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Guideline

Polish consensus guidelines on the use of acyclovir in the treatment and prevention of VZV and HSV infections

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ABSTRACT

A physician has to perform a benefit-risk assessment each time acyclovir is prescribed "off label" for children. A group of Polish infectious disease experts was created to develop evidence-based guidelines on the use of acyclovir in the treatment and prevention of varicella zoster and herpes simplex infections. In primary varicella zoster virus infections, oral acyclovir treatment is recommended in children over 12 years of age and should be considered in younger children who fall into one of the groups at risk of severe varicella. Intravenous acyclovir therapy in varicella is recommended in patients with immune deficiencies, newborns and in complicated cases. When there is a justified need for prevention of varicella, oral *acyclovir prophylaxis* may be considered if immunoglobulin cannot be administered, and if it is too late for vaccination. Oral acyclovir treatment of herpes zoster may be beneficial to otherwise healthy patients with a rash in places other than the trunk and in patients over 50 years of age. In immunocompetent patients with herpes simplex infections, indications for treatment with oral acyclovir include primary (genital herpes, skin herpes in children with atopic dermatitis, ocular herpes simplex, severe gingivostomatitis, paronychia and pharyngitis) and recurrent infections. Intravenous acyclovir should be administered for herpes infections in neonates, immunocompromised patients and patients who develop complications including neurological.

1. Introduction

The efficacy of acyclovir in inhibiting replication of the varicella zoster virus (VZV) and the herpes simplex virus (HSV) and the availability of cheap oral medications has led to a discussion among practitioners on its usefulness and administration methods. Each time acyclovir is to be prescribed "off label", a physician has to perform a benefit-risk assessment considering clinical efficacy, the risk of adverse reactions and potential induction of acyclovir resistance. As a result, effective acyclovir treatment is underprescribed in Poland. Additionally, products from different brands vary in terms of label use and recommended dosage, which is usually lower than that used in the most recent clinical trials. The majority of acyclovir products are not approved for use in children

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under 2 years of age. In order to guide physicians and standardize therapeutic practices, a Working Group was established using the best available evidence and recommendations for the treatment and prophylaxis of HSV and VZV infections with acyclovir.

2. Materials and methods

The recommendations were developed by a Polish group of infectious disease experts in order to provide healthcare practitioners with up-to-date guidelines on acyclovir use in the treatment and prevention of VZV and HSV infections in Poland. The 12 members of the Working Group were chosen because of their competence and knowledge regarding the prophylaxis and treatment of HSV and VZV infections in both research and clinical practice. All members gave their time voluntarily and declared no personal financial conflicts. Any relationships links with the pharmaceutical or health industry were disclosed prior to the start of the Group's work (April 2013). Two members of the Working Group (E.K. and B.K-G.) were given the task of searching the literature and identifying relevant data. PubMed, Scopus, Web of Science and Cochrane databases were searched with the following keywords: (varicella OR chickenpox OR Herpes OR shingles OR zoster) AND (therapy OR Acyclovir). After removing any duplicates, 1321 articles were identified. The two experts independently checked all titles and their abstracts for compliance with the following criteria: (1) published in English; (2) evaluation of acyclovir use in varicella, zoster and HSV infections (3) studies were valid, consistent, applicable, clinically relevant and the recommendations were supported by fair evidence. Systematic reviews were included. If either of the reviewers considered an abstract to be potentially suitable, full-text articles were sourced and then assessed by both reviewers for their suitability for inclusion. Ultimately, 39 publications were selected and studied by each of the Working Group's members. Aside from the peer-reviewed literature, data from the following sources was considered: Recommendations from the AAP Committee on Infectious Diseases, recent reports from major scientific conferences, safety warnings and prescribing information from the FDA and the authors' clinical and research experience relevant to the topic.

