scattered ulcers in the trachea or a severe ulcerative process resulting in an obstructed and inflamed tracheobronchial membrane may be evident on direct examination [27].

Parenchymal involvement begins in lungs, adjacent to the terminal and respiratory bronchioles, but may extend throughout the lobule [33, 56]. Diffuse alveolar damage comprising interstitial lymphocyte infiltration, air space hemorrhage, intraalveolar fibrinous exudate, edema, fibroblast proliferation, type 2 hyperplasia, and hyaline membrane formation is often evident [33, 56].

Cytology demonstrates multinucleated giant cells with enlarged, molded, basophilic nuclei of ground-glass appearance or cells with large intranuclear eosinophilic inclusions ("owl-eyes"-Cowdry type A inclusion bodies) in the alveolar or bronchial cells and macrophages obtained in washings or biopsies [56].

24.6.4 Radiology

Radiologic changes in HSV pneumonia are often nonspecific [3, 6, 36, 65]. These changes are similar to those seen in other viral pneumonias and are not different from those seen in immunocompetent patients [65].

Chest x-ray may be near normal early in the disease [18]. In advanced disease, however, focal, multifocal, or diffuse bilateral opacities with predominantly mixed (partly airspace consolidation and partly interstitial) or airspace consolidation is often seen [18, 65]. Less frequently seen are unilateral consolidation, large atelectasis, and pleural effusion [56, 65].

High-resolution computed tomography (CT) scans are used for better delineation of the disease process [25]. HSV-1 shows multifocal, subsegmental, and ground-glass attenuation with consolidation, reticular, and nodular opacities; HSV-2 demonstrates diffuse alveolar damage, small centrilobular nodules, and interstitial pneumonia [6, 25]. Large nodules and pleural effusions are also seen [6, 25].

24.7 Management

24.7.1 Treatment

Acyclovir is the most widely used and effective therapy for HSV pneumonia [11, 68]. However, empiric therapy based on suspicion of HSV pneumonia has not been recommended [18]. HSV-specific treatment of pneumonia has been reported to prevent progression to respiratory failure and mortality in patients with hematologic malignancies and in HSCT patients [23, 25, 35]. Improvement in oxygenation status can be seen in 3–5 days, and patients may be able to be weaned off the ventilator [18]. However, treatment has showed no significant effect on mortality, duration of mechanical ventilation, length of intensive care unit (ICU) stay, or length of hospitalization in a group of immunocompromised patients (patients with lymphoma, with solid-organ transplants, or with AIDS or systemic lupus erythematosus [SLE]) as compared to immunocompetent patients [60].

HSV is susceptible to acyclovir, valacyclovir, famciclovir, foscarnet, cidofovir, and, to a lesser extent, ganciclovir [37]. Table 24.2 shows the mechanisms of action, recommended dosages, and mechanisms of resistance for these drugs.

Foscarnet is used to treat acyclovir-resistant strains. However, strains resistant to foscarnet and acyclovir are now being reported [7]. Cidofovir is the only drug used to treat double-resistant HSV [42], although use of cidofovir is associated with significant renal toxicity [7].

A significant proportion of patients with HSV pneumonia may have concomitant bacterial pneumonia [3, 40, 56]. Thus, empirical broad-spectrum antibiotic therapy that includes an anti-staphylococcal drug can be used in patients with progressive HSV pneumonia who are unresponsive to antiviral therapy.

