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Acyclovir for treating varicella in otherwise healthy children and adolescents: a systematic review of randomised controlled trials

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Abstract

Background: Acyclovir has the potential to shorten the course of chickenpox which may result in reduced costs and morbidity. We conducted a systematic review of randomised controlled trials that evaluated acyclovir for the treatment of chickenpox in otherwise healthy children.

Methods: MEDLINE, EMBASE, and the Cochrane Library were searched. The reference lists of relevant articles were examined and primary authors and Glaxo Wellcome were contacted to identify additional trials. Two reviewers independently screened studies for inclusion, assessed study quality using the Jadad scale and allocation concealment, and extracted data. Continuous data were converted to a weighted mean difference (WMD). Overall estimates were not calculated due to differences in the age groups studied.

Results: Three studies were included. Methodological quality was 3 (n = 2) and 4 (n = 1) on the Jadad scale. Acyclovir was associated with a significant reduction in the number of days with fever, from -1.0 (95% CI -1.5,-0.5) to -1.3 (95% CI -2.0,-0.6). Results were inconsistent with respect to the number of days to no new lesions, the maximum number of lesions and relief of pruritis. There were no clinically important differences between acyclovir and placebo with respect to complications or adverse effects.

Conclusion: Acyclovir appears to be effective in reducing the number of days with fever among otherwise healthy children with chickenpox. The results were inconsistent with respect to the number of days to no new lesions, the maximum number of lesions and the relief of itchiness. The clinical importance of acyclovir treatment in otherwise healthy children remains controversial.

Background

Varicella, or chickenpox, is a common, highly contagious illness caused by the varicella-zoster virus (VZV) [1]. It is primarily a disease of early childhood with 90% of cases occurring in children 1 to 14 years of age [2]. The disease spreads by direct person-to-person contact of open lesions or airborne droplets [1], and tends to increase in severity with each subsequent case within a household [3]. The period of transmission begins one to two days before any rash appears [4] and continues for the first five to six days [1]. The disease may be more severe in neonates [5,6], adults [7], and individuals who have impaired immune

systems [8,9]. After one episode of varicella, individuals usually have lifelong immunity [1].

Chickenpox is generally self-limiting in young children and is manifested by fever, mild constitutional symptoms, and a pruritic, vesicular rash. Symptoms usually appear 11–20 days after exposure to VZV [2]. The rash most often appears in three successive crops of lesions numbering on average 300 to 400 [10]. The lesions progress from macules through to crusted lesions over a three-day period [11]. The rash is most commonly distributed over the trunk, scalp and face. Diagnosis can be made clinically by the rash characteristic of chickenpox [2] and a history of contact [1].

Complications of chicken pox are varied and may occur in 5–10% of all patients. Complications among otherwise healthy children are rare [12,13], but are more common among neonates, adults and immunocompromised individuals [2,14]. Data with respect to complication rates among specific subgroups are lacking. Complications primarily involve the skin, the central nervous system, and the respiratory system [13,15]. The most frequent complication is bacterial infection secondary to cutaneous lesions [2,13]. The most common neurological complications are cerebellar ataxia and encephalitis. Complications of the respiratory system include pneumonia and upper respiratory tract infections (particularly otitis media).

Traditional treatment for chickenpox is symptomatic through the use of lotions to relieve itchiness [1] and acetaminophen to reduce fever and pain [4]. Newer treatments include immunoglobulins, vaccines, and anti-viral drugs for the prevention of chicken pox, as well as immunoglobulins and anti-viral drugs to moderate and shorten the course of the disease. As an anti-viral drug, acyclovir prevents the replication of the VZV [16,17] and has the potential to eradicate VZV and relieve symptoms more rapidly. Since the drug is only absorbed by the cells that are infected with the virus, acyclovir has minimal adverse effects [18]. Some reported adverse effects to the oral administration of acyclovir include nausea, vomiting, diarrhea, and vertigo [18].

