Interventions for pityriasis rosea

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[Intervention Review]

Interventions for pityriasis rosea

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ABSTRACT

Background

Pityriasis rosea is a scaly, itchy rash that mainly affects young adults and lasts for 2 to 12 weeks. The effects of many available treatments are uncertain. This is an update of a Cochrane Review first published in 2007.

Objectives

To assess the effects of interventions for the management of pityriasis rosea in any individual diagnosed by a medical practitioner.

Search methods

We updated our searches of the following databases to October 2018: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS. We searched five trials registers. We also checked the reference lists of included and excluded studies, contacted trial authors, scanned the abstracts from major dermatology conference proceedings, and searched the CAB Abstracts database. We searched PubMed for adverse effects to November 2018.

Selection criteria

Randomised controlled trials of interventions in pityriasis rosea. Treatment could be given in a single therapy or in combination. Eligible comparators were no treatment, placebo, vehicle only, another active compound, or placebo radiation treatment.

Data collection and analysis

We used standard methodological procedures expected by the Cochrane. Our key outcomes were good or excellent rash improvement within two weeks, rated separately by the participant and medical practitioner; serious adverse events; resolution of itch within two weeks (participant-rated); reduction in itch score within two weeks (participant-rated); and minor participant-reported adverse events not requiring withdrawal of the treatment.

Main results

We included 14 trials (761 participants). In general, risk of selection bias was unclear or low, but risk of performance bias and reporting bias was high for 21% of the studies.

Participant age ranged from 2 to 60 years, and sex ratio was similar. Disease severity was measured by various severity indices, which the included studies did not categorise. Six studies were conducted in India, three in Iran, two in the Philippines, and one each in Pakistan, the USA, and China. The included studies were conducted in dermatology departments and a paediatric clinic. Study duration ranged from 5 to 26 months. Three studies were funded by drug manufacturers; most studies did not report their funding source. The included studies assessed macrolide antibiotics, an antiviral agent, phototherapy, steroids and antihistamine, and Chinese medicine.

None of the studies measured participant-rated good or excellent rash improvement. All reported outcomes were assessed within two weeks of treatment, except for adverse effects, which were measured throughout treatment.

There is probably no difference between oral clarithromycin and placebo in itch resolution (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.47 to 1.52; 1 study, 28 participants) or rash improvement (medical practitioner-rated) (RR 1.13, 95% CI 0.89 to 1.44; 1 study, 60 participants). For this comparison, there were no serious adverse events (1 study, 60 participants); minor adverse events and reduction in itch score were not measured; and all evidence was of moderate quality.

When compared with placebo, erythromycin may lead to increased rash improvement (medical practitioner-rated) (RR 4.02, 95% CI 0.28 to 56.61; 2 studies, 86 participants, low-quality evidence); however, the 95% CI indicates that the result may also be compatible with a benefit of placebo, and there may be little or no difference between treatments. Itch resolution was not measured, but one study measured reduction in itch score, which is probably larger with erythromycin (MD 3.95, 95% CI 3.37 to 4.53; 34 participants, moderate-quality evidence). In the same single, small trial, none of the participants had a serious adverse event, and there was no clear difference between groups in minor adverse events, which included gastrointestinal upset (RR 2.00, CI 0.20 to 20.04; moderate-quality evidence).

Two trials compared oral azithromycin to placebo or vitamins. There is probably no difference between groups in itch resolution (RR 0.83, 95% CI 0.28 to 2.48) or reduction in itch score (MD 0.04, 95% CI −0.35 to 0.43) (both outcomes based on one study; 70 participants, moderate-quality evidence). Low-quality evidence from two studies indicates there may be no difference between groups in rash improvement (medical practitioner-rated) (RR 1.02, 95% CI 0.52 to 2.00; 119 participants). In these same two studies, no serious adverse events were reported, and there was no clear difference between groups in minor adverse events, specifically mild abdominal pain (RR 5.82, 95% CI 0.72 to 47.10; moderate-quality evidence).

Acyclovir was compared to placebo, vitamins, or no treatment in three trials (all moderate-quality evidence). Based on one trial (21 participants), itch resolution is probably higher with placebo than with acyclovir (RR 0.34, 95% CI 0.12 to 0.94); reduction in itch score was not measured. However, there is probably a significant difference between groups in rash improvement (medical practitioner-rated) in favour of acyclovir versus all comparators (RR 2.45, 95% CI 1.33 to 4.53; 3 studies, 141 participants). Based on the same three studies, there were no serious adverse events in either group, and there was probably no difference between groups in minor adverse events (only one participant in the placebo group experienced abdominal pain and diarrhoea).

One trial compared acyclovir added to standard care (calamine lotion and oral cetirizine) versus standard care alone (24 participants). The addition of acyclovir may lead to increased itch resolution (RR 4.50, 95% CI 1.22 to 16.62) and reduction in itch score (MD 1.26, 95% CI 0.74 to 1.78) compared to standard care alone. Rash improvement (medical practitioner-rated) was not measured. The trial reported no serious adverse events in either group, and there may be no difference between groups in minor adverse events, such as headache (RR 7.00, 95% CI 0.40 to 122.44) (all results based on low-quality evidence).

Authors' conclusions

When compared with placebo or no treatment, oral acyclovir probably leads to increased good or excellent, medical practitioner-rated rash improvement. However, evidence for the effect of acyclovir on itch was inconclusive. We found low- to moderate-quality evidence that erythromycin probably reduces itch more than placebo.

Small study sizes, heterogeneity, and bias in blinding and selective reporting limited our conclusions. Further research is needed to investigate different dose regimens of acyclovir and the effect of antivirals on pityriasis rosea.

PLAIN LANGUAGE SUMMARY

Treatments for pityriasis rosea

Background

Pityriasis rosea is a common scaly rash prevalent in young adults. A patch of redness and scales is followed by widespread rash. Pityriasis rosea usually resolves within 2 to 12 weeks; however, the rash can resemble a serious contagious skin condition, causing concern. Moreover, pityriasis rosea can cause moderate to severe itching, making effective treatment necessary.

Review question

We wanted to evaluate the effectiveness and safety of treatments for pityriasis rosea. Eligible treatments were topical, systemic (oral or injected medicines that work throughout the entire body), or light therapy, given alone or in combination with another treatment, and compared against no treatment, placebo (an identical but inactive treatment), vehicle (inactive ingredients that help deliver an active

treatment) only, or another active treatment. As spontaneous recovery usually occurs between 2 and 12 weeks in cases of untreated pityriasis rosea, we considered outcomes reported at two weeks.

Study characteristics

The evidence is current to October 2018.

We included 14 studies with a total of 761 participants aged between 2 and 60 years (similar numbers of males and females). Most studies were conducted in Asia in dermatology departments and lasted between 5 to 26 months. Three studies were funded by drug manufacturers; most studies did not report their funding sources. Disease severity was assessed by various measures, but participants were not categorised into mild, moderate, or severe disease. Important treatments assessed by the studies included various antibiotics and acyclovir (a drug meant to treat herpes infections), which were compared to placebo, no treatment, or standard care. Additional treatments included phototherapy, corticosteroids and antihistamine, and Chinese medicine (potenline). Most studies assessed treatment used for one week.

All reported outcomes were assessed within two weeks of treatment, except for side effects, which were measured throughout treatment.

None of the included studies reported on the participant's rating of rash improvement. Itch was always participant-assessed. Rash improvement was rated as good or excellent.