The Working Group met on 26th April 2013 when a round-table discussion was held to define the therapeutic indications. After the meeting, two experts (L.Sz. and E.D.) prepared the initial Draft Recommendations, which were later reviewed independently by each member of the Working Group. To help identify any disagreements or inconsistencies, the Group's members kept in touch through conference call and emails to provide comments and update the recommendations before the final version was established in September 2014. We search for new evidence systematically and we intend to update the recommendations regularly as new information becomes available.

The recommendations are based on levels of evidence simplified from the NHMRC's "Quality of evidence ratings" (Table 1) [1].

3. General information on acyclovir use

Acyclovir treatment in individual patients is based on a benefit-risk assessment. The benefits of the treatment include: shortening recovery time or alleviating the severity of the disease and the prevention of complications. The risks include: adverse reactions following acyclovir administration, possible negative impact on antiviral adaptive immunity and potential induction of acyclovir resistance in VZV and HSV.

Table 1
Levels of evidence (simplified from the NHMRC's "Quality of evidence ratings") [1].

E1	Level I	Systematic review or meta-analysis of all relevant randomized controlled trials (RCTs)
E2	Level II	Well-designed RCTs
E3	Level III	Well-designed cohort or case–control studies
E4	Level IV	Consensus from an expert committee

3.1. The benefits of treating VZV and HSV infections with acyclovir

3.1.1. Varicella (chickenpox)

A double-blind study assessing the administration of acyclovir (80 mg/kg/day) for 5 days in 815 otherwise healthy children aged 2–12 years old, beginning within 24 h of the onset of a rash, showed a significant reduction in the number of lesions (by approx. 25%) and a one day reduction in the number of days with a fever. The treatment had no effect on the number of complications [1,2]. However, in adolescents and adults the treatment reduced the number of residual hypopigmented lesions on the skin [3]. In adults, early treatment of varicella with acyclovir eased the disease and reduced the number of lesions [4].

Note: The studies have not demonstrated the effects on the frequency of complications but as far as neurological complications are concerned, the studies have not shown such effects due to a limited number of groups in relation to the absolute frequency of complications [1–3].

We identified only one small case-controlled study concerning acyclovir use in post-exposure prophylaxis. In this study conducted among VZV-seronegative children, acyclovir administered for 7 days starting 7–9 days after family exposure to varicella was able to prevent or modify the course of the varicella in 84% of patients [5].

3.1.2. Herpes zoster

The studies were mainly conducted among adults. Antiviral treatment resulted in a shorter healing time (reduced number and spread of lesions, lesions scabbing over sooner and a shortened disease duration, which is vital considering the complications of zoster) [7–9]. The study by Huff et al. indicates that early zoster treatment alleviated acute zoster pain [10]. Acyclovir was found to be especially efficient in the treatment of herpes zoster ophthalmicus, as it reduced the frequency and intensity of complications [11].

3.1.3. Oral herpes

Several placebo-controlled clinical trials were performed among children with primary herpetic gingivostomatitis. The study by Ducoulombier et al. showed that drooling disappeared faster in the group treated with acyclovir [12]. A clinical study in which oral acyclovir was administered in syrup form at a dose of 600 mg/m^2 for 10 days showed an improvement in the following symptoms: drooling (4 vs. 8 days), gum inflammation (5 vs. 7 days), mucous membrane healing process (6 vs. 8 days), development of new lesions during treatment (57% vs. 94%) and complete of viral shedding in saliva (4 vs. 10 days). In the study by Amir et al. acyclovir suspension administered at a dose of 15 mg/kg 5 times a day for 7 days, compared with a placebo, shortened the time new lesions developed (4 vs. 10 days, 95%CI 4–8 days), the duration of the fever (1 vs. 3 days; 95%CI 0.8–3.2 days), pain while eating (4 vs. 7 days; 95%CI 1.31–4.69), drinking (3 vs. 6 days; 95%CI 1.1–4.9) and the time required for complete viral shedding in saliva (1 vs. 5 days; 95%CI 2.9–5.1) [13]. No effect on the oral HSV infection recurrence was demonstrated [14].