The economic burden associated with chickenpox results from costs associated with hospitalisations, physician visits, prescription and non-prescription medications, and lost income by caregivers who must remain at home during the course of the child's illness [19]. It has been estimated that lost wages account for more than 95% of the total costs [20]. The U.S. Centers for Disease Control and Prevention recommend that children remain at home for six days after the rash onset [10]. These recommendations vary according to local public health authorities; others advocate return to normal activity earlier, particularly with milder forms of the disease [21]. The Canadian Pediatric Society recommends that children return to school as soon as they feel well enough to resume normal activities, regardless of the state of the rash [22]. Because of the potential costs associated with lost time from work by primary caregivers, an intervention that reduces the length of illness may be well received.

We conducted a systematic review to assess the evidence on the efficacy of acyclovir in: (a) alleviating symptoms (number of lesions, pruritis, fever); and, (b) shortening the duration of the illness. The secondary objective was to examine complications of chickenpox and adverse effects associated with acyclovir, as reported in the relevant efficacy trials. This review was conducted in association with the Acute Respiratory Infections Group of The Cochrane Collaboration [23].

Methods

A comprehensive search was conducted to identify all relevant studies regardless of language of publication or publication status. MEDLINE (1966-October 2001), EMBASE (1988-September 2001), and the Cochrane Controlled Trials Register (2002, Issue 2) were searched. The reference lists of all relevant articles were reviewed for additional studies. A letter was sent to the primary author of relevant studies as well as the pharmaceutical company that manufactures acyclovir (GlaxoSmithKline) in order to identify any other relevant trials. Finally, PubMed was searched towards the completion of the review to identify any recent publications (January 2001-April 2002). The complete search strategies are presented in an additional file (See Additional File 1: search_strategies.pdf).

The output from the searches was screened independently by two reviewers (NW, EMB or LH). All potentially relevant studies were retrieved as full manuscripts and then independently reviewed for inclusion according to established criteria. Differences regarding inclusion were resolved by consensus reached after discussion. Studies were included if they: 1) were randomised controlled trials; 2) evaluated otherwise healthy children 0–18 years of age who had chickenpox; 3) compared acyclovir to placebo; 4) evaluated at least one objective outcome (i.e., amount of time to no new lesions, maximum number of lesions, time to resolution of fever and pruritis, complications, and adverse events).

All relevant studies were masked by obscuring the authors' names and institutions, the locations of the study, reference lists, journal of publication and any other potential identifiers. Each of the included studies was evaluated for methodological quality using the previously validated Jadad 5-point scale to assess randomisation (0–2 points),

double blinding (0–2 points) and withdrawals and dropouts (0–1 point) [24]. Concealment of allocation was described as adequate, inadequate or unclear [25]. Two observers independently assessed quality (NW, TPK). Differences were resolved by consensus.

Data were extracted using a structured form that captured the following information: patient demographics; patient status (inpatient or outpatient); the intervention (including dosage and route of administration); outcomes (i.e. length of time from randomisation to no new lesions, crusting, defervescence (i.e. reduction in fever), and cessation of pruritis); funding source; and, whether the studies used an intention-to-treat analysis. All complications from chickpox reported in the studies were recorded. As well, information on all adverse effects related to the use of acyclovir was collected. Two reviewers (NW, EMB) extracted data independently, and results were compared. Differences were resolved by referring to the original paper.

Data were analysed using Review Manager 4.1 (Cochrane Collaboration, 2001); Splus 2000 (Insightful Corporation, 1999) was used for imputations. Continuous data (e.g., duration of symptoms in days and maximum number of lesions) were converted to the weighted mean difference (WMD). Medians were substituted for means for all outcomes in the study by Balfour et al. [26]. Means were calculated from proportions of patients remaining with lesions [27], fever [27,28], and pruritis [27]. Day 5 (fever, pruritis) and day 7 (new lesions) were used as the last possible day for the event to occur. These substitutions give less conservative estimates of variance. Interquartile ranges were converted into variances [26]. Imputing using upper bound p-values gave conservative variances in both treatment groups [27,28].

Weighted mean differences were not combined into an overall estimate due to the varied age groups between studies. There were too few studies to consider statistical heterogeneity between studies or to perform subgroup or sensitivity analyses. Publication bias was also not assessed for the same reason. Power analyses for complications were exploratory. Individual study results were pooled and chi-square tests were the bases of the power analyses. Since the adverse event data were not independent (the numbers were reported by event not by patient), risk differences could not be calculated, nor any further analysis.