There is probably no difference between clarithromycin and placebo in medical practitioner-rated rash improvement or itch resolution, and no serious adverse events were reported (all moderate-quality evidence). Reduction in itch score and minor side effects were not measured.

Similarly, there may be no difference in medical practitioner-rated rash improvement between azithromycin and placebo or vitamins, but erythromycin may lead to increased rash improvement when compared to placebo; however, the results show there may be a benefit with placebo or little or no difference between treatments (low-quality evidence for both outcomes). There is probably no difference between azithromycin and comparators in itch resolution or reduction in itch score; there was no clear difference in minor side effects, such as mild abdominal pain (both moderate-quality evidence). When comparing erythromycin to placebo, itch resolution was not measured, but there is probably a greater reduction in itch score with erythromycin. There was no clear difference in the likelihood of minor side effects, such as gastrointestinal upset, between groups (moderate-quality evidence for both outcomes).

A single study suggested that acyclovir is probably less effective than placebo in achieving itch resolution (but itch score reduction was not measured). However, results from three studies indicate that acyclovir is probably significantly more beneficial than placebo, no treatment, or vitamin tablets in medical practitioner-rated rash improvement. There is probably no difference between acyclovir and placebo in the incidence of minor side effects: one participant in the placebo group experienced mild abdominal pain and diarrhoea (all outcomes based on moderate-quality evidence).

A single trial indicated that acyclovir used in combination with standard care (calamine (anti-itch lotion) and the antihistamine cetirizine) may reduce itch score and increase itch resolution (low-quality evidence). Medical practitioner-rated rash improvement was not measured. There may be no difference between groups in minor side effects, such as headache, increased sleep, sickness, and impact on taste.

None of the studies reported serious adverse events (low- to moderate-quality evidence).

Quality of the evidence

The quality of the evidence for the main comparisons was low to moderate. Many of the results were based on a small number of trials, with a low number of participants. There was also some variation amongst the trial results and concerns over study design.

Summary of findings for the main comparison. Clarithromycin compared to placebo for pityriasis rosea

Clarithromycin compared to placebo for pityriasis rosea

Patient or population: pityriasis rosea
Setting: outpatient dermatology clinic
Intervention: clarithromycin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with clarithromycin				
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by the participant	-	-	-	-	-	Not measured
Serious adverse events, i.e. serious enough to require withdrawal of the treatment	-	-	Not estimable	60 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	No participants in either group experienced serious adverse events.
The proportion of participants with resolution of itch within 2 weeks, as rated by the participant	Study population		RR 0.84 (0.47 to 1.52)	28 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	-
	667 per 1000	560 per 1000 (313 to 1000)				
Reduction in itch score within 2 weeks, as rated by the participant	-	-	-	-	-	Not measured
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by a medical practitioner	Study population		RR 1.13 (0.89 to 1.44)	60 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	-
	767 per 1000	866 per 1000 (682 to 1000)				
Minor participant-reported adverse events not requiring withdrawal of the treatment	-	-	-	-	-	Not measured

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk is calculated from the single-study analysis or meta-analysis, using the number of events or mean difference in the control group(s).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level to moderate-quality evidence for imprecision due to small sample size.

Summary of findings 2. Erythromycin compared to placebo for pityriasis rosea

Erythromycin compared to placebo for pityriasis rosea

Patient or population: pityriasis rosea
Setting: outpatient dermatology clinic
Intervention: erythromycin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with erythromycin				
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by the participant	-	-	-	-	-	Not measured
Serious adverse events, i.e. serious enough to require withdrawal of the treatment	-	-	Not estimable	34 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	No participants in either group experienced serious adverse events.
The proportion of participants with resolution of itch within 2 weeks, as rated by the participant	-	-	-	-	-	Not reported

Reduction in itch score within 2 weeks as rated by the participant Assessed with: visual analogue scale Scale from: 0 to 10 (higher score = worse itch)	The mean reduction in itch score within 2 weeks as rated by the participant was 1.76.	MD 3.95 higher (3.37 higher to 4.53 higher)	-	34 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	-
The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner Assessed with: complete cure	Study population		RR 4.02 (0.28 to 56.61)	86 (2 RCTs)	⊕⊕⊖⊖ Low [b]	-
	33 per 100	100 per 100 (9 to 100)				
Minor participant-reported adverse events not requiring withdrawal of the treatment: Gastrointestinal upset. Assessed with: presence or absence of the side effect	Study population		RR 2.00 (0.20 to 20.04)	34 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	-
	6 per 100	12 per 100 (1 to 100)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). The assumed risk is calculated from the single-study analysis or meta-analysis, using the number of events or mean difference in the control group(s).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level to moderate-quality evidence for imprecision due to small sample size.
[b]Downgraded by two levels to low-quality evidence: one level for imprecision due to small sample size and one level for inconsistency due to heterogeneity amongst studies.

Summary of findings 3. Azithromycin compared to placebo or vitamins for pityriasis rosea

Azithromycin compared to placebo or vitamins for pityriasis rosea

Patient or population: pityriasis rosea
Setting: outpatient dermatology and paediatric clinics
Intervention: azithromycin
Comparison: placebo or vitamins

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or vitamins	Risk with azithromycin				
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by the participant	-	-	-	-	-	Not measured
Serious adverse events, i.e. serious enough to require withdrawal of the treatment	-	-	Not estimable	119 (2 RCTs)	⊕⊕⊕⊖ Moderate [a]	No participants in either group experienced serious adverse events.
The proportion of participants with resolution of itch within 2 weeks, as rated by the participant	Study population		RR 0.83 (0.28 to 2.48)	70 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	-
	171 per 1000	142 per 1000 (48 to 425)				
Reduction in itch score within 2 weeks, as rated by the participant Assessed with: visual analogue scale Scale from: 0 to 10 (higher score = worse itch)	The mean reduction in itch score within 2 weeks was 0.47.	MD 0.04 higher (0.35 lower to 0.43 higher)	-	70 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	-
The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner. Assessed with: complete or partial resolution, no response	Study population		RR 1.02 (0.52 to 2.00)	119 (2 RCTs)	⊕⊕⊖⊖ Low[b]	-
	441 per 1000	449 per 1000 (229 to 881)				
Minor participant-reported adverse events not requiring withdrawal of the treatment: Mild abdominal pain. Assessed with: presence or absence of the side effect	See comment	See comment	RR 5.82 (0.72 to 47.10)	119 (2 RCTs)	⊕⊕⊕⊖ Moderate [a]	No participants in the placebo group reported mild abdominal pain versus 5/60 participants in the azithromycin group.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __MD:__ mean difference; __RCT:__ randomised controlled trial; __RR:__ risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level to moderate-quality evidence for imprecision due to small sample size.
[b]Downgraded by two levels to low-quality evidence: one level for imprecision due to small sample size, and a further level for study limitations due to high risk of reporting bias in one study (Amer 2006). It was stated that the presence of pruritus was measured at baseline and at each follow-up, but this information was not included in the results. There was also no report on concomitant treatment used, although this was stated to have been recorded at each follow-up. Also, random sequence generation and allocation concealment were unclear.