3.1.4. Genital herpes

Acyclovir is the antiviral drug that has been most thoroughly examined in the treatment of genital herpes in children and adults [15,16]. Oral acyclovir products are effective in the treatment of

primary and recurrent HSV infections. Early treatment yields the best possible results. The clinical outcome is better in patients with primary HSV infection (intravenous acyclovir administration) than in patients with HSV1 (IgG+) antibodies and infected with HSV2 [17]. In a placebo-controlled study, acyclovir at a dose of 200 mg administered 5 times a day for 5–10 days significantly shortened the time taken for complete viral shedding (1–6 days vs. 13–15 days in the placebo group), the appearance of new lesions after 48 h of the onset of therapy (in 0–4% vs. 43–44% patients), the time taken for the lesions to scab over and heal (10–12 vs. 16–21 days) and the worsening of symptoms [18]. In adult patients with recurrent genital herpes, acyclovir (200 mg 5 times a day for 5 days) in comparison to placebo shortened the time taken for complete viral shedding (1–2 vs. 2–4 days), healing time (5–6 vs. 6–7 days) and reduced the development of new lesions after the onset of treatment (in 2–10% vs. 19–25% of patients) [19]. In the trials mentioned above no significant adverse reactions to the acyclovir treatment were observed even though the participants had not been instructed to drink enough fluids [17–19].

Topical acyclovir (ointments and creams) is considered to be widely ineffective [20].

3.2. Adverse reactions following acyclovir administration

Extensive research and many years of clinical practice indicate that acyclovir is a safe medication. The frequently reported side effects (≥1/100 to <1/10) of oral acyclovir products include: headache and vertigo (usually in patients with renal disorders or with other predisposing factors), nausea, vomiting, diarrhea, abdominal pain, itching, rash (as well as a rash caused by hypersensitivity to light). Other symptoms occur rarely (≥1/10,000 to <1/1000) or very rarely (<1/10,000, including unique cases). When receiving acyclovir treatment, patients should be well hydrated. Temporary renal dysfunction may occur in patients with chronic kidney disease. The dysfunction usually subsides once the patient is properly hydrated and (or) the dose of the drug is reduced or the drug is discontinued. Caution is recommended when using acyclovir in patients with renal dysfunction. In the treatment of VZV infections, the recommendation is that the frequency of acyclovir administration is reduced to twice daily (about every 12 h) in patients with acute renal failure (creatinine clearance rate – CrCl less than 10 ml/min) and to three times daily (about every 8 h) in patients with moderate renal failure (CrCl 10–25 ml/min). Impaired renal excretion may lead to acyclovir accumulation in blood and relative overdosing, which may cause adverse reactions [21]. As acyclovir does not show a hepatotoxic effect there is no need for a liver function test during acyclovir use. In two population analyses, oral acyclovir was shown to be well tolerated by infants and small children [22,23]. Many years of clinical practice show that it may be safely used at recommended doses and for many months (as prophylaxis against recurrent ocular herpes, genital herpes and reactivation of infections in immunocompromised patients) [24].

3.2.1. Acyclovir use in pregnant and lactating women

There is limited data on acyclovir use by pregnant women. Numerous *in vitro* and *in vivo* studies have failed to show a mutagenic effect of acyclovir and suggest that it is unlikely to pose a genetic threat to humans [25]. Acyclovir is a pregnancy FDA category B drug. No experimental studies have been conducted, but due to the risk that VZV infection presents for a pregnant woman and her fetus, and based on many years of experience and descriptions of acyclovir use in pregnant women, it is deemed safe for acyclovir to be safely used by pregnant women in clinical practice [26].

After oral acyclovir administration at a dose of 200 mg 5 times daily, acyclovir levels in the mother's milk equaled between 60% and 410% of the plasma concentration. Such concentration in the mother's milk could result in the baby consuming a daily dose of 0.3 mg/kg of body weight; therefore caution is recommended when administering the drug to breastfeeding women [27].