Results

Description of studies

Five hundred and ninety unique references were retrieved. Eight studies were identified as being potentially relevant. Four of the studies were excluded because they were not RCTs [29–32]; one RCT was excluded because it evaluated immediate versus delayed anti-viral treatment therefore all patients eventually received acyclovir [33]. Three studies were included in this analysis [26–28]. There was 100% agreement between the two reviewers with respect to study relevance.

The three relevant trials are described in Table 1. They were all conducted in the United States and published in English. All three studies were placebo-controlled and evaluated the efficacy of acyclovir among immunocompetent children in an outpatient setting.

Methodological quality of included studies

The quality scores of included studies, as measured by the Jadad scale, were four in one trial [26] and three in the remaining two trials [27,28]. All three studies were described as being randomised and double-blinded. Only one trial described a detailed and appropriate method of randomisation [26]. One trial [26] described an appropriate method of double-blinding. Two of the three trials adequately discussed withdrawals [27,28]. Allocation concealment was unclear in all three trials. Two studies [27,28] performed intention-to-treat analyses on adverse events and on a select few of the remaining outcomes. All three studies received pharmaceutical sponsorship. In addition, two studies received financial support from other external sources [26,28].

Primary outcome: number of days to no new lesions

Two of the studies found a statistically significant advantage to taking acyclovir (figure 1). The number of days to no new lesions was reduced by 1.2 (95% CI -1.5,-1.0) and 1.1 days (95% CI -1.8,-0.5), respectively [27,28]. The third study found no statistically significant difference (0 days; 95% CI-0.5,0.5) [26].

Additional outcomes

The results with respect to the maximum number of lesions appeared to be homogeneous, however, only two of three studies reported a significant difference favouring treatment with acyclovir (figure 2). The WMDs ranged from -24 (95% CI -74,26) [28] to -164 (95% CI -228,-100) [26].

The number of days to no fever was reduced by treatment with acyclovir in all three trials: -1.1 days (95% CI-1.3,-0.9), -1.0 (95% CI -1.5,-0.5), and -1.3 (95% CI -2.0,-0.6) [27,26,28] (figure 3).

The number of days to relief of pruritis was reported in two studies: Dunkle et al. found a 0.8 day advantage with acyclovir treatment (95% CI -1.0,-0.7) [27] and Balfour et al., found no advantage (0 days; 95% CI -0.6,0.6) [26] (figure 4).