24.7.2 Prophylaxis

HSV pneumonia accounted for 9% of pneumonias in HSCT patients, prior to acyclovir prophylaxis [56]. Prophylaxis of HSV infection has led to decreased

Table 24.2 Antiviral drugs used in HSV pneumonia

Drug	Susceptibility	Mechanism of action	Doses for pneumonia	Prophylaxis	Side effects	Mechanism of Resistance	FDA-labeled indications	Non-FDA-labeled indications
Acyclovir	Synthetic purine nucleoside analog with in vitro and in vivo inhibitory activity against HSV-1, HSV-2, VZV	Affinity for viral enzyme thymidine kinase (TK) leads to (1) competitive inhibition of viral DNA polymerase, (2) incorporation into and termination of the growing viral DNA chain, and (3) inactivation of the viral DNA polymerase. Metabolized by kidneys.	500 mg/m^2 or 10 mg/kg IV Q12h × 14–21 days	250 mg/m^2 or 5 mg/kg IV Q12h, or 200 mg TID to 800 mg BID	Nausea, vomiting, diarrhea, headache, confusion, coma, hematologic dysfunction, liver failure, renal failure, rash	Qualitative and quantitative changes in the viral TK and/or DNA polymerase	Congenital herpes simplex, HSV encephalitis, genital HSV, herpes labialis, mucocutaneous HSV infections, herpes zoster, varicella	Acute retinal necrosis, eczema herpeticum, HSV proctitis, meningitis, hepatitis, respiratory and ophthalmic infections; HZV auricularis and encephalitis; herpetic whitlow; VZV prophylaxis, pneumonia and transverse myelitis, viral encephalitis
Valacyclovir	Same as acyclovir	Same as acyclovir.	500 mg BID × 10 days	500 mg BID	TTP/HUS, neurologic effects, renal impairment	Same as acyclovir	Recurrent genital HSV, herpes labialis, HZV, VZV	Acute retinal necrosis, CMV infection and prophylaxis, nongenital HSV
Famciclovir	Same as acyclovir	The active ingredient is acyclovir. Same as acyclovir, better absorption allows less frequent dosing.	500 mg BID × 10 days	500 mg BID × 3–5 weeks with chemotherapy or after HSCT (longer in children with acute leukemia	Headache, paresthesia, migraine, nausea, vomiting diarrhea, hematologic, liver dysfunction, carcinogenic	Same as acyclovir	HZV, mucocutaneous HSV in HIV, recurrent genital HSV	Acute retinal necrosis, genital HSV, hepatitis B

(continued)

Table 24.2 (continued)

Drug	Susceptibility	Mechanism of action	Doses for pneumonia	Prophylaxis	Side effects	Mechanism of Resistance	FDA-labeled indications	Non-FDA-labeled indications
Foscarnet	Activation (phosphorylation) by thymidine kinase or other kinases NOT required, hence, is active in vitro against HSV TK deficient and CMV UL97 mutants	Selective inhibition at the pyrophosphate-binding site on virus-specific DNA polymerases at concentrations that do not affect cellular DNA polymerases	60 mg/kg IV Q12h, or 40 mg/kg IV Q8h × 7–21 days or until complete healing	N/A	Renal impairment, electrolyte imbalance, seizures, fever, nausea, vomiting, diarrhea, headache, anemia	Resistance due to DNA polymerase mutations have emerged	CMV-retinitis s in AIDS patients, acyclovir-resistant mucocutaneous HSV	Intravitreal use in CMV retinitis, CMV pneumonia, HSV keratitis
Cidofovir	In vitro against CMV, HSV-1, HSV-2	Suppresses CMV replication by selective inhibition of viral DNA synthesis	5 mg/kg once a week × 2 weeks, then once every 2 weeks combined with probenecid and hydration	N/A	Renal impairment, neutropenia, decreased intraocular pressure, anterior uveitis/iritis, metabolic acidosis	Resistance to cidofovir has been selected for in the laboratory setting and occurs through mutations in the viral DNA polymerase. In vivo resistant strains have been reported	CMV retinitis in AIDS	Condyloma acuminatum

AIDS Acquired immune deficiency syndrome, *BID* twice a day, *CMV* cytomegalovirus, *HIV* human immunodeficiency virus, *HSCT* hematopoietic stem cell transplant, *HSV* human herpes simplex virus, *IV* intravenous, *N/A* not available, *Q12h* every 12 hourly, *TID* thrice a day, *TTP/HUS* thrombotic thrombocytopenic purpura, *VZV* Varicella Zoster virus

prevalence of HSV pneumonia (less than 2% of HSCT recipients) [9, 41, 49].