3.3. Possible negative impact on antiviral adaptive immunity

Acyclovir does not have a negative effect on natural antiviral immunity despite viral replication inhibition which could affect antigen expression. Titers of specific VZV antibodies assessed on the 28th day following varicella treated only with acyclovir did not differ between the group of children treated with acyclovir and the placebo group [3,28]. The treatment was not found to affect cellular immunity [29]. Studies evaluating the influence of acyclovir therapy for varicella on herpes zoster are scarce. A recent epidemiological study by Wen et al. does not provide reliable evidence, that acyclovir use in the treatment of varicella significantly increases the risk of pediatric herpes zoster [30]. There is no evidence that acyclovir use reduces patient contagiousness. Suzuki et al. showed the presence of VZV DNA in 33–100% of throat swabs on the 7th day after the onset of the disease in both treated and non-treated patients [31].

3.4. Potential induction of acyclovir resistance in VZV and HSV

Acyclovir's effect on inducing the resistance of HSV and VZV to acyclovir is secondary and hardly noticeable. Acyclovir-resistant strains are selected very rarely and only in patients with cellular immune-deficiencies receiving long-term acyclovir therapy/secondary prophylaxis. During 6 years of continuous acyclovir use in immunocompetent hosts, no acyclovir-resistant HSV strains were identified [32]. The risk of VZV developing acyclovir resistance is even lower than for HSV, however acyclovir resistant strains in AIDS patients taking acyclovir on a long-term basis have been reported [33]. In practice, transmission of acyclovir-resistant HSV and VZV isolates from person-to-person has not been documented.

4. Treatment and post-exposure prophylaxis of varicella zoster virus (VZV) infections

4.1. Treatment of varicella

4.1.1. Immunocompetent patients

In most cases, only small children with varicella do not need to be treated with antivirals. Routine acyclovir therapy is not recommended for use in otherwise healthy children under 12 years of age suffering from typical complication-free varicella, who do not belong to a group at risk of severe varicella [E4] [34,35]. Oral acyclovir treatment is indicated in all patients ≥12 years of age due to a documented risk of complications from varicella that increases with age [34,35].

In younger children acyclovir treatment should be administered in the following cases:

- chronic pulmonary disease (including mucoviscidosis),
- severe skin diseases (e.g. atopic dermatitis),
- short-term or intermittent use of corticosteroids,
- use of inhaled corticosteroids,
- long-term salicylate therapy,
- infection through close contact (intensive long-term contact – close relatives) [E4] [34,35].

It has been indicated that in domestic infections the incubation period is shortened and complications are more frequent – probably due to a more intense viral transmission. A valid indication for acyclovir use may be a negative effect of VZV infection on the course of underlying chronic diseases (exacerbation, decompensation). For this reason acyclovir therapy should be considered in patients with diabetes and congenital metabolic diseases [E4] [33]. In children ≤2 years of age the off-label use of acyclovir should be discussed with the parents as their written consent to the treatment is required by law.

Oral acyclovir administration is preferred and the oral use of acyclovir is limited only by indications (i.v. treatment of CNS infections or use in immunodeficient patients) and in early infancy due to the immaturity of the swallowing reflex. Acyclovir use in the treatment of varicella diagnosed after the first 24 h of the disease's onset is controversial because of a lack of measurable benefits. The Working Group considers it justified in patients who are:

- hospitalized due to varicella (primary severe course of the disease) and its complications
- hospitalized due to an underlying disease with varicella as a comorbidity.

Antiviral therapy does not guarantee a faster recovery but is justified if started during the infectious stage of the disease (non-clustered blisters). In the opinion of the Working Group, the potential benefits of the treatment outweigh the costs and risk of adverse events. Acyclovir treatment was not shown to significantly affect the course of cerebellitis but the potential benefits undoubtedly outweigh the risk of its use. Due to its better bioavailability, we recommend intravenous treatment with acyclovir in patients who develop complications (including neurologic) [E4] [35].

