ClinicalEvidence

Chickenpox: treatment

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ABSTRACT

INTRODUCTION: Chickenpox is extremely contagious. More than 90% of unvaccinated people will become infected during their lifetime, but infection occurs at different ages in different parts of the world. In the US, the UK, and Japan, more than 80% of people have been infected by the age of 10 years, and by the age of 20 to 30 years in India, South East Asia, and the West Indies. It is usually a mild and self-limiting disease, but it can be severely complicated by pneumonitis or disseminated disease in some individuals, particularly neonates and those who are immunocompromised. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatment for chickenpox in healthy adults and children (including neonates) within 24 hours after onset of rash? What are the effects of treatment for chickenpox in healthy adults and children (including neonates) later than 24 hours after onset of rash? What are the effects of treatment for chickenpox in immunocompromised adults and children (including neonates)? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). RESULTS: We found six studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic overview we present information relating to the effectiveness and safety of aciclovir, within 24 hours of onset of rash or later than 24 hours of onset of rash, in otherwise-healthy adults and children (including neonates); and aciclovir in immunocompromised adults and children (including neonates).

QUESTIONS

What are the effects of treatment for chickenpox in healthy adults and children (including neonates) within 24 hours after onset of rash? . . . 3

What are the effects of treatment for chickenpox in healthy adults and children (including neonates) later than 24 hours after onset of rash? . . . 6

What are the effects of treatment for chickenpox in immunocompromised adults and children (including neonates)? . . . 9

INTERVENTIONS

TREATMENT (WITHIN 24 HOURS) IN HEALTHY ADULTS AND CHILDREN (INCLUDING NEONATES)

Likely to be beneficial

Aciclovir . . . 3

TREATMENT (AFTER 24 HOURS) IN HEALTHY ADULTS AND CHILDREN (INCLUDING NEONATES)

Unlikely to be beneficial

Aciclovir (unlikely to be beneficial in people without severe disease, but intravenous aciclovir may be used in people with severe disease) . . . 6

TREATMENT IN IMMUNOCOMPROMISED ADULTS AND CHILDREN (INCLUDING NEONATES)

Likely to be beneficial

Aciclovir for treatment in immunocompromised adults* . . . 9

Aciclovir for treatment in immunocompromised children (including neonates) . . . 10

Footnote

*Based on consensus.

Key points

- Chickenpox is caused by primary infection with the varicella zoster virus. In healthy people, it is usually a mild, self-limiting illness, characterised by low-grade fever, malaise, and a generalised, itchy, vesicular rash.

  Disease can be severely complicated by pneumonitis or disseminated disease in some individuals, such as neonates, pregnant women, and those who are immunocompromised.

- Treatment of chickenpox with oral aciclovir given within 24 hours of onset of rash may be more effective than placebo in otherwise healthy children. It also seems to be more effective than placebo at treating chickenpox in otherwise healthy adults.

  When given later than 24 hours after onset of rash, aciclovir does not seem so effective at treating chickenpox compared with placebo, although the evidence for this is sparse.

  In clinical practice, intravenous aciclovir is used to treat severe disease irrespective of time of onset of rash. However, this is not based on evidence from placebo-controlled RCTs, as such studies would be considered unethical.

- Intravenous aciclovir may be more effective than placebo at reducing time to full crusting and clinical deterioration from chickenpox in children with malignancy and receiving chemotherapy.

  We found no evidence comparing intravenous aciclovir and placebo in other immunocompromised children.

- We found no evidence assessing aciclovir for the treatment of chickenpox in immunocompromised adults.

Placebo-controlled RCTs assessing antivirals, such as aciclovir, in treating immunocompromised adults are unlikely to be carried out, as this is now considered unethical. However, the treatment effects of aciclovir are likely to be the same for immunocompromised adults as they are for immunocompromised children.

In clinical practice, treatment of chickenpox in immunocompromised adults is usually initiated with intravenous aciclovir due to the poor absorption of oral aciclovir and the potential risk of rapid disease progression.

DEFINITION

Chickenpox is caused by primary infection with varicella zoster virus. In healthy people, it is usually a mild, self-limiting illness, characterised by low-grade fever, malaise, and a generalised, itchy, vesicular rash. [1] However, severe disease can develop leading to pneumonitis, hepatitis, thrombocytopenia, or encephalitis. Risk of severe disease is higher in pregnancy, in neonates (<28 days of life), and in people who are immunocompromised due to medication or disease. In most people, infection is uncomplicated. The most common complication in immunocompetent people is secondary bacterial skin infection, often seen in children younger than 5 years of age. Less commonly, acute cerebellar ataxia can occur in older children. At all ages, infection can be complicated by soft tissue or deeper invasive group A streptococcal infection. Following primary infection, the varicella zoster virus remains latent in the body. Subsequently, it can re-activate to cause herpes zoster (shingles). The prevention and treatment of herpes zoster is outside the scope of this review (see review on Postherpetic neuralgia).