Summary of findings 4. Acyclovir compared to placebo, vitamins, or no treatment for pityriasis rosea

Acyclovir compared to placebo, vitamins, or no treatment for pityriasis rosea

Patient or population: pityriasis rosea
Setting: outpatient dermatology clinic
Intervention: acyclovir
Comparison: placebo, vitamins, or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo, vitamins, or no treatment	Risk with acyclovir				
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by the participant	-	-	-	-	-	Not measured
Serious adverse events, i.e. serious enough to require withdrawal of the treatment Assessed with: presence or absence	-	-	Not estimable	141 (3 RCTs) [a]	⊕⊕⊕⊖ Moderate [b]	No serious adverse events were reported in either group.
Proportion of participants with resolution of itch within 2 weeks, as rated by the participant	Study population		RR 0.34 (0.12 to 0.94)	21 (1 RCT) [c]	⊕⊕⊕⊖ Moderate [b]	-
	80 per 100	27 per 100 (10 to 75)				

Reduction in itch score within 2 weeks, as rated by the participant	-	-	-	-	-	Not reported
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by a medical practitioner Assessed with: decrease or absence of erythema	Study population 28 per 100	67 per 100 (37 to 100)	RR 2.45 (1.33 to 4.53)	141 (3 RCTs) [a]	⊕⊕⊕⊖ Moderate [d]	-
Minor participant-reported adverse events not requiring withdrawal of the treatment	Study population 7 per 100	2 per 100 (0 to 54)	RR 0.31 (0.01 to 7.02)	141 (3 RCTs) [a]	⊕⊕⊕⊖ Moderate [b]	1 participant in the placebo group experienced abdominal pain and diarrhoea. No adverse events were reported with acyclovir.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). The assumed risk is calculated from the single-study analysis or meta-analysis, using the number of events or mean difference in the control group(s).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Singh 2016 and Ganguly 2014 utilised a dose of 800 mg 5 times per day for 7 days. Rassai 2011 utilised a dose of 400 mg 5 times per day for 7 days.
[b] Downgraded by one level to moderate-quality evidence for imprecision due to small sample size.
[c] Singh 2016 utilised a dose of 800 mg 5 times per day for 7 days.
[d] Downgraded by one level to moderate-quality evidence due to study limitations, as one of the trials had a high risk of performance bias and unclear risk of selection bias (allocation concealment), detection bias, and attrition bias (10 dropouts with unknown numbers and reasons per group) (Rassai 2011).

Summary of findings 5. Acyclovir + calamine + cetirizine compared to calamine + cetirizine for pityriasis rosea

Acyclovir + calamine + cetirizine compared to cetirizine + calamine for pityriasis rosea

Patient or population: pityriasis rosea
Setting: outpatient dermatology clinic
Intervention: acyclovir + calamine + cetirizine
Comparison: calamine + cetirizine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with calamine + cetirizine	Risk with acyclovir + calamine + cetirizine				
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by the participant	-	-	-	-	-	Not measured
Serious adverse events, i.e. serious enough to require withdrawal of the treatment Assessed with: presence or absence	-	-	Not estimable	24 (1 RCT)	⊕⊕⊖⊖ Low [a]	No serious adverse events requiring withdrawal were reported in either group.
The proportion of participants with resolution of itch within 2 weeks, as rated by the participant Follow-up: 2 weeks	Study population		RR 4.50 (1.22 to 16.62)	24 (1 RCT)	⊕⊕⊖⊖ Low [a]	-
	167 per 1000	750 per 1000 (203 to 1000)				
Reduction in itch score within 2 weeks, as rated by the participant Assessed with: visual analogue scale Scale from: 0 to 10 (higher score = worse itch)	The mean reduction in itch score within 2 weeks was 0.58.	MD 1.26 higher (0.74 higher to 1.78 higher)	-	24 (1 RCT)	⊕⊕⊖⊖ Low [a]	-
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by a medical practitioner	-	-	-	-	-	Not measured[b]
Minor participant-reported adverse events not requiring withdrawal of the treatment: Headache. Assessed with: presence or absence	See comment	See comment	RR 7.00 (0.40 to 122.44)	24 (1 RCT)	⊕⊕⊖⊖ Low [a]	No events in the control group versus 3/12 participants in the acyclovir group

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by two levels to low-quality evidence: one level for study limitations due to high risk of performance bias (participants were not blinded) and one level for imprecision. The sample size of this trial was only 24 (12 per group).
[b]This study did not report on this precise outcome. However, it did evaluate participants for reduction in lesional score (a measure of rash severity), which was calculated by addition of erythema score (0 if absent, 1 if present), scaling score (0 if absent, 1 if present), and number of lesions score (< 30 lesions was given a score of 1, 30 to 100 lesions a score of 2, and > 100 lesions a score of 3). The mean change in lesional score was significantly larger when acyclovir was added to the standard of care (6.08 ± 0.69 versus 2.84 ± 0.74; MD 3.24, 95% CI 2.67 to 3.81; Analysis 5.3). Downgraded by one level to moderate-quality evidence for imprecision; outcome assessors were blinded.

Summary of findings 6. Acyclovir compared to erythromycin for pityriasis rosea

Acyclovir compared to erythromycin for pityriasis rosea

Patient or population: pityriasis rosea
Setting: outpatient dermatology clinic
Intervention: acyclovir
Comparison: erythromycin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with erythromycin	Risk with acyclovir				
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by the participant	-	-	-	-	-	Not measured
Serious adverse events, i.e. serious enough to require withdrawal of the treatment	-	-	Not estimable	30 (1 RCT)	⊕⊕⊕⊖ Moderate [a]	All participants completed the trial and no adverse events are reported in either group.
The proportion of participants with resolution of itch within 2 weeks, as rated by the participant	See comment	See comment	RR 13.22 (0.91 to 192.02)	14 (1 RCT)	⊕⊕⊖⊖ Low [b]	All 8 participants in the acyclovir group had resolution of itch versus zero in the erythromycin group. Hence, the assumed and corresponding risks could not be calculated.

Reduction in itch score within 2 weeks, as rated by the participant	-	-	-	-	-	Not measured
The proportion of participants with good or excellent rash improvement within 2 weeks, as rated by a medical practitioner Assessed with: complete response	-	-	Not estimable	30 (1 RCT)	⊕⊕⊖⊖ Low [b]	Zero events in both groups
Minor participant-reported adverse events not requiring withdrawal of the treatment	-	-	Not estimable	30 (1 RCT)	⊕⊕⊖⊖ Low[b]	No participants in either group experienced adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level to moderate-quality evidence for imprecision due to very small sample size and a small number of events in terms of response measures.
[b]Downgraded by two levels to low-quality evidence: one level for imprecision due to very small sample size and a small number of events in terms of response measures and one level for study limitations (unclear risk of selection bias, performance bias, and detection bias), as this trial does not specify randomisation methods, and very little information is provided on blinding of participants and outcome assessors.