4.1.2. Pregnant women

The AAP recommends acyclovir oral therapy for primary VZV infections during the 2nd and 3rd trimester of pregnancy and the UK Advisory Group recommends this within 24 h of the onset of symptoms in pregnant women ≥20 weeks [33,34]. In the opinion of Lamonti et al. all pregnant women should be treated [36]. Our recommendation is that oral acyclovir treatment should be considered in pregnant women who are either in the second half of their pregnancy or have additional risk factors of severe varicella (e.g. chronic lung disease, atopic skin syndrome) [E4]. Oral therapy with acyclovir in pregnant women is justified within 24–72 h of developing a rash [7,34–36]. In pregnant women who develop complications and/or are immunocompromised the drug should be administered intravenously [E4] [34,36,37]. It is advisable to discuss this off-label use of the drug each with the pregnant patient and obtain her written consent to the treatment. Recommended doses are given in Table 2 [34,36,38,39].

4.1.3. Newborns and infants

Varicella Zoster Immunoglobulin (VZIG) is recommended in high-risk neonates with exposure:

- whose mothers developed varicella from 5 days before to 2 days after delivery,
- who were born at <28 weeks gestation or who weighed <1000 g at birth irrespective of maternal history of chickenpox,
- who were born at ≥28 weeks gestation whose mothers have not had chickenpox or whose status is unknown [E4] [35–37].

Those, who did not receive VZIG prophylaxis or developed severe varicella despite passive immunization should be treated with intravenous acyclovir [E4] [37]. Parenteral treatment is also indicated in infants with varicella who are immunocompromised, present general symptoms, develop complications or have serious underlying diseases [E4] [34–37].

4.1.4. Immunocompromised patients

In immunocompromised patients (especially those with cellular immunity defects) routine acyclovir intravenous therapy for varicella is recommended [E4] [34,35]. The start of acyclovir treatment is indicated on both the first and later days of the disease.

Note: oral acyclovir used in immunocompromised patients might carry a risk of insufficient efficacy (lack of studies and conclusions based on plasma drug levels) but when intravenous administration is not available, oral therapy should be started as soon as possible rather than waiting until intravenous administration is possible [E4].

4.2. Indications for the treatment of herpes zoster

Oral Acyclovir treatment is indicated in otherwise healthy patients ≥50 years of age [E2] [8,10,11] and may be beneficial in all patients with neuritis, severe rash or rash in places other than the trunk (the face and head in particular) [E4]. Treatment should be started as soon as possible using the oral doses given in Table 2.

Intravenous acyclovir should be administered in immunodeficient patients [E2] [35,40] and in herpes zoster affecting mucous membranes, especially the eye [E4] (doses in Table 2). After clinical improvement is observed, oral treatment may be continued at the doses prescribed for immunocompetent patients [34]. Topical antiviral drugs, antibiotics or powders and pulps are not recommended [E4].

4.3. Post-exposure prophylaxis for varicella

4.3.1. Definition of exposure

Significant exposure is defined as domestic contact, close face-to-face contact for at least 5 min, being in the same room for at least 1 h, hospital room: shared room or neighboring beds, close contact (hugging, touching) with a person with herpes zoster, a newborn delivered by a mother who developed varicella between 5 days before and 2 days after delivery [35].

4.3.2. Immunoglobulins

It is recommended that immunocompromised patients, pregnant women and high risk newborn babies (as defined in “Newborns and Infants” subsection) use VZIG as a prophylaxis against infection [34–36].

4.3.3. Vaccination

The vaccine may be administered to immunocompetent children over 9 months of age as a post-exposure prophylaxis. Vaccination within 72 h of exposure protects against varicella in 90% of cases. Administration on the 4th or 5th day after exposure is less efficient (around 70%). Patients who do not develop varicella due to vaccination should receive a second dose of the vaccine 6 weeks from the initial one. Vaccination is contraindicated in patients with T-lymphocyte immunodeficiency and during pregnancy [34–36].