INCIDENCE/ PREVALENCE

Chickenpox is extremely contagious. More than 90% of unvaccinated people will become infected during their lifetime, but infection occurs at different ages in different parts of the world. In the US, the UK, and Japan, more than 80% of people have been infected by the age of 10 years, and by the age of 20 to 30 years in India, South East Asia, and the Caribbean. [2] [3] [4]

AETIOLOGY/ RISK FACTORS

Chickenpox is caused by primary infection with the varicella zoster virus.

PROGNOSIS

Infants and children In healthy children, the illness is usually mild, self-limiting, and uncomplicated. In the US, mortality in infants and children (aged 1–14 years) with chickenpox was about 7/100,000 in infants, and 1.4/100,000 in children. [5] However, mortality has fallen with the introduction of universal varicella vaccination in the US. [6] In Australia, mortality from chickenpox is about 0.5 to 0.6/100,000 in children aged 1 to 11 years, and about 1.2/100,000 in infants. [7] Bacterial skin sepsis is the most common complication in children under 5 years of age, and acute cerebellar ataxia is the most common complication in older children; both cause hospital admission in 2–3/10,000 children. [1] **Adults** Mortality in adults is higher, at about 31/100,000, reflecting the more severe clinical course seen overall in this age group. [5] Varicella pneumonia is the most common manifestation of severe disease, causing 20 to 30 hospital admissions/10,000 adults. [1] Activation of latent varicella zoster virus infection can cause herpes zoster, also known as shingles (see review on Postherpetic neuralgia). **Cancer chemotherapy** One case series found that more children receiving chemotherapy developed progressive chickenpox with multiple organ involvement compared with those in remission (19/60 [32%] of children receiving chemotherapy *v* 0/17 [0%] of children in remission), and more children died (4/60 [7%] of children receiving chemotherapy *v* 0/17 [0%] of children in remission). [8] **HIV infection** One retrospective case series (45 children with AIDS; no treatment reported) found that one in four (25%) children with AIDS who acquired chickenpox in hospital developed pneumonia, and 5% died. [9] In a retrospective cohort study (73 children with HIV and chickenpox; 83% with symptomatic HIV; 14 children received varicella zoster immunoglobulin, of which nine received varicella zoster immunoglobulin within 48 hours of exposure), infection beyond 2 months occurred in 10 children (14%), and recurrent varicella zoster virus infections occurred in 38 children (55%). There was a strong association between an increasing number of recurrences and low CD4 cell counts. [10] Half of recurrent infections involved generalised rashes, and the other half had zoster. **Newborns** Newborns are at high risk if they develop chickenpox within the first 28 days of life. Exposure in these cases is often from a mother who has been infected with the varicella zoster virus in late pregnancy. If the mother develops a rash between 7 days before to 7 days after delivery, there will be no passive transfer of protective antibody from the mother to the baby, putting the neonate at high risk. We found no cohort studies of untreated children with perinatal exposure to chickenpox. One cohort study (281 neonates receiving varicella zoster immunoglobulin because their mothers had developed a chickenpox rash during the month before or after delivery) found that 134 (48%) developed a chickenpox rash and 19 (14%) developed severe chickenpox. [11] Sixteen (84%) of the 19 cases of severe chickenpox occurred in neonates of mothers whose rash had started between 4 days before and 2 days after delivery. [11] **Pregnancy** There is a higher risk of severe chickenpox at all stages of pregnancy. During the first trimester there is a risk of developing fetal varicella syndrome which may lead to fetal death, even with non-severe maternal disease.

AIMS OF INTERVENTION

To reduce the duration of illness and complications of chickenpox, with minimal adverse effects of treatment.

OUTCOMES **Duration of illness** (time to no new lesions, and disappearance of fever); **disease severity**; **complications of chickenpox**; **mortality**; **adverse effects**.