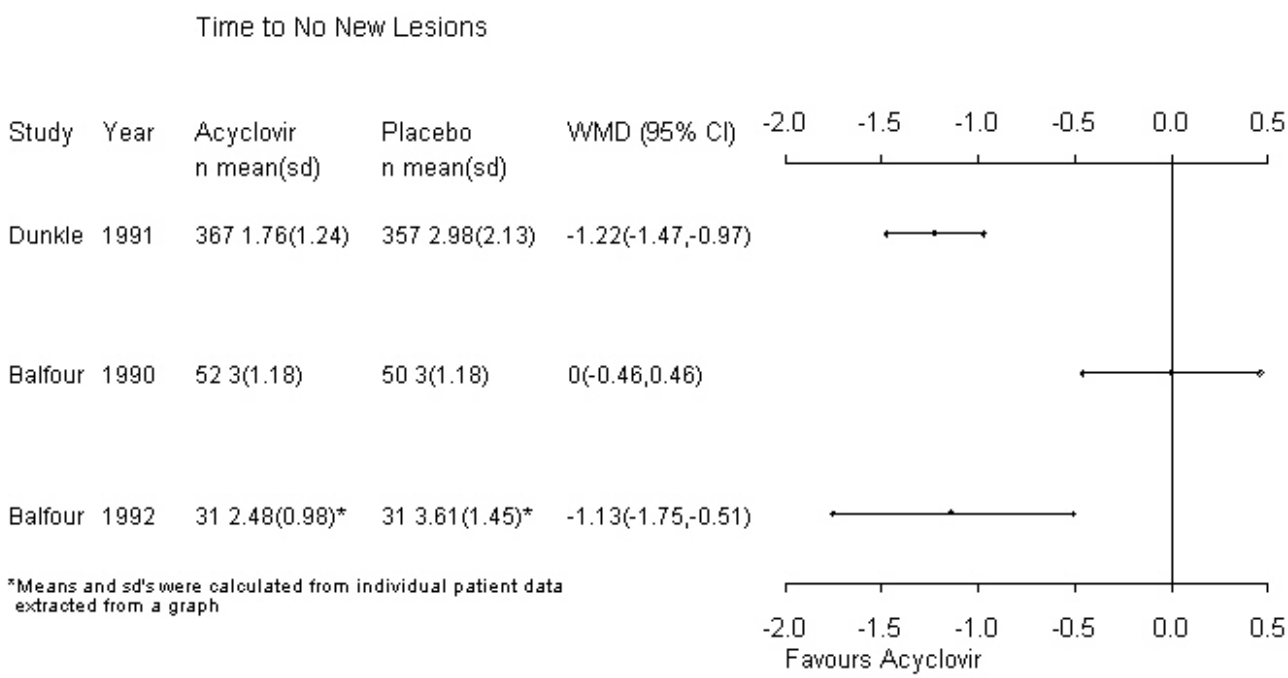

Figure 1
Metagraph of Acyclovir versus Placebo: time to no new lesions

Table 1: Characteristics of randomised controlled trials comparing acyclovir to placebo among immunocompetent children

Study	Number of participants		Age Range (mean)	Acyclovir protocol	Outcomes	Quality	
	Total	Per group				Jadad Score	Allocation Concealment
Balfour 1990	102	50 – acyclovir 50 – placebo	5–16 years (8.1)	5–7 years: 20 mg/kg 7–12 years: 15 mg/kg 12–16 years: 10 mg/kg 4x/days for 5-7 days	• Days to fever, crusting, no new lesions, maximum number of lesions, decrease in number of lesions and cessation of itching • Maximum number of lesions	4	Unclear
Dunkle 1991	815	408 – acyclovir 407 – placebo	2–12 years (5.2)	20 mg/kg 4×/day for 5 days	• Maximum number of lesions • Number with >500 lesions • Residual lesions at day 28	3	Unclear
Balfour 1992	62	31 – acyclovir 31 – placebo	13–18 years (14.8)	800 mg 4×/day for 5 days	• Days to maximum number of lesions and cessation of itching • Maximum number of lesions • Residual lesions at day 28	3	Unclear