4.3.4. Chemoprophylaxis

Routine use of acyclovir as a post-exposure prophylaxis is not recommended. However, if vaccination cannot be performed and immunoglobulin is not available and there is a justified need (e.g. immunocompromised patients, adults and children with risk factors for a severe course of the disease) acyclovir may be considered to prevent the VZV infection after exposure. Oral

Table 2
Acyclovir doses for VZV infections [34,36,38,39].

Recommended dose and treatment duration	Age	Route	Therapeutic indications
Immunocompetent patients			
80 mg/kg/day in 4 doses for 5 days, maximum dose: 3200 mg/day	All ages	Oral	Varicella – uncomplicated cases
30 mg/kg/day in 3 doses, or (>1year of age) 1500 mg/m^2 for 7–10 days	All ages	IV	Varicella with CNS infections, with complications or when oral treatment is not possible herpes zoster involving mucous membranes
80 mg/kg/day in 4 doses for 5–7 days, maximum dose: 3200 mg/day	<12 years	Oral	Herpes zoster (without the involvement of mucus membranes)
800 mg 4–5 times daily for 5–7 days	≥12 years	Oral	Herpes zoster (without the involvement of mucus membranes)
Immunocompromised patients			
30 mg/kg/day in 3 doses for 7–10 days	≤12 months	IV	Varicella
1500 mg/m^2/day (optionally 30 mg/kg/day) every 8 h for 7 days or up to 2 days after the last lesions developed and then orally 20 mg/kg/day every 6 h up to 10 days of treatment	>12 months	IV	Varicella
60 mg/kg/day in 3 doses for 7–10 days	<12 years	IV	Herpes zoster
30 mg/kg/day in 3 doses for 7–10 days	>12 years	IV	Herpes zoster
Pregnant women			
800 mg 5 times daily for 7–10 days		Oral	Varicella – uncomplicated cases
30–45 mg/kg/day for 5–10 days		IV	Varicella – complicated cases

therapy (4 × 20 mg/kg/dose, max. 800 mg) may be started 7–10 days after exposure and be continued for no more than 7 days [35].

5. HSV 1 and 2 infections

5.1. Immunocompetent patients

Oral acyclovir may be indicated for all clinical presentations of HSV1 and HSV2 infections (except for encephalitis – 3 weeks of intravenous treatment) in immunocompetent patients. Local treatment with acyclovir is ineffective [20].

5.1.1. Oral herpes

Despite the lack of unequivocal evidence, small clinical trials and clinical practice show that early treatment (within 72–96 h) alleviates the symptoms and shortens the recovery time [12–14]. As acyclovir is easy to use, relatively cheap, clinically efficient and does not induce unacceptable adverse reactions, acyclovir treatment is indicated in symptomatic primary and recurrent infections.

Acyclovir treatment is justified for gingivostomatitis leading to difficulties with eating and drinking [E2] [13,14], skin herpes in children with atopic dermatitis, ocular herpes simplex, severe paronychia and pharyngitis [E4]. Doses are given in Table 3 [13,20,38,41].

For recurrent infections, especially when the episodes reoccur more often than 6 times in a year, long-term treatment for 6 months or longer should be considered [E4] [20]. There are no clinical studies among children. In the USA a dose of 30 mg/kg in three doses is recommended for children (max. 1 g/day) and a follow-up evaluation of the effects of the treatment is recommended after 6–12 months. Adults should take a 400 mg dose twice daily [20].