BACKGROUND

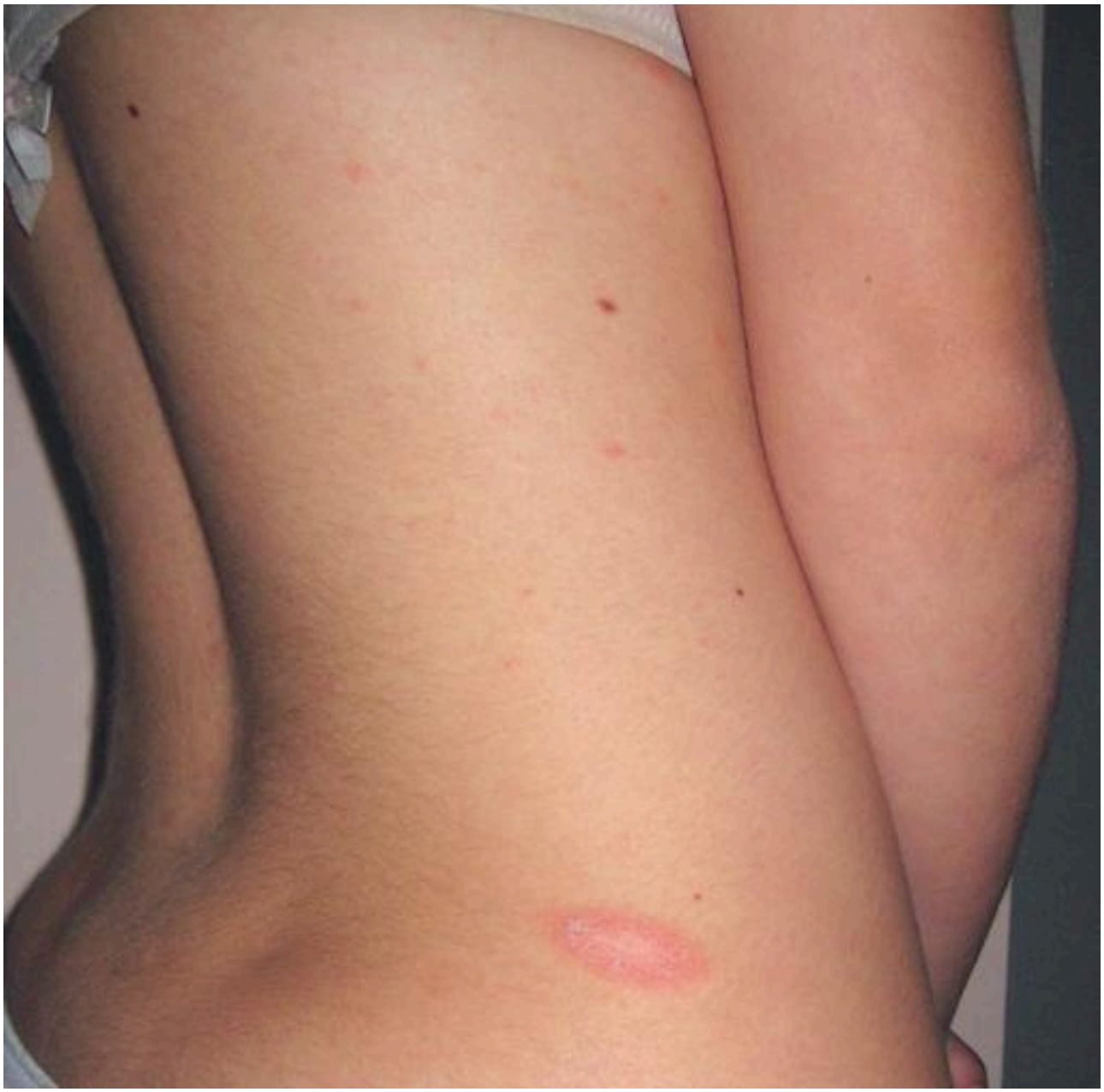
Description of the condition

Description and epidemiology

Pityriasis rosea (PR) is a benign, self-limited skin disease characterised by the sudden appearance of multiple, discrete patches of skin rash in a distinctive pattern over the trunk and limbs. 'Pityriasis' (meaning bran-like) indicates that there are fine scales in the skin lesions (Percival 1932). 'Rosea' means rose-like and describes the typical colour of the rash (Percival 1932), although the colour varies to a wide extent in people of different races (Ahmed 1986).

A characteristic of PR is the apparently 'programmed' course of events. A single larger lesion, measuring about 1 to 3 centimetres, usually precedes the widespread rash for up to two weeks. This initial lesion, also known as the 'herald patch', most commonly appears on the trunk (Figure 1). It is oval-shaped, with a rose, scaly, slightly elevated border and paler centre. The herald patch may not be identifiable in many people, thus its absence does not necessarily exclude a diagnosis of PR.

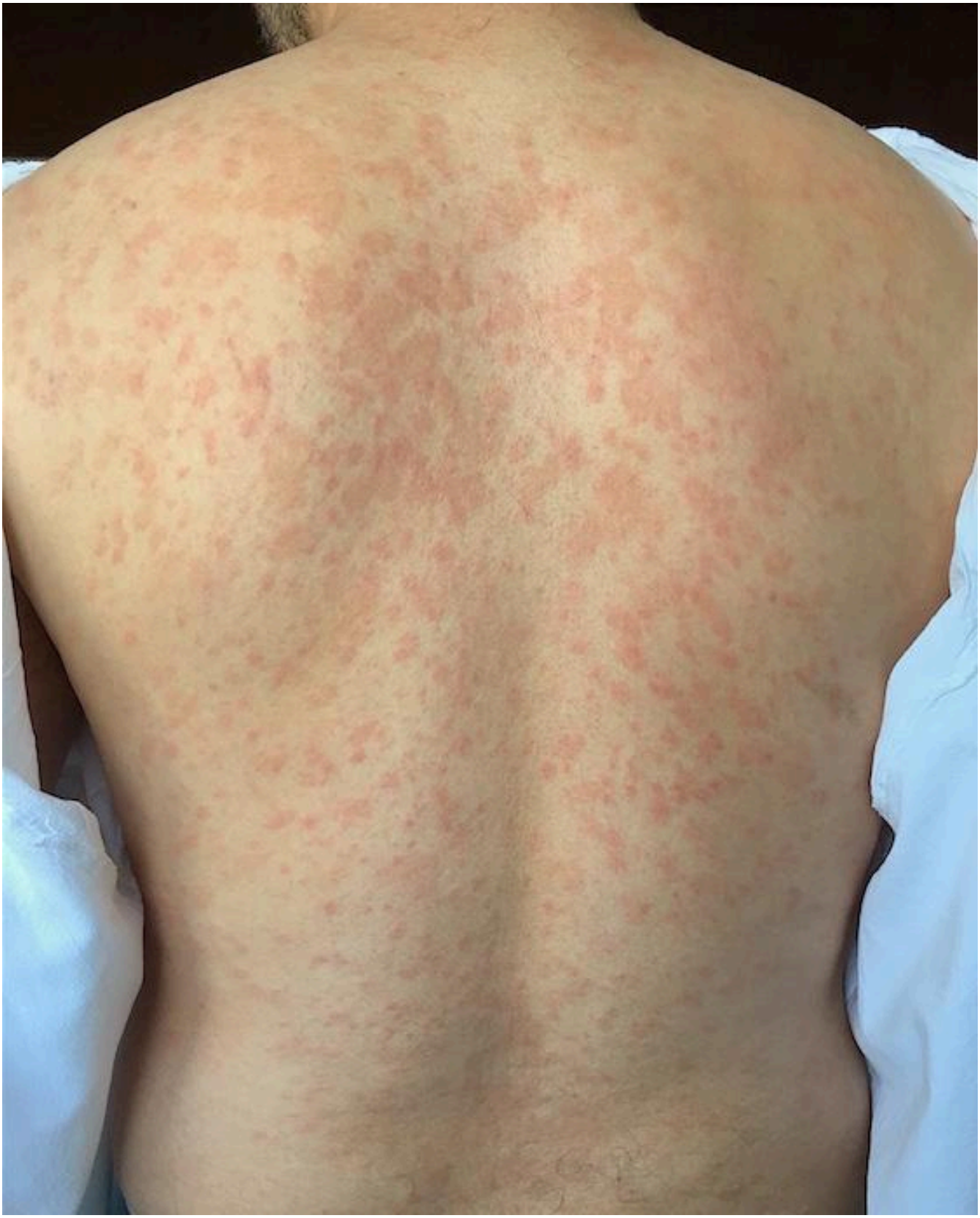
Figure 1. Classical pityriasis rosea. The largest lesion is the herald patch. The other lesions are the secondary eruption.