METHODS **Search strategy** *BMJ Clinical Evidence* search and appraisal January 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to January 2014, Embase 1980 to February 2014, The Cochrane Database of Systematic Reviews 2013, issue 12 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded, and containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the review. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Data and quality** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue which may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatment for chickenpox in healthy adults and children (including neonates) within 24 hours after onset of rash?**

OPTION **ACICLOVIR (WITHIN 24 HOURS AFTER ONSET OF RASH) FOR TREATMENT IN HEALTHY ADULTS AND CHILDREN (INCLUDING NEONATES)**

- For GRADE evaluation of interventions for Chickenpox: treatment, see table, p 13 .
- Oral aciclovir may be more effective than placebo at treating chickenpox in otherwise-healthy children if administered within 24 hours of onset of rash.
- Oral aciclovir seems to be more effective than placebo at treating chickenpox in otherwise-healthy adults if administered within 24 hours of onset of rash.

Benefits and harms

Aciclovir (within 24 hours after onset of rash) versus placebo in healthy children (including neonates):

We found one systematic review (search date 2008), which included three RCTs comparing aciclovir with placebo, given within 24 hours of onset of rash in otherwise-healthy children and adolescents aged 0 to 18 years. [12]

Duration of illness

Aciclovir compared with placebo in healthy children Aciclovir given within 24 hours of onset of rash may be more effective at reducing the duration of fever in otherwise healthy children, but is no more effective at reducing the time to no new lesions (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to no new lesions					
[12] Systematic review	979 children and adolescents 3 RCTs in this analysis	**Time to no new lesions** with aciclovir (n = 450) with placebo (n = 438) See Further information on studies	MD –0.8 days P = 0.055 95% CI –1.6 days to +0.02 days Significant heterogeneity (P = 0.00003), I^2 = 91%	⟷	Not significant
Duration of fever					
[12] Systematic review	979 children and adolescents 3 RCTs in this analysis	**Duration of fever** with aciclovir (n = 429) with placebo (n = 427) See Further information on studies	MD –1.1 days 95% CI –1.3 days to –0.9 days P <0.00001	○○○	aciclovir given within 24 hours of onset of rash

Mortality

No data from the following reference on this outcome. [12]

Complications of chickenpox

No data from the following reference on this outcome. [12]

Disease severity

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	979 children and adolescents 3 RCTs in this analysis	**Adverse effects** with aciclovir	The review found no significant differences between treatment and control groups, or unfavourable trends in children tak-		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with placebo	ing aciclovir (no further data reported)		

Aciclovir (within 24 hours after onset of rash) versus placebo in healthy adults:

We found one systematic review (search date 1997, 3 RCTs). [13] The review did not perform a meta-analysis, and so we report data from relevant studies separately. Two RCTs compared aciclovir given more than 24 hours after the onset of rash versus placebo and are not discussed here.

Duration of illness

Aciclovir compared with placebo in healthy adults Aciclovir given within the first 24 hours of onset of rash seems more effective at reducing the time to full crusting in otherwise healthy adults (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to full crusting					
[13] Systematic review	148 adults Data from 1 RCT	**Time to full crusting** 5.6 days with aciclovir 7.4 days with placebo 76 people in this analysis The RCT also assessed the effects of late administration of aciclovir versus placebo	P = 0.001	○○○	aciclovir given within 24 hours of rash

Mortality

No data from the following reference on this outcome. [13]

Complications of chickenpox

No data from the following reference on this outcome. [13]

Disease severity

Aciclovir compared with placebo in healthy adults Aciclovir given within the first 24 hours of onset of rash seems more effective at reducing the number of lesions in otherwise healthy adults (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Number of lesions					
[13] Systematic review	148 adults Data from 1 RCT	**Number of lesions** 268 lesions with aciclovir 500 lesions with placebo 76 people in this analysis The RCT also assessed the effects of late administration of aciclovir versus placebo	P = 0.04	○○○	aciclovir given within 24 hours of rash

Adverse effects

No data from the following reference on this outcome. [13]

Further information on studies

[12] The systematic review noted that all three RCTs in the analysis had unclear allocation concealment and were sponsored by pharmaceutical companies. For 'time to no new lesions', a sensitivity analysis removing one study (where the systematic review authors had substituted the median for the mean) gave an overall significant result (–1.2 days, 95% CI –1.4 to –1.0) and heterogeneity (I^2) was reduced from 91% to 0%. The systematic review concluded that the clinical importance of aciclovir treatment in otherwise-healthy children remains uncertain.

Comment: In healthy people who make an uneventful recovery from chickenpox without treatment, the effect on the measured outcomes was small and of questionable clinical importance.

