



**2nd
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Leukemia**

**Recommendations for HSV management in
patients with leukemia**

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MANAGEMENT OF HSV INFECTION AND DISEASE IN PATIENTS TREATED FOR LEUKEMIA

- Recommendations for patients with leukemia treated by chemotherapy alone or by high-dose conditioning followed by hematopoietic stem cell transplantation (HSCT)

EPIDEMIOLOGY OF HSV INFECTION AND DISEASE IN PATIENTS WITH LEUKEMIA

- Up to 80% of adult patients with leukemia are HSV seropositive (II).
- HSV infection in patients with leukemia results in most cases from reactivation of latent virus, whereas primary infection is unusual (II).
- Both HSV types 1 and 2 are a common cause of HSV disease (HSV type 1 more frequent)(II).

EPIDEMIOLOGY OF HSV INFECTION AND DISEASE IN PATIENTS WITH LEUKEMIA

- The incidence of HSV infection among HSV seropositive patients receiving chemotherapy for acute leukemia was 61% and 66%, respectively, in two large series (I).
- The incidence of HSV infection among HSV seropositive HSCT recipients is about 80% (II).
- The majority of HSV infection occur during the first 4 weeks after HSCT (II).

CLINICAL MANIFESTATIONS OF HSV DISEASE IN PATIENTS WITH LEUKEMIA

- The most frequent clinical manifestations of HSV disease are mucocutaneous lesions.
- The sites of mucocutaneous HSV lesions are the oro-facial region in 85-90% of cases and the genital area in 10-15% (I).
- Esophageal HSV disease is present in about 10% of patients with upper gastro-intestinal symptoms (II).
- Uncommon HSV disease manifestations are pneumonia (2-3% of patients in the absence of prophylaxis), hepatitis, meningitis, encephalitis, and bone marrow suppression (III).

MONITORING FOR AND DIAGNOSIS OF HSV INFECTION

- Patients with leukemia should be tested for HSV serology before induction chemotherapy or HSCT for risk stratification of HSV reactivation (BII).
- Serological results are not helpful in confirming the diagnosis of HSV reactivation during immunosuppressive treatment (DIII).
- Routine surveillance for HSV infection by culture or PCR during chemotherapy or after HSCT is not required (CIII).

MONITORING FOR AND DIAGNOSIS OF HSV INFECTION

- Virus culture is one of the standard methods for detection of HSV in clinical specimens, and usually yields results within 48 hours of inoculation (III).
- Virus culture is required for testing of antiviral drug resistance (III).

DIAGNOSIS OF HSV DISEASE

- The diagnosis of mucocutaneous HSV disease can often be made on clinical grounds and may be confirmed by appropriate diagnostic techniques (BIII).
- In the presence of severe mucositis following chemotherapy or irradiation, the diagnosis of oropharyngeal HSV disease is difficult and identification of virus by appropriate diagnostic techniques is required (BIII).
- HSV PCR in CSF is indicated in the diagnosis of HSV meningitis and encephalitis (AII).

PREVENTION OF HSV DISEASE: HSV SERONEGATIVE PATIENTS

- Primary HSV infection in patients treated for leukemia is unusual, and antiviral drug prophylaxis is thus not recommended in HSV seronegative leukemic patients during chemotherapy or after HSCT (DIII).

PREVENTION OF HSV DISEASE: HSV SEROPOSITIVE PATIENTS

- HSV seropositive patients undergoing allogeneic HSCT for acute leukemia should receive antiviral drug prophylaxis (AI).
- HSV seropositive patients treated for acute leukemia by chemotherapy alone should be considered for antiviral drug prophylaxis (BIII).
- Intravenous or oral acyclovir (AI), or oral valaciclovir (BIII) should be given prophylactically for 3-5 weeks after start of chemotherapy or after HSCT, and for longer periods of time in children treated for acute leukemia.