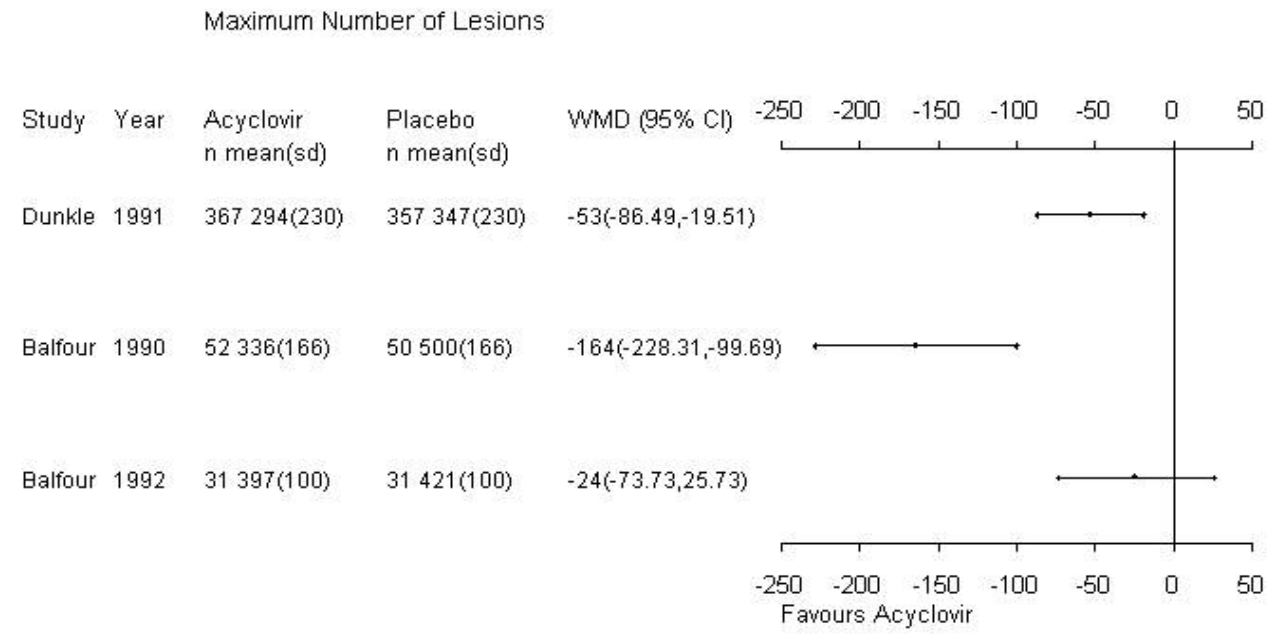

Figure 2
Metagraph of Acyclovir versus Placebo: maximum number of lesions

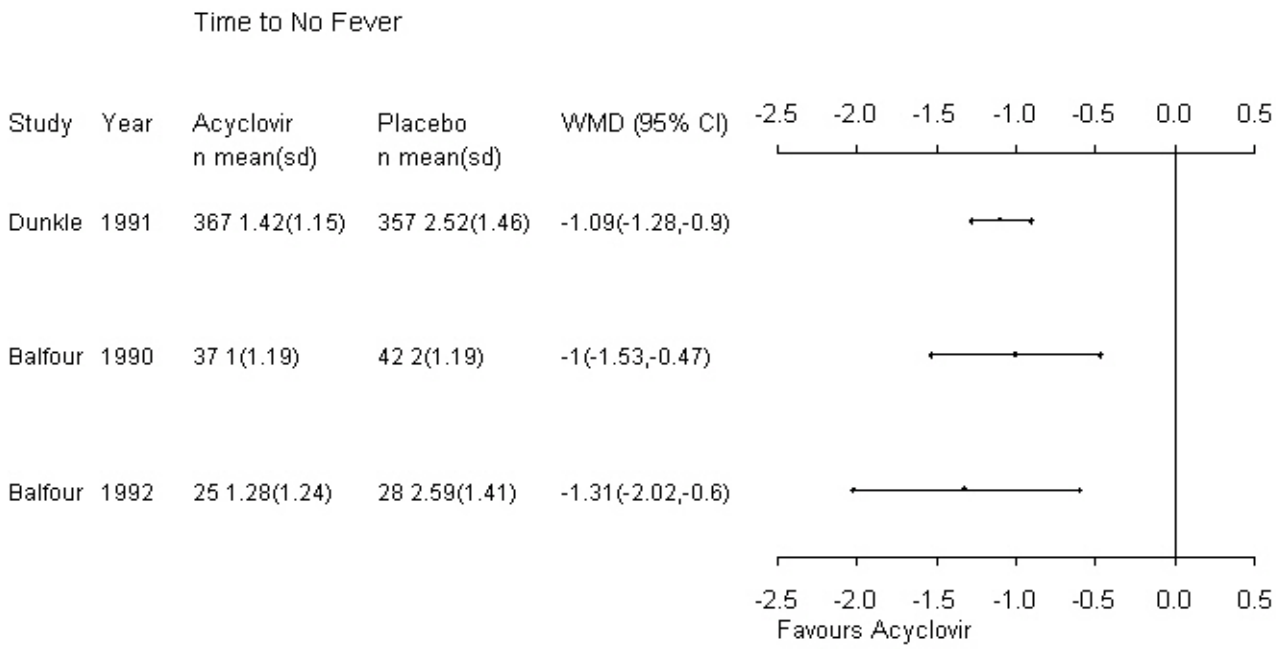

Figure 3
Metagraph of Acyclovir versus Placebo: time to no fever

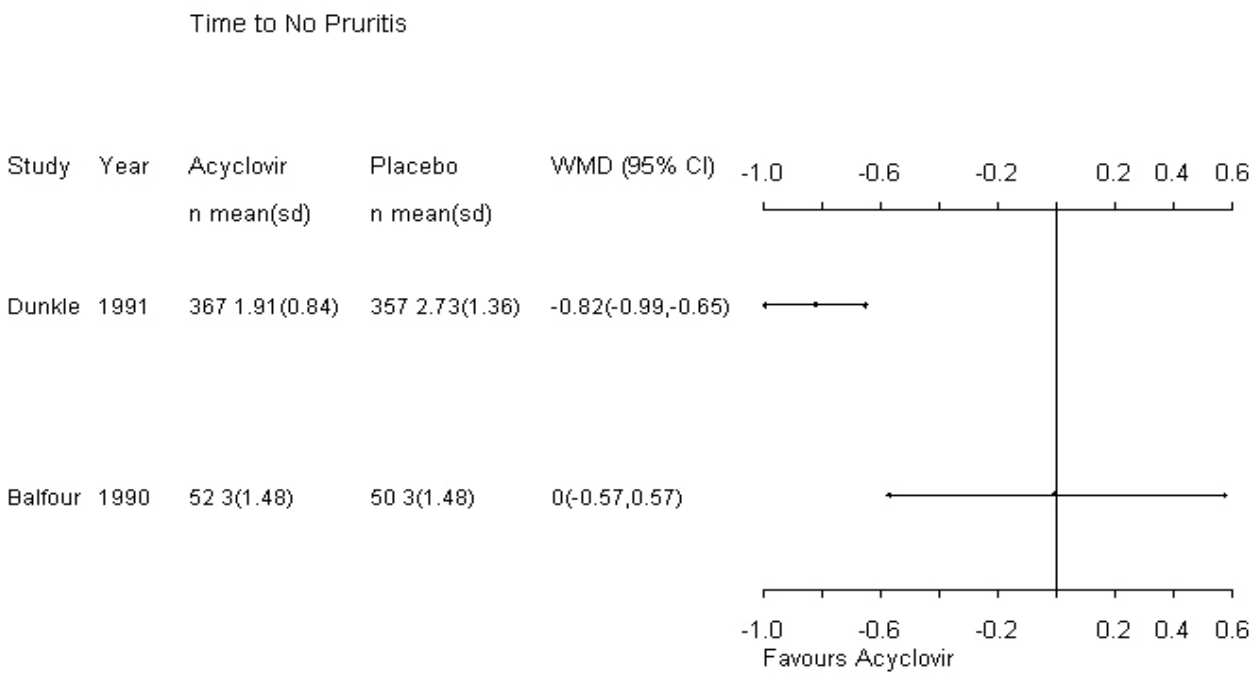

Figure 4
Metagraph of Acyclovir versus Placebo: time to no pruritis

The earlier Balfour study [26] results were imputed from non-parametric data and may have produced less precise results. If so, this may indicate a stronger advantage for taking acyclovir in the number of days to no new lesions and relief of itching. This might also indicate a smaller advantage for taking acyclovir in reducing the maximum number of lesions.

Adverse effects

Reported adverse effects related to the use of acyclovir involving the gastrointestinal system included: anorexia (23 acyclovir; 30 placebo); diarrhea (25 acyclovir; 18 placebo); nausea/vomiting (11 acyclovir; 10 placebo); stomach ache/abdominal pain (22 acyclovir; 14 placebo); flatulence (2 acyclovir; 4 placebo). Those involving the respiratory system included: coryza (18 acyclovir; 23 placebo); cough (23 acyclovir; 29 placebo); ear pain/redness (5 acyclovir; 6 placebo); sore throat (24 acyclovir; 33 placebo). The following adverse effects involving the skin were noted: hives (1 acyclovir; 1 placebo); rash, other than varicella (3 acyclovir; 1 placebo). Other reported effects were: conjunctivitis (acyclovir 8; placebo 11); headache (acyclovir 21; placebo 22); malaise (acyclovir 25; placebo 28); irritability (acyclovir 1); skin odour (acyclovir 1); insomnia (acyclovir 5; placebo 5); nose bleed (acyclovir 2; placebo 1); dizziness (acyclovir 3; placebo 2); restlessness (acyclovir 1; placebo 1); arthralgia (placebo 3); frequency (placebo 1); night sweats (placebo 1); hyperkinesias (acyclovir 1; placebo 1); pain (acyclovir 1); spasmodic hand movements (acyclovir 1; placebo 1).