Clinical guide

Evidence is sparse, but symptomatic treatments are commonly used in practice, and may be beneficial. Paracetamol is used to reduce fever, topical calamine or crotamiton to soothe the skin and possibly relieve itching, and a sedating antihistamine at night to help sleep and possibly break the itch-scratch-itch cycle.

Should viral complications of chickenpox (e.g., pneumonia or encephalitis) develop in healthy people, aciclovir is indicated, irrespective of time of onset.

Aciclovir was the earliest developed antiviral for varicella zoster virus infection. It is available both orally and intravenously for systemic therapy. Other antivirals for varicella zoster include valaciclovir and famciclovir. Valaciclovir is an oral pro-drug of aciclovir with better bio-availability than oral aciclovir. We found no placebo-controlled RCTs for valaciclovir in treating chickenpox. However, the effects of valaciclovir are likely to be similar to aciclovir. Famciclovir is an oral pro-drug of penciclovir, and is only licensed for use in herpes zoster and genital herpes simplex virus infection. It has a similar mechanism of action to aciclovir; therefore, the effects of famciclovir are likely to be similar to aciclovir. Again, we found no placebo-controlled RCTs for famciclovir in treating chickenpox. Furthermore, we found no head-to-head comparisons of valaciclovir or famciclovir versus aciclovir. The lack of evidence for valaciclovir and famciclovir may be due, in part, to the available published literature for aciclovir.

QUESTION What are the effects of treatment for chickenpox in healthy adults and children (including neonates) later than 24 hours after onset of rash?

OPTION ACICLOVIR (LATER THAN 24 HOURS AFTER ONSET OF RASH) FOR TREATMENT IN HEALTHY ADULTS AND CHILDREN (INCLUDING NEONATES)

- For GRADE evaluation of interventions for Chickenpox: treatment, see table, p 13 .
- When given later than 24 hours after onset of rash, aciclovir does not seem so effective for treatment of chickenpox in otherwise-healthy adults compared with placebo, although the evidence is sparse.
- We found no direct information from RCTs comparing aciclovir given later than 24 hours after onset of rash versus no active treatment in otherwise-healthy children and adolescents.
- In clinical practice, intravenous aciclovir can be used to treat severe disease irrespective of time of onset of rash. However, this is not based on RCT evidence, as such studies would be considered unethical.

Benefits and harms

Aciclovir (later than 24 hours after onset of rash) versus placebo in healthy adults:

We found one systematic review (search date 1997, 3 RCTs). [13] It did not perform a meta-analysis.

Duration of illness

Aciclovir compared with placebo Aciclovir started later than 24 hours after the onset of rash seems no more effective at reducing the time to full crusting or time to no new lesions in otherwise-healthy adults (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to full crusting					
[13] Systematic review	148 adults Data from 1 RCT	**Time to full crusting** 7 days with aciclovir given 24 to 72 hours after onset of rash 6.8 days with placebo 72 people in this analysis The RCT also assessed the effects of early administration of aciclovir (within 24 hours of rash) versus placebo	P >0.2	⟷	Not significant
Time to no new lesions					
[13] Systematic review	68 adults Data from 1 RCT	**Time to no new lesions** 1 day with aciclovir given >24 hours after onset of rash 1 day with placebo	P = 0.55	⟷	Not significant
[13] Systematic review	100 adults Data from 1 RCT	**Time to no new lesions** with aciclovir given >24 hours after onset of rash with placebo Absolute results not reported	P values reported separately for different severities of eruption; all P >0.05	⟷	Not significant

Mortality

No data from the following reference on this outcome. [13]

Complications of chickenpox

No data from the following reference on this outcome. [13]

Disease severity

No data from the following reference on this outcome. [13]

Adverse effects

No data from the following reference on this outcome. [13]

Different timings of administration of aciclovir (later than 24 hours after onset of rash) versus each other in healthy adults and children:

We found one RCT. [14]

Duration of illness

Starting aciclovir on second day from onset of rash compared with starting aciclovir on third day from onset of rash