PREVENTION OF HSV DISEASE: HSV SEROPOSITIVE PATIENTS

- The intravenous route is preferred in patients who develop chemotherapy- or irradiation-induced mucositis which impedes intake of oral medication (CIII).
- Allogeneic HSCT recipients who develop graft-versus-host disease or receive immunosuppressive treatment, including steroids, usually require a prolonged HSV prophylaxis (BII).

PREVENTION OF HSV DISEASE: RECOMMENDED REGIMENS

- Acyclovir 250 mg/m² or 5 mg/kg q12h iv (AI)
- Acyclovir from 3x200 mg/d to 2x800 mg/d po (AI)
- Valaciclovir 2x500 mg/d po (AI)

THERAPY OF HSV DISEASE

- Intravenous acyclovir remains the therapy of choice for severe mucocutaneous or visceral HSV disease (AI).
- Oral acyclovir, valaciclovir, or famciclovir may be considered as alternative for less serious manifestations of HSV disease (CIII).
- Firm recommendation for therapy of HSV pneumonia or HSV meningitis and encephalitis cannot be made since data on antiviral treatment of these conditions in leukemic patients are limited (CIII).

THERAPY OF HSV DISEASE: RECOMMENDED REGIMENS

Mucocutaneous or esophageal disease

- Acyclovir 250 mg/m² or 5 mg/kg q8h iv for 7-10 d (AI)
- Acyclovir from 5x200 mg/d to 5x400 mg/d po for 10 d (AI)
- Famciclovir 2x500 mg/d po for 10 d (BIII)
- Valaciclovir 2x 500 mg/d po for 10 d (BIII)

Pneumonia, hepatitis, meningitis, encephalitis

- Acyclovir 500 mg/m² or 10 mg/kg q8h iv for 14-21 d (AIII)

HSV RESISTANCE TO ANTIVIRAL DRUGS

- The emergence of resistant HSV strains that cause disease unresponsive to antiviral drugs is reported with increasing frequency in patients with hematologic malignancy (III).
- Retrospective data of acyclovir prophylaxis after HSCT show a 2-year probability of acyclovir-resistant HSV disease of 1.3% with 30 days of acyclovir, of 0.2% with 1 year of acyclovir, and of 0% with acyclovir given for more than 1 year. Thus, the longer the duration of acyclovir prophylaxis the lower the probability of HSV resistant disease (II).

HSV RESISTANCE TO ANTIVIRAL DRUGS

- The mechanism of resistance in the vast majority of clinical HSV strains isolated to date is a deficiency in viral thymidine kinase resulting in reduced activation of acyclovir in HSV-infected cells (III).
- Acyclovir-resistant HSV isolates are usually susceptible to antiviral agents, such as foscarnet and cidofovir, that do not require viral thymidine kinase for activation (III).
- In several cases, multidrug-resistant HSV strains causing disease have been documented (III).
- If HSV disease is unresponsive to antiviral therapy given at maximum dose, resistance testing should be performed (CIII).

HSV RESISTANCE TO ANTIVIRAL DRUGS: ALTERNATIVE TREATMENT REGIMENS

Resistance to acyclovir or famciclovir

- Foscarnet 60 mg/kg q12h iv or 40 mg/kg q8h iv for 7-21 d or until complete healing (BIII)
- Topical trifluridine 5% ophthalmic solution q8h* (CIII)
- Topical cidofovir gel 0.3% or 1% once daily* (CIII)

**For accessible cutaneous lesions*

HSV RESISTANCE TO ANTIVIRAL DRUGS: ALTERNATIVE TREATMENT REGIMENS

Resistance to foscarnet

- Cidofovir 5 mg/kg once a week for 2 weeks, then once every 2 weeks* (BIII)
- Topical trifluridine 5% ophthalmic solution q8h[†] (CIII)
- Topical cidofovir gel 0.3% or 1% once daily[†] (CIII)

**Combined with probenecide and iv hydration*

†For accessible cutaneous lesions