The subsequent, abrupt, generalised eruption is known as the secondary eruption. Lesions are similar to the herald patch but smaller. Their distribution commonly follows the skin cleavage lines in what is referred to as the 'Christmas tree pattern' (Figure 2).

The rash usually occurs on the trunk and extends to the upper arms and upper thighs, rarely to the forearms and legs. The eruption only occasionally spreads to the palms and soles, although the herald patch can sometimes present at these sites (Deng 2007; Robati 2009; Polat 2012; Bas 2015). Involvement of the face or scalp is also rare but has been reported, more frequently in people with black skin (Klauder 1924; Jacyk 1980; Amer 2007; Zawar 2010a).

Figure 2. The secondary eruption in pityriasis rosea showing the 'Christmas tree pattern'.



More lesions will appear in the first two to six weeks. All lesions will then disappear spontaneously without treatment. The entire disease duration is usually between 2 and 12 weeks, but it may last for as long as 7 months (Chuah 2014; Drago 2015a). Some darkening or lightening of the affected skin can remain for months after recovery (Percival 1932; Amer 2007).

A variety of constitutional symptoms have been reported as preceding or occurring simultaneously with the onset of skin eruption. These include prodromal malaise, loss of appetite, headache, symptoms of upper respiratory tract infection, abdominal pain, joint pain, swelling of lymph nodes, and mild fever (Percival 1932; Cheong 1989; Tay 1999; Sharma 2000; Sharma 2008; Ozyürek 2014; Drago 2015b). The rash is not painful, but about 30% to 50% of people with PR will experience itching of moderate to severe intensity.

Whilst multiple recurrences are possible, most individuals who experience an episode of PR will not have another attack (Percival 1932; Chuang 1982; Zawar 2009; Chuah 2014; Sankararaman 2014; Drago 2014a).

Pityriasis rosea is a relatively common condition with an approximate incidence of 0.5% to 2% (Zawar 2010b). One study reported that for every 100,000 people in the community, about 170 will have PR in any one year (Chuang 1982). Pityriasis rosea is diagnosed in about 0.3% to 1.2% of all patients seen by dermatologists worldwide, although it seems to occur more frequently in several African countries, with annual incidence rates ranging from 2.2% up to 4.8% of dermatological patients (Jacyk 1980; Ahmed 1986; Olumide 1987; Harman 1998; Nanda 1999; Tay 1999; Kyriakis 2006; Sharma 2008).

The incidence of PR peaks between the ages of 15 and 30 years (Chuang 1982; Harman 1998; Sharma 2008; Zawar 2010b). Most epidemiological studies report that girls and women are more likely to experience PR, with the overall male to female ratio of about 1:1.1-1.4 (Jacyk 1980; Chuang 1982; Olumide 1987; Harman 1998; Nanda 1999; Kyriakis 2006; Ozyürek 2014). In contrast, PR seems to occur more frequently in men in Singapore and India (Cheong 1989; Tay 1999; Sharma 2008).

The data on seasonal variation in occurrence of PR is conflicting and varies between different geographical regions, but seasonal incidence seems to be highest during the colder months (Percival 1932; Chuang 1982; Ahmed 1986; Harman 1998; Sharma 2008). Furthermore, it is known that cases of PR tend to occur in clusters (Messenger 1982; Chuh 2003a; Chuh 2005b).

Terminology

Pityriasis rosea is also known by the following names: pityriasis rosea of Gibert, pityriasis rosea of Vidal, pityriasis circinata et marginata, and pityriasis maculata et circinata (Percival 1932).

Causes

The exact cause of PR is unknown. Several facts suggest that PR is caused by an infectious agent. The first is that the disease course, as mentioned above, is 'programmed', similar to the course of some viral rashes such as measles or chickenpox. The constitutional, prodromal symptoms that accompany or precede the onset of rash also suggest an infectious origin, as well as the epidemiological data on seasonal variations and case clustering. Furthermore, most people who have suffered from the eruption will not have another attack during their lifetime.

Numerous infectious agents have been considered as possible causes of PR, but the human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) have been studied most extensively. However, different investigators have reported conflicting results. There are positive reports supporting the role of one or both of these viruses (Drago 1997a; Drago 1997b; Watanabe 1999; Drago 2002; Watanabe 2002, Vag 2004; Broccolo 2005; Canpolat Kirac 2009; Drago 2015b), as well as many negative reports (Kempf 1999; Yasukawa 1999; Yoshida 1999; Kosuge 2000; Offidani 2000; Chuh 2001; Wong 2001; Karabulut 2002; Yildirim 2004). Whilst still controversial, a causative relationship with HHV-6 and HHV-7 seems likely, and it has been suggested that PR is associated with the reactivation of these infections (Watanabe 2002; Broccolo 2005; Drago 2009a). Evidence has shown that PR is not associated with herpes simplex virus 1 and 2, Epstein–Barr virus, or cytomegalovirus (Bozdag 2005; Canpolat Kirac 2009), whereas the only two studies on the possible association with HHV-8 infection have yielded conflicting results (Chuh 2006; Prantsidis 2009).

Some drugs can produce a skin rash as a side effect that can resemble PR; however, these rashes are different in nature (Drago 2014b). Pityriasis rosea and PR-like eruptions have also been described as occurring after vaccinations against smallpox, tuberculosis, H1N1 influenza virus, human papillomaviruses, and other infectious agents (Chen 2011; Drago 2014c; Drago 2015c).

Impact

About 80% to 90% of people with PR experience itching. In one-third to one-half of cases, itching is of moderate to severe intensity (Percival 1932; Cheong 1989; Sharma 2008; Ozyürek 2014).

The quality of life of people with PR (or parents of children with the disease) may be significantly affected. They may experience anxiety related to uncertainties about the cause, nature, and possible infectivity of the eruption, as well as concern regarding physical appearance of the skin (Chuh 2003c; Chuh 2005a; Kaymak 2008). In dark-skinned individuals, prominent pigmentary changes, especially when involving the face, may represent a serious cosmetic problem.

It is likely that many people with PR will consult a primary care physician, but primary care physicians have been reported to significantly underdiagnose the disease (Pariser 1987). Consulting a primary care physician and then not receiving a precise diagnosis of PR could potentially make an individual even more anxious about the nature of the eruption and its prognosis.

The most important, although only recently recognised, effect of PR is the impact it may have on the outcome of pregnancy. It has been reported that PR occurring in pregnant women may be followed by premature delivery, neonatal hypotonia, or even foetal death, with an abortion rate of 13% overall and up to about 60% if the rash developed within first 15 weeks of pregnancy (Drago 2008; Drago 2014d).

Description of the intervention

Both topical and systemic treatments are currently used to treat pityriasis rosea. Current standard of care is aimed at controlling

symptoms and consists of topical emollients and antipruritic lotions, topical corticosteroids, and oral antihistamines.

Topical treatments mainly comprise emollients and topical corticosteroids. The aim of topical treatment is to reduce the signs of acute inflammation, primarily by reducing the erythema and scaling thus to decrease the visibility of the lesions, but also to reduce the pruritus that often accompanies the rash. Corticosteroids, both topical and systemic, have a broad, non-specific anti-inflammatory effect and are therefore widely used in the treatment of various inflammatory skin diseases. Topical corticosteroids come in the form of a cream or an ointment, and are ranked based on their potency. Examples include the following: clobetasol propionate, betamethasone dipropionate, mometasone furoate, fluticasone propionate, betamethasone valerate, fluocinolone acetonide, and hydrocortisone acetate. Emollients are basic care in the management of various forms of eczema and other inflammatory skin diseases and are aimed at improving the skin barrier function and reducing dryness and the associated scaling and pruritus (van Zuuren 2017). They are often used as a placebo intervention or comparator in the evaluation of other topical treatments in dermatological clinical trials.

Systemic treatments that have been tried thus far include medications for symptomatic control of itch such as oral antihistamines, systemic corticosteroids, intravenous glycyrrhizin, oral antibiotics of the macrolide group, the antiviral agent acyclovir, and sunlight and artificial ultraviolet radiation (usually as narrowband ultraviolet B) (Castanedo 2003; Chuh 2007; Drago 2009b).

Oral antihistamines are used as symptomatic treatment of pruritus in various disease states, regardless of the cause. Examples include the following: chloropyramine, loratadine, desloratadine, cetirizine, levocetirizine, bilastine, and others. Acyclovir is an antiviral drug specifically used for the treatment of infections with herpes viruses. Similar treatments include famciclovir and valacyclovir. In the context of the current hypothesis on the viral aetiology of PR, the use of acyclovir is somewhat controversial because it has weak activity against HHV-6 and no activity against HHV-7 in laboratory conditions (Yoshida 1998). Macrolide antibiotics are often used for their broad-spectrum antibiotic effects in cases of bacterial infections, but also due to their non-specific anti-inflammatory and immunomodulatory effects. The most common ones include erythromycin, azithromycin, and clarithromycin.

Ultraviolet irradiation (usually delivered as narrow-band ultraviolet B phototherapy) is used in the treatment of various inflammatory skin diseases such as psoriasis, atopic eczema, or vitiligo, but also in various disease states accompanied by itch (Rivard 2005).

How the intervention might work

Topical corticosteroids have broad anti-inflammatory effects through the regulation of gene expression of various cytokines, cellular enzymes, and other elements in the intra- and intercellular signalling pathways. Emollients restore the epidermal aqueous and lipid content, which in turn prevents perpetuation of skin inflammation and reduces skin dryness, scaling, and the associated itch (Rerknimitr 2017).

Antihistamines are standard systemic treatment of aetiologically varying forms of pruritus, caused by dermatological or non-dermatological diseases. Antihistamines work by inhibiting H1 histamine receptors. Acyclovir specifically inhibits DNA synthesis in herpes viruses and may be effective in PR due to the possible causative role of HHV-6 and HHV-7 in the development of this clinical entity. Macrolide antibiotics may be effective in PR primarily due to their immunomodulatory and anti-inflammatory effects (Scheinfeld 2003). It has been hypothesised that phototherapy exerts its antipruritic effect through release of endogenous antipruritic mediators or by direct effect on the sensitivity of cutaneous sensory nerves (Legat 2018).

Why it is important to do this review

The previous version of this review found inadequate evidence for the efficacy of most treatments for PR (Chuh 2007). Potential clinical benefit was shown only for oral erythromycin, but this evidence came from a single, small trial. Since Chuh 2007, which included only three trials, several studies evaluating the efficacy of various macrolide antibiotics as well as that of acyclovir have been published. The current review summarises the existing evidence and provides an updated conclusion on the currently available treatments for PR.

Pityriasis rosea is essentially a self-limiting disease, and the rash disappears for the most part at 2 to 12 weeks, with or without treatment. The benefits associated with the use of any active intervention should therefore outweigh any potential adverse effects. Adverse effects may be short term (such as stomach upsets caused by antibiotics) or long term (such as the risk of skin cancer caused by ultraviolet radiation, or the effects of systemic corticosteroids on bones). The use of antibiotics and antivirals may theoretically induce resistance to bacteria and viruses, thus affecting not only the individual but also the community as a whole.

There are many questions regarding the treatment of PR that do not have answers. It is unknown whether many of the available treatments can modify the disease course, relieve itch, or improve quality of life. A systematic review would help determine the most effective therapies, when and for whom they should be used, the duration of treatment, possible risks and side effects, and the level of treatment acceptability. This review would also enable an assessment of the level and quality of the currently available evidence, and identify areas of uncertainty or gaps in knowledge that require further research.

OBJECTIVES

To assess the effects of interventions for the management of pityriasis rosea in any individual diagnosed by a medical practitioner.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) that evaluate the effectiveness of interventions for pityriasis rosea (PR).

Types of participants

Any individual who has been diagnosed with PR by a medical practitioner. Studies including only a subset of relevant participants will be included but analysed separately.

Types of interventions

- Topical therapy
  - Emollients
  - Antihistamine creams or ointments
  - Corticosteroid creams or ointments
- Light therapy
  - Sunlight
  - Artificial ultraviolet light therapy
- Systemic therapy
  - Oral antihistamines
  - Oral corticosteroids
  - Oral antibiotics
  - Oral antiviral agents
  - Intravenous Chinese medicine agents

The interventions may be either single or combination therapy. The comparators may be no treatment, placebo, vehicle only, another active compound, or placebo radiation treatment.

Types of outcome measures

Primary outcomes

- The proportion of participants with good or excellent rash improvement within two weeks, as rated by the participant.
- Serious adverse events, i.e. serious enough to require withdrawal of the treatment.

Secondary outcomes

- The proportion of participants with resolution of itch within two weeks, as rated by the participant.
- Reduction in itch score within two weeks, as rated by the participant.
- The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner.
- Improvement in quality of life as rated by the participant by the use of questionnaires or other methods.
- Minor participant-reported adverse events not requiring withdrawal of the treatment.

Timing of outcome assessment

We chose 2 weeks as the timing of the outcome assessment, as people without any active treatment usually have spontaneous recovery between 2 and 12 weeks. Any improvement after two weeks with active treatment would be difficult to differentiate whether the improvement is due to spontaneous recovery from the disease or to the treatment.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

For this update, we revised all of our search strategies in line with current Cochrane Skin practices. Details of the previous search strategies are shown in Chuh 2007.

The Cochrane Skin Information Specialist searched the following databases up to 29 October 2018:

- the Cochrane Skin Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) (2018, Issue 9), in the Cochrane Library using the strategy in Appendix 2;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 3;
- Embase via Ovid (from 1974) using the strategy in Appendix 4; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 5.

Trials registers

We (JCR, SP) searched the following trials registers up to 29 October 2018 using the strategy in Appendix 6:

- ISRCTN registry (www.isrctn.com);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/); and
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

References from published studies

We checked the bibliographies of the included and excluded studies for further references to relevant RCTs.

Unpublished literature

We contacted the leading researchers identified in the trial register search in an attempt to identify relevant unpublished data. We contacted the authors of the published trials in order to obtain data on outcomes that were assessed but not reported in the published papers.

Conference proceedings

We scanned abstracts from the following major dermatology conference proceedings for further RCTs:

- Annual Meeting of the American Academy of Dermatology (2009 to 2017);
- Congress of the European Academy of Dermatology and Venereology (2000 to 2017);
- World Congress of Dermatology (2011 to 2017); and
- International Congress of Dermatology (2011 to 2017).