Aciclovir started on the second day from onset of rash may be more effective at reducing the duration of rash in healthy children, and it may be more effective at reducing duration of fever in adolescents. However, we don't know how starting aciclovir on the second day of rash compares with starting aciclovir on the third day at reducing rash in adolescents and adults, or at reducing fever in children and adults (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of rash					
[14] RCT	77 children, adolescents, and adults	**Median number of days to no new lesions in children** 4 days with aciclovir started on second day from onset of rash 5 days with aciclovir started on third day from onset of rash	P <0.04	○○○	aciclovir started on second day from onset of rash
[14] RCT	77 children, adolescents, and adults	**Median number of days to no new lesions in adolescents and adults** with aciclovir started on second day from onset of rash with aciclovir started on third day from onset of rash Absolute results not reported	P >0.05	⟷	Not significant
Duration of fever					
[14] RCT	77 children, adolescents, and adults	**Median number of days to lowering of fever in adolescents** 2 to 3 days with aciclovir started on second day from onset of rash 3 to 4 days with aciclovir started on third day from onset of rash	P <0.02	○○○	aciclovir started on second day from onset of rash
[14] RCT	77 children, adolescents, and adults	**Median number of days to lowering of fever in children and adults** with aciclovir started on the second day from onset of rash with aciclovir started on the third day from onset of rash Absolute results not reported	P >0.05	⟷	Not significant

Mortality

No data from the following reference on this outcome. [14]

Complications of chickenpox

No data from the following reference on this outcome. [14]

Disease severity

No data from the following reference on this outcome. [14]

Adverse effects

No data from the following reference on this outcome. [14]

Comment: **Clinical guide**

See Comment section for Aciclovir (within 24 hours after onset of rash) for treatment in healthy adults and children (including neonates), p 3 .

Although there have been no placebo-controlled studies of aciclovir for the treatment of people with severe disease (i.e., with complications such as hepatitis, pneumonitis, thrombocytopenia, or encephalitis), it is considered standard practice to use intravenous aciclovir in these individuals, irrespective of time of onset. Placebo-controlled studies of aciclovir for severe disease are unlikely to be carried out as they would be considered unethical.

QUESTION What are the effects of treatment for chickenpox in immunocompromised adults and children (including neonates)?

OPTION ACICLOVIR FOR TREATMENT IN IMMUNOCOMPROMISED ADULTS

- For GRADE evaluation of interventions for Chickenpox: treatment, see table, p 13 .
- We found no direct information from RCTs about the effects of aciclovir for treating chickenpox in immunocompromised adults (see Comment section). However, the effects of aciclovir are likely to be the same for immunocompromised adults as they are for immunocompromised children.

Benefits and harms

Aciclovir:

We found no systematic review or RCTs assessing aciclovir for treating chickenpox in immunocompromised adults (see Comment section, p 9). However, the effects of aciclovir are likely to be the same for immunocompromised adults as they are for immunocompromised children.

Comment: Despite scarce evidence, aciclovir is indicated in immunocompromised people because of the poor prognosis without treatment and the relatively minor harmful effects of the drug. Placebo-controlled RCTs assessing antivirals, such as aciclovir, in immunocompromised adults are unlikely to be carried out as this is now considered unethical — see Comment section for Aciclovir (within 24 hours after onset of rash) for treatment in healthy adults and children (including neonates), p 3 . However, the effects of aciclovir are likely to be the same for immunocompromised adults as they are for immunocompromised children — see option on Aciclovir treatment in immunocompromised children (including neonates), p 10 .

In clinical practice, treatment of chickenpox in immunocompromised adults is usually initiated with intravenous aciclovir due to the poor absorption of oral aciclovir and the potential risk of rapid disease progression.

OPTION ACICLOVIR FOR TREATMENT IN IMMUNOCOMPROMISED CHILDREN (INCLUDING NEONATES)

- For GRADE evaluation of interventions for Chickenpox: treatment, see table, p 13 .
- In children with malignancy and receiving chemotherapy, intravenous aciclovir may reduce time to full crusting and clinical deterioration from chickenpox compared to placebo.

Benefits and harms

Intravenous aciclovir versus placebo in immunocompromised children:

We found two placebo-controlled RCTs of intravenous aciclovir in children with cancer who were receiving chemotherapy. [15] [16]

Duration of illness

Intravenous aciclovir compared with placebo Intravenous aciclovir may be more effective at reducing time to full crusting of lesions in children with cancer who are receiving chemotherapy. However, we don't know whether intravenous aciclovir is more effective at reducing duration of fever (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to full crusting					
[15] RCT	50 children with cancer, aged 1 to 14 years, with chickenpox, 60% of whom had a rash for >24 hours	**Time to full crusting of lesions (children not transferred to open-label aciclovir)** 5.7 days with aciclovir 7.1 days with placebo	P <0.013 Exclusion from the analysis of children taking placebo who deteriorated clinically means that the effect of placebo may have been over-estimated	◌◌◌	aciclovir
Duration of fever					
[15] RCT	50 children with cancer, aged 1 to 14 years, with chickenpox, 60% of whom had a rash for >24 hours	**Duration of fever (children not transferred to open-label aciclovir)** with aciclovir with placebo Absolute results not reported	Reported as not significant P value not reported Exclusion from the analysis of children taking placebo who deteriorated clinically means that the effect of placebo may have been over-estimated	⟷	Not significant