Antiviral drug prophylaxis is not recommended in HSV-seronegative leukemic patients during chemotherapy or after SCT, since primary HSV infection in these patients is unusual [62]. In HSV-seropositive patients, antiviral drug prophylaxis has been shown to prevent the development of active HSV disease and to reduce mortality rates [29, 69].

Antiviral drug prophylaxis is part of the standard management at many cancer centers for patients with hematologic malignancies undergoing chemotherapy or for patients undergoing HSCT [62, 63, 67, 69]. Acyclovir has been the most common antiviral drug used [28]. However, newer antivirals such as valaciclovir and famciclovir are also active against HSV and have an oral bioavailability three to five times superior to that of oral acyclovir [53, 62]. Both of these agents are used to prevent HSV reactivation during induction chemotherapy for leukemia or after HSCT [49]. Prophylaxis should be given for 3–5 weeks, after the start of chemotherapy or during the pre-engraftment stage in the first month after HSCT [58, 62, 63, 67]. Children, allogeneic HSCT patients who develop GVHD, or patients who require immunosuppressant treatment should receive prolonged prophylaxis [62].

24.7.3 Resistance to Antivirals

Long-term prophylaxis with acyclovir in HSCT patients appears to prevent the emergence of drug-resistant HSV disease [21]. However, several centers have reported increased incidence of acyclovir-resistant HSV disease, especially in patients who have undergone unrelated HSCT or HLA-mismatched transplant patients with GVHD [16, 40]. Acyclovir resistance is associated with serious morbidity and mortality [7, 16]. Poor response to acyclovir indicates possible resistance, and the patient should be promptly switched to foscarnet or cidofovir [7, 16].

Activation of acyclovir, ganciclovir, valacyclovir, or famciclovir requires initial phosphorylation by viral thymidine kinase (TK) [37]. Resistance to acyclovir can be caused by lack of TK, altered TK, or TK strains with mutations in viral DNA polymerase [37]. TK-negative mutants may cause severe disease in infants and immunocompromised adults [37]. Cross-resistance between acyclovir and foscarnet results from their interaction at the same site on HSV DNA polymerase; however, susceptibility to cidofovir is unaffected by the same viral mutation [26].

24.7.4 Vaccine

There is no licensed effective vaccine for HSV [37].

24.8 Outcome

Patients with HSV pneumonia can require mechanical ventilation and prolonged hospitalization [64]. Mortality in immunocompetent patients has been reported to be about 27% [54]. However, patients with hematologic malignancies and HSCT patients may have high mortality rates (up to 75–100%), if left untreated [46, 56]. Patients with solid tumors and patients with solid-organ transplants have mortality rates that range from 20% to 100%, with a higher percentage of mortality after liver transplants [3, 4, 31].

Severe respiratory distress necessitating mechanical ventilation or worsening respiratory status on a ventilator is often seen in untreated patients with HSV pneumonia, and ARDS or respiratory failure may occur without treatment [54, 56, 64]. Damage to lung function has not been reported in patients that recover from the infection.

24.9 Prognosis

The prognosis of patients with HSV pneumonia depends on the immunologic status of the patient and the type of underlying disease [27]. In immunocompetent hosts, HSV pneumonia is not necessarily a fatal disease [48]. In immunocompromised patients, however, HSV pneumonia can lead to respiratory failure and the need for mechanical ventilation or failure to wean off the ventilator and subsequent mortality [18, 24, 25, 27, 40, 56].

Although rare, HSV pneumonia should be considered in neutropenic hematologic patients undergoing chemotherapy with "suggestive" radiologic findings who have not improved after conventional antibacterial and/or antifungal treatments [18, 24, 25, 27, 40, 56].

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