We searched the CAB Abstracts (Ovid) database up to November 2017 using the following text words: Pityriasis rosea, Pityriasis of Vidal, Pityriasis circinata, and Pityriasis marginata.

Adverse effects

We searched PubMed for adverse effects using the strategy in Appendix 7 up to November 2018.

Data collection and analysis

Selection of studies

Two review authors (JCR, CJG) independently checked the titles and abstracts identified from the searches. If it was clear to both review authors that the study did not refer to an RCT on PR, it was excluded. Any discrepancies were resolved by further analysing the full publication or by contacting study authors. We excluded quasi-randomised trials, where allocation was by non-random methods such as alternation or was based on characteristics such as date of birth, name, or case number.

We obtained the full texts of those studies deemed potentially relevant, and two review authors (JCR, CJG) independently assessed each study to determine whether it met the predefined selection criteria, with any differences being resolved through discussion with the review team. Review authors were not blinded as to the origin or conclusions of the article for eligibility assessment, data extraction, or quality assessment. We listed the excluded studies and the reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (ICK and CJG) independently performed data extraction, and three other review authors (SP, JCR, LR) checked for and resolved any discrepancies between the data extraction. We obtained missing data from the trial authors where possible. We developed and piloted a data collection form to summarise the trials. Two review authors (CJG, SP) checked and entered the data into Review Manager 5 (Review Manager 2014).

Assessment of risk of bias in included studies

At least four review authors (CJG, LR, ICK, SP) independently assessed the risk of bias of each trial using a simple form and according to the domain-based evaluation described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Review authors (CJG, LR, JCR, SP, ICK) discussed any discrepancies and achieved consensus on the final assessment.

We assessed the following domains as low, high, or unclear risk of bias.

- Generation of allocation sequence
- Allocation concealment
- Blinding (of participants, personnel, and outcome assessors)
- Incomplete outcome data
- Selective reporting
- Other sources of bias

Generation of allocation sequence (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to permit an assessment as to whether it should produce comparable groups.

We assessed the method as:

- low risk (any truly random process, e.g. random number table; computer random number generator); or
- unclear risk (the trial was described as randomised, but the method used for allocation sequence generation was not described).

Allocation concealment (checking for possible selection bias)

We described for each included study the methods used to conceal the allocation sequence in sufficient detail to permit an assessment as to whether the intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment.

We assessed the methods as:

- low risk (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk (trial was described as randomised, but the method used to conceal the allocation was not described).

Blinding or masking (checking for possible performance and detection bias)

We described for each included study the methods used, if any, to blind study participants and personnel from the knowledge of which intervention a participant received. We judged studies as at low risk of bias if they were blinded, or if we judged that the results would not have been affected by lack of blinding. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed blinding methods as:

- low risk, high risk, or unclear risk for participants;
- low risk, high risk, or unclear risk for personnel; and
- low risk, high risk, or unclear risk for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We assessed methods on outcome data as:

- low risk (any one of the following): no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome; missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportions of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) amongst missing outcomes was not enough to have a clinically relevant impact on observed effect size; or missing data were imputed using appropriate methods;

- high risk (any one of the following): reason for missing outcome data was likely to be related to true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) amongst missing outcomes was enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; or potentially inappropriate application of simple imputation; or
- unclear risk (any one of the following): insufficient reporting of attrition/exclusions to permit a judgement of 'low risk' or 'high risk' (e.g. number randomly assigned not stated, no reasons provided for missing data); or the study did not address this outcome.

Free of other bias (bias due to problems not covered elsewhere in the table)

We described for each included study any important concerns we had about other possible sources of bias (baseline imbalance, sponsorship bias, differential verification bias, partial verification bias and incorporation bias, bias of the presentation data, etc.):

- low risk of bias: the trial appears to be free of other components that could put it at risk of bias;
- high risk of bias: other factors in the trial could put it at risk of bias (e.g. no sample size calculation made, academic fraud, industry involvement, extreme baseline imbalance);
- unclear risk of bias: the trial may or may not be free of other components that could put it at risk of bias.

In addition, the quality assessment included:

- degree of certainty that the participants have PR (e.g. whether the diagnoses were made by primary care physicians or dermatologists);
- whether participants with drug-induced PR-like rashes were excluded.

We recorded the information in the Risk of bias in included studies section. We used the results of the methodological quality assessment as the basis for sensitivity analysis and not as exclusion criteria.

Measures of treatment effect

We presented data as risk ratios (RR) with 95% confidence intervals (CIs) for dichotomous variables and according to the information provided in the trials by the authors, and as mean differences (MD) and 95% CIs for continuous variables.

Unit of analysis issues

We did not have any unit of analysis issues. The unit of allocation and analysis was the individual participant for all included studies, and no studies were of a repeated measure, longitudinal nature, cluster trial, or cross-over design. In the only case of a study with three groups (Lazaro-Medina 1996), each of the three comparisons was analysed separately, and given that none of these could be pooled, we did not have to correct for omission or double-counting of participants.

Given the nature of pityriasis rosea, we did not expect to find any within-participant trials.

Dealing with missing data

In the case of uncertainty we contacted trial authors for clarification and to obtain missing data. When this additional information was available, it was clearly specified in the Characteristics of included studies tables.

If we identified any studies where 2×2 tables or means and standard deviations were still not available, we would use the available data such as odds ratio (OR), RR, or MD with their 95% CI.

Regarding analysis of continuous outcome data, when standard deviations were not available for changes from baseline and information was insufficient to calculate them, standard deviations were imputed as recommended in Section 16.1.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In such cases, a correlation coefficient of 0.7 was used, alongside a sensitivity analysis using coefficients ranging from a more conservative estimate of 0.5 up to 0.8 to examine the impact of imputation on the final analysis results (Dias 2011). Use of different coefficients did not change the overall result for any of the outcomes where imputation of standard deviation was used.

Assessment of heterogeneity

We investigated heterogeneity with visual examination of the forest plots. In addition, we used the Chi^2 test and I^2 statistic for testing statistical heterogeneity between studies. Only trials considered clinically and methodologically similar were pooled. We assessed the presence of statistical heterogeneity as a value of I^2 as per the *Cochrane Handbook for Systematic Reviews of Interventions*, as follows: 0% to 40%: not important; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity (Higgins 2011). If heterogeneity (> 30%) existed between studies, reasons for heterogeneity were assessed by examining the characteristics of the studies, types of participants, disease severity, dosage and duration of treatment, and study quality, and subgroup analyses or sensitivity analyses were undertaken if possible (see Subgroup analysis and investigation of heterogeneity). If there was considerable heterogeneity, we downgraded the quality of the evidence using the GRADE approach (GRADE Handbook).

Assessment of reporting biases

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed reporting methods using Review Manager 5 software, Review Manager 2014, per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), as follows:

- low risk (any one of the following): the study protocol is available and all of the study's prespecified (primary and secondary) outcomes of interest in the review have been reported in the prespecified way, or the study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon);

- high risk (any one of the following): not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered into a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study; or
- unclear risk: information is insufficient to permit judgement of 'low risk' or 'high risk'.

If we identified selective publication in studies, we downgraded the evidence according to the GRADE criteria considering study design, study size, lag bias, search strategy, etc. (GRADE Handbook).

Data synthesis

For studies with a similar type of intervention and comparator (e.g. oral antibiotics versus placebo), we performed a meta-analysis to calculate a weighted treatment effect across trials using a random-effects model in Review Manager 5 (Review Manager 2014). Where it was not possible to perform a meta-analysis, we summarised the data for each trial.

We listed non-randomised controlled studies in the Characteristics of excluded studies table; these are not discussed further.

We described studies relating to adverse effects qualitatively.

A consumer (MLS-R) was involved throughout the review process to ensure the readability of the final review.

Subgroup analysis and investigation of heterogeneity

As stated in the protocol, parallel trials and the first phase of cross-over trials would be analysed as separate subgroups before pooling. However, we did not identify any cross-over trials in the previous version of this review or in this current version. We considered subgroup analyses for the following factors: age of participants (children versus adults), dosage, duration of treatment, type of treatment (topical, systemic, combination), or relapse. However, in view of the limited number of included studies covering any one specific intervention, we did not conduct any of these subgroup analyses.

Sensitivity analysis

We would have conducted sensitivity analyses to examine the effects of excluding studies where necessary. We planned to conduct a sensitivity analysis by removing studies at high or unclear risk of bias. We did not undertake any sensitivity analyses due to the limited number of included studies.

'Summary of findings' tables and GRADE

Assessment of the quality of the evidence using the GRADE approach

For this update we assessed the quality of the evidence using the GRADE approach, as outlined in the GRADE Handbook (GRADE Handbook). We used GRADEpro GDT to import data from Review Manager 5 in order to create a 'Summary of findings' table (GRADEpro GDT; Review Manager 2014).

Two review authors (JCR, CJG) produced a summary of the intervention effect and a measure of quality for each of the above outcomes using GRADEpro GDT. GRADE evaluates five criteria (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome. The body of evidence is graded according to its quality as follows.

- **High:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

We downgraded the evidence from high quality by one level for serious, or by two levels for very serious, factors affecting its quality. We described the rationale for downgrading in the footnotes of the respective tables. Two other review authors (SP, ICK) then reviewed the tables and criteria used to downgrade the evidence, and any discrepancies were discussed until agreement was reached.

We have presented summaries of the intervention effect and measures of quality according to the GRADE approach in the 'Summary of findings' tables, which include the most clinically relevant comparisons, as follows.

- Clarithromycin versus placebo
- Erythromycin versus placebo
- Azithromycin versus placebo (or vitamins)
- Acyclovir versus placebo (or vitamins) or no treatment
- Acyclovir + calamine + cetirizine versus calamine + cetirizine
- Acyclovir versus erythromycin

The 'Summary of findings' tables include all primary outcomes (proportion of participants with good or excellent rash improvement; serious adverse events) and four secondary outcomes (proportion of participants with resolution of itch; reduction in itch score; proportion of participants with good or excellent rash improvement; and minor adverse events).

RESULTS

Description of studies

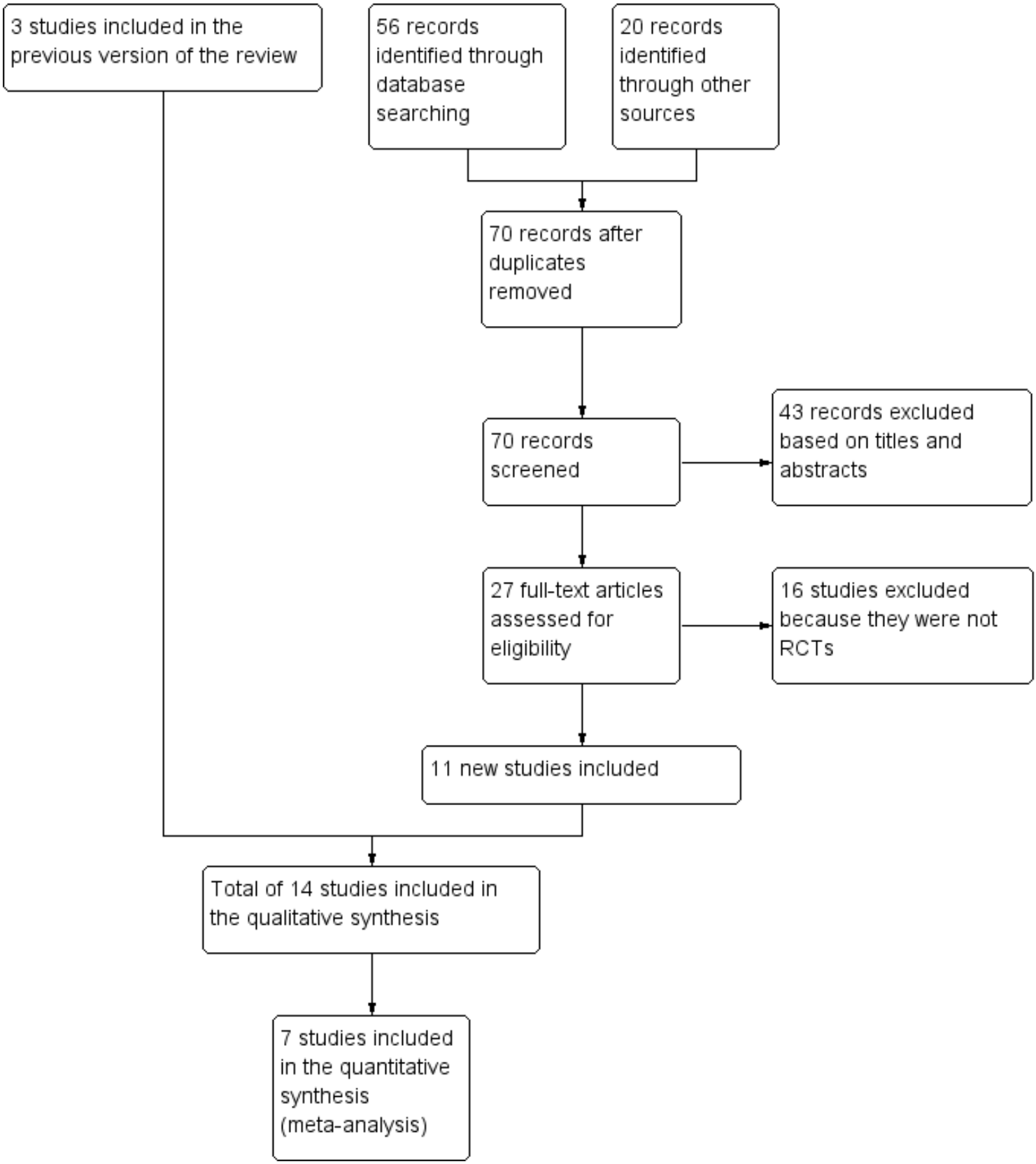
Results of the search

This is an updated version of Chuh 2007, published in Issue 2, 2007 of the Cochrane Library. The searches of the electronic databases retrieved 56 records (Electronic searches). Our searches of other resources identified 20 additional studies that appeared to meet the inclusion criteria. We therefore had a total of 76 records, of which two references were duplicates. One further record was identified as a duplicate since the trial was published. Of the remaining 73 records, we excluded 43 records based on titles and abstracts. We obtained the full text of the remaining 30 records. We excluded a further 16 studies (see Characteristics of excluded

studies). We did not identify any studies awaiting classification or any ongoing studies.

The review includes 14 studies (11 newly identified studies and three studies found in the previous review). One trial did not report outcomes at week two; therefore, although it was included in the Description of studies and 'Risk of bias' assessment, we were not able to formally add it to the analysis or derive information from it (Jairath 2015). For a further description of our screening process, see the study flow diagram (Figure 3).

Figure 3. Selection of studies.



Regarding adverse events, our search