No data from the following reference on this outcome. [16]

Disease severity

Intravenous aciclovir compared with placebo In children with cancer who are receiving chemotherapy, intravenous aciclovir may be more effective at reducing the proportion of children who deteriorate clinically (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical deterioration					
[15] RCT	50 children with cancer, aged 1 to 14 years, with chickenpox, 60% of whom had a rash for >24 hours	**Proportion of children who deteriorated clinically (transferred to open-label aciclovir)** 1/25 (4%) with aciclovir 12/25 (48%) with placebo	RR 0.08 95% CI 0.01 to 0.59	●●●	aciclovir
[16] RCT	20 children with cancer, mean age 6.4 years	**Proportion of children who deteriorated clinically (transferred to open-label aciclovir)** 1/8 (12%) with aciclovir 5/12 (42%) with placebo	RR 0.30 95% CI 0.04 to 2.10 RCT was too small to exclude a clinically important difference	⟷	Not significant

Mortality

No data from the following reference on this outcome. [15] [16]

Complications of chickenpox

No data from the following reference on this outcome. [15] [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT	50 children with cancer, aged 1 to 14 years, with chickenpox, 60% of whom had a rash for >24 hours	**Adverse effects** with aciclovir with placebo 2/25 (8%) children on aciclovir developed transient elevated blood urea nitrogen levels, compared with 2 children who developed other transient minor adverse effects on placebo	Significance not assessed		
[16] RCT	20 children with cancer, mean age 6.4 years	**Adverse effects** with aciclovir with placebo The RCT reported no adverse effects in the 8 children receiving aciclovir, except 1 child with a self-limiting maculopapular rash lasting 1 day	Significance not assessed		

Comment: Despite scarce evidence, intravenous aciclovir is indicated in immunocompromised children (including neonates) because of the poor prognosis without treatment and the relatively minor harmful effects of the drug — see Comment section for Aciclovir (within 24 hours after onset of rash) for treatment in healthy adults and children (including neonates), p 3 .

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Varicella zoster immunoglobulin (VZIG) Prepared from units of donor plasma selected for high titres of antibodies to varicella zoster virus.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Aciclovir (later than 24 hours after onset of rash) for treatment in healthy adults and children (including neonates) Evidence re-evaluated. Categorisation changed from 'unknown effectivenss' to 'unlikely to be beneficial'.

Aciclovir for treatment in immunocompromised adults Existing evidence re-evaluated. Categorisation changed from 'unknown effectiveness' to 'likely to be beneficial' by consensus.

REFERENCES

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GRADE **Evaluation of interventions for Chickenpox: treatment.**

Important outcomes			Complications of chickenpox, Disease severity, Duration of illness, Mortality						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatment for chickenpox in healthy adults and children (including neonates) within 24 hours after onset of rash?									
3 (979) [12]	Duration of illness	Aciclovir (within 24 hours after onset of rash) versus placebo in healthy children (including neonates)	4	–2	0	0	0	Low	Quality points deducted for unclear allocation concealment and pharmaceutical-sponsored studies
1 (76) [13]	Duration of illness	Aciclovir (within 24 hours after onset of rash) versus placebo in healthy adults	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (76) [13]	Disease severity	Aciclovir (within 24 hours after onset of rash) versus placebo in healthy adults	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of treatment for chickenpox in healthy adults and children (including neonates) later than 24 hours after onset of rash?									
3 (240) [13]	Duration of illness	Aciclovir (later than 24 hours after onset of rash) versus placebo in healthy adults	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (77) [14]	Duration of illness	Different timings of administration of aciclovir (later than 24 hours after onset of rash) versus each other in healthy adults and children	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; consistency point deducted for conflicting results in children and adolescents
What are the effects of treatment for chickenpox in immunocompromised adults and children (including neonates)?									
1 (50) [15]	Duration of illness	Intravenous aciclovir versus placebo in immunocompromised children	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and possibility of over-estimation of effect of placebo; directness point deducted for narrow population
2 (70) [15] [16]	Disease severity	Intravenous aciclovir versus placebo in immunocompromised children	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and possibility of over-estimation of effect of placebo; directness point deducted for narrow population

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.