5.1.2. Genital herpes

Irrespective of the route (oral or intravenous) of acyclovir administration for primary or recurrent episodes of genital herpes the treatment has no effect on the frequency of recurrences. Oral acyclovir is the drug of choice in the treatment of anorectal herpes in primary and recurrent infections in children [E4] [15,16], pregnant women [E3] [26] and adults [E2] [18,19] (doses in Table 3). Parenteral acyclovir is indicated in prevention and treatment of HSV infections in neonates [E2] [20,27,42] and in therapy of all patients with primary infection who develop complications such as encephalitis or urine retention [E4] [20,41] (doses in Table 3). Acyclovir has the same efficacy as newer drugs: valacyclovir and famciclovir [43,44] In recurrent infections, especially when more than 6 episodes occur in a year, long-term acyclovir use should be considered (for 6 months or more) [E2] [32,44,45] (doses in Table 3).

5.2. Immunocompromised patients

Immunocompromised patients may experience more frequent, severe or prolonged episodes of genital herpes and should be treated with higher doses of acyclovir as given in Table 3 [20,38,41].

6. Summary and recommendations

6.1. Acyclovir use for the treatment and post-exposure prophylaxis of varicella zoster virus infections

- Routine acyclovir treatment is not recommended in otherwise healthy children <12 years of age experiencing typical, complication-free, benign varicella, who do not belong to a group at risk of severe varicella [E4] [34,35].
- Oral acyclovir treatment for varicella is indicated in all patients ≥12 years of age [E4].
- Oral acyclovir treatment for varicella is indicated in children <12 years of age in the case of: chronic pulmonary disease (including mucoviscidosis), severe skin disease (e.g. atopic dermatitis), short-term or intermittent use of corticosteroids, use of inhaled corticosteroids, long-term salicylate therapy, infection through close contact (intensive prolonged contact with relatives or others in the household) [E4] [34,35].
- Oral acyclovir treatment for varicella should be considered in patients with diabetes and other congenital metabolic diseases [E4] [34].
- Acyclovir therapy for varicella should be started within the first 24 h of the rash appearing [E2] [3,4,6].
- Acyclovir use in the treatment of varicella diagnosed after the first 24 h of the disease is justified in patients who are: immunocompromised, hospitalized with severe varicella or its complications or due to an underlying disease with varicella as a comorbidity and in pregnant women [E4].

Table 3
Therapeutic indications and recommendations for acyclovir use in children with various primary and recurrent forms of HSV 1 and 2 infections [13,20,38,41].

Recommended dosage and treatment duration	Age	Route	Therapeutic indications
Immunocompetent patients			
First symptomatic incident			
60 mg/kg/day in 3 doses for 14–21 days	Birth to 3 months	I.V.	Neonatal HSV infection
80 mg/kg/day in 4 doses for 5–10 days, maximum dose: 3200 mg/day	All ages	Oral	Herpetic gingivostomatitis, Pharyngitis, Paronychia Herpes dermatitis in patients with atopic dermatitis (consider I.V. therapy) Ocular herpes simplex (consider I.V. therapy)
40–80 mg/kg/day in 4 doses for 5–10 days, maximum dose 1000 mg/day	<12 years	Oral	Herpes genitalis
1000–1200 mg/day in 3–5 doses for 7–10 days	≥12 years	Oral	Herpes genitalis
60 mg/kg/day in 3 doses for 14–21 days	<3 months	I.V	Encephalitis
30–45 mg/kg/day in 3 doses for 14–21 days	≥3 months		
Recurrent infections			
1000 mg/day in 5 doses for 5 days, or 1600 mg/day in 2 doses for 5 days, or 2400 mg/day in 2 doses for 2 days[a]	≥12 years	Oral	Herpes genitalis
800 mg/day in 2 doses for 6–12 months, 30 mg/kg in 3 doses max. 1000 mg/day reassess after 6–12 months	≥12 years and under	Oral	Chronic preventive treatment of HSV infection (suppression of HSV replication), in recurring herpes dermatitis, herpes ocular and genital herpes – with frequent recurrences (>6 incidents/year)
Immunocompromised patients			
First symptomatic incident			
1000 mg/day in 3–5 doses for 7–14 days	<12 years	Oral	Herpetic gingivostomatitis, Pharyngitis, Paronychia,
1000 mg/day in 3–5 doses for 7–14 days, or 400 mg 3 times daily for 7–14 days	≥12 years	Oral	Herpes dermatitis in patients with atopic dermatitis (consider I.V. therapy)
30 mg/kg/day in 3 doses for 7–14 days	All ages	I.V.	Ocular herpes simplex (consider I.V. therapy) Herpes genitalis
60 mg/kg/day in 3 doses for 14–21 days	<12 years	I.V.	Encephalitis
30–45 mg/kg/day in 3 doses for 14–21 days	≥12 years		
Recurrent infections			
1200 mg in 3 doses for 7–14 days	≥12 years	Oral	Herpes genitalis
400–800 mg 2–3 times daily reassess after 12 months	≥12 years and less	Oral	Chronic preventive treatment of genital herpes
600–1000 mg/day in 3–5 doses during period of risk	≥2 years	Oral	Prophylaxis of HSV infection in immunocompromised hosts who are HSV seropositive