Complications

Complications from chickenpox were grouped by those involving the skin, central nervous system, or respiratory system (figure 5). Fifteen patients developed secondary bacterial skin infections (5 acyclovir; 10 placebo). Central nervous system complications included cerebellar ataxia (1 placebo) and meningoencephalitis (1 placebo). Respiratory ailments included pneumonia (1 acyclovir), otitis media (2 acyclovir; 4 placebo), pharyngitis (2 acyclovir; 2 placebo), and bronchitis (1 acyclovir). There were no significant differences between the treatment groups with respect to all the grouped complications arising from chickenpox. Skin complications gave the largest simply pooled difference at 1%. The review is not sufficiently powered to detect this difference, however, the size of difference is not deemed clinically important. The central nervous system and respiratory simply pooled differences were less than 0.5%.

Discussion

This systematic review of acyclovir for the treatment of chickenpox in otherwise healthy children supports a reduction in disease severity and a shorter course of disease.

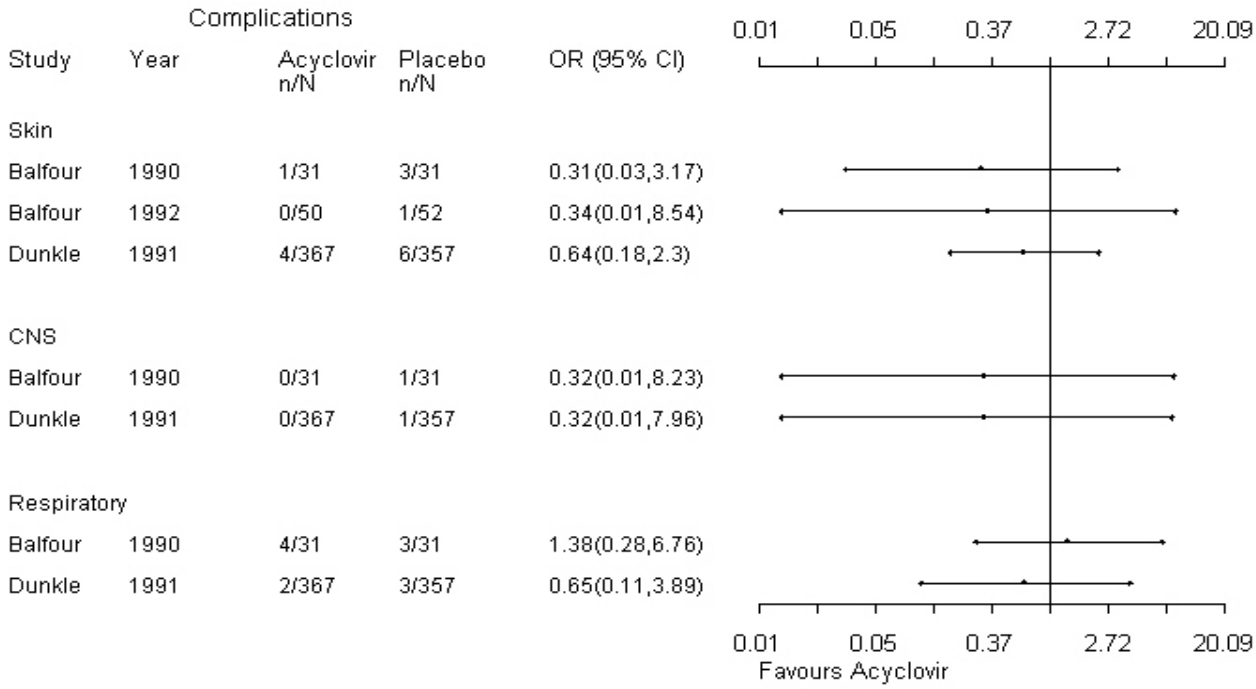

Figure 5
Metagraph of Acyclovir versus Placebo: complications Complications are grouped as skin, CNS and respiratory.

This is demonstrated by a one-day reduction in the number of days with fever. Results were inconsistent, however, with respect to the number of days to no new lesions, the maximum number of lesions and the number of days to relief of pruritis. The results for the earlier Balfour study [26] were imputed from non-parametric data and may therefore be less precise possibly strengthening the evidence that supports the use of acyclovir in otherwise healthy children. There were no clinically important differences between acyclovir and placebo with respect to complications associated with chickenpox or adverse effects associated with the drug.

The quality of the included studies was relatively good as measured by the Jadad scale, thus having a low risk of bias in the studies' conduct. However, caution is heeded when interpreting the results given that all studies had pharmaceutical sponsorship and some of the authors were affiliated with the original manufacturer of acyclovir. Research has shown that study conclusions are associated with authors' affiliations [34,35] and that studies with pharmaceutical sponsorship are more likely to have outcomes favouring the drug under study [36].

We identified only three studies relevant to this review. These studies were heterogeneous in that each studied a different age group. Because of the small number of studies and their different study populations, we did not feel that it was appropriate to provide overall estimates of efficacy. Publication bias was also not assessed because of the small number of trials.

Although these studies have demonstrated the efficacy of acyclovir, the clinical importance of acyclovir treatment in otherwise healthy children remains controversial. The debate in the literature features four common themes:

First, the treatment appears to confer at best modest benefits for a disease that is self-limiting and has few complications in otherwise healthy children [13,19].

Second, trials have demonstrated acyclovir to be efficacious when treatment was initiated within 24 hours of rash onset. Various authors have criticized this as being impractical in that many patients may not detect disease onset, and obtain a prescription until well after this 24-hour window [15,19,37]. In a recent trial Balfour et al. showed that patients who initiated acyclovir within 24 hours of rash onset showed better clinical response to therapy compared to those who initiated treatment at 48 or 72 hours [33]. Further, patients who began therapy after 48 hours responded more favourably than those who

started after 72 hours. Others have questioned the extent of compliance in practice with the treatment regimens that have been studied (i.e., four doses per day) [37,38]. Alterations in compliance may dilute already moderate results [19].

Third, while no formal cost-benefit analysis has been conducted, various critics have suggested that treatment benefits do not justify the additional costs of the drug as well as the physician visits required to obtain a prescription [13,37,38]. If treatment with acyclovir does not significantly alter the complication rate of varicella, then the rate of hospitalisations, and their associated costs, is unlikely to change [36]. In addition, only one study specifically measured the impact of acyclovir treatment on school attendance [26]. This study found no difference in the number of days missed from school between the acyclovir and placebo groups. Treatment with acyclovir may not have a substantial impact on the number of days missed from school as public health authorities in some jurisdictions move towards more permissive policies regarding school attendance following VZV infection [22].

Finally, concerns have been raised regarding the emergence of an acyclovir resistant strain of VZV [13,37–39]. There is evidence to suggest that resistant strains of VZV do not occur [33,40,41].

At present, there appear to be too many unanswered questions to advocate the widespread use of acyclovir in otherwise healthy children. The treatment of chickenpox with acyclovir may become immaterial as public health authorities worldwide move towards adopting the varicella vaccine to protect against VZV [10,15].

This review has raised questions for further research. First a comprehensive cost-benefit analysis is required. Second, there were few data available on the impact of acyclovir on the number of days missed from school or work. If one of the more important advantages of acyclovir is to allow individuals to return to their activities sooner, this needs to be specifically evaluated and documented. Third, there is no evidence regarding different doses of acyclovir treatment. Smaller doses may reduce costs and increase compliance. Fourth, further research needs to focus on the identification and treatment of immunocompetent children who are at higher risk of more severe diseases such as children with chronic respiratory conditions or children exposed through intrafamilial contact. Finally, other antivirals against varicella with improved bioavailability are now available (i.e., valaciclovir and famciclovir) and need to be studied in pediatric populations.

Conclusions

When initiated within 24 hours of rash onset, treatment with acyclovir shows a therapeutic benefit by reducing the length of time with fever in immunocompetent children. However, the results are inconsistent with respect to the number of days to no new lesions, the maximum number of lesions and relief of pruritis. The existing evidence does not support the widespread use of acyclovir among young immunocompetent children in which chickenpox is self-limiting and results in few complications.

Competing interests

None declared.

Authors' contributions

TPK conducted the quality assessment, provided overall methodological and clinical expertise, and contributed to the final manuscript. EMB screened studies for inclusion, performed data extraction, and contributed to the final manuscript. NW screened studies for inclusion, performed the statistical analyses and quality assessment, and contributed to the final manuscript. LH assisted with searching and screening studies for inclusion, provided input on the analyses, and contributed to the final manuscript. All authors read and approved the final manuscript.

Additional material

Additional file 1

Search strategies This file contains the detailed search strategies for MEDLINE, EMBASE, CENTRAL (Cochrane Library), and PubMed.
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