[a] Near-term pregnant women should be treated until delivery.

- In immunocompromised patients, routine acyclovir intravenous treatment for varicella is indicated even if symptoms present after 24 h [E4] [34,35]. If intravenous treatment is not available, oral treatment should be started as soon as possible [E4].
- Oral acyclovir treatment should be considered during the first 24–72 h of the appearance of a rash in pregnant women who are in the second half of their pregnancy or have additional risk factors for severe varicella [E4] [34,37].
- In pregnant women with varicella who develop complications, intravenous acyclovir should be administered at any stage of the pregnancy [E4] [34,36,37].
- Due to its better bioavailability, we recommend intravenous use of acyclovir in patients who develop varicella complications (including neurologic and pulmonary) [E4] [35].
- Intravenous acyclovir treatment is recommended in high risk neonates who did not receive VZIG prophylaxis or developed severe varicella despite passive immunization [E4] [37] and in infants who are immunocompromised, present general symptoms, develop complications or have serious underlying diseases [E4] [34–37].
- Oral acyclovir treatment is recommended for herpes zoster in otherwise healthy patients ≥50 years of age [E2] [8,10,11].
- Oral acyclovir treatment should be considered in patients at any age who develop herpes zoster in places other than the trunk (the face and head in particular), severe rash or neuritis [E4].
- Intravenous acyclovir is indicated in herpes zoster affecting mucous membranes, especially the eye [E4].
- Immunocompromised patients with zoster should receive intravenous acyclovir treatment [E2] [40].
- Topical antiviral drugs, antibiotics or powders and pulps are not recommended in the treatment of VZV infections [E4].
- Routine use of acyclovir as a post-exposure prophylaxis is not recommended [E4] [35].
- Post-exposure prophylaxis with acyclovir may be considered in susceptible individuals if there is justified need, vaccination cannot be administered and Varicella-Zoster Immune Globulin is not available [E4] [35].

6.2. Acyclovir use in treatment of herpes simplex infections

- Oral acyclovir treatment is recommended for HSV1 gingivostomatitis leading to eating and drinking difficulties [E2] [13,14].
- Oral acyclovir treatment is indicated in skin herpes in children with atopic dermatitis, ocular herpes simplex, severe paronychia and pharyngitis [E4].
- Long-term treatment for 6 months or longer should be considered in the event of recurrent HSV1 infections (>6 episodes per year) [E4] [20].
- Oral acyclovir is the treatment of choice for primary and recurrent anorectal herpes in children [E4] [15,16], and adults [E2] [18,19], including pregnant women [E3] [26].
- Intravenous acyclovir is the treatment of choice for prevention and treatment of neonatal HSV infections [E2] [20,27,42].
- Parenteral acyclovir treatment is indicated in primary genital herpes infection associated with serious clinical symptoms and/or complications such as encephalitis or urine retention [E4] [17,20].

- In recurrent HSV 2 infections long-term acyclovir use for at least 6 months should be considered [E2] [32,44,45].

Conflicts of interest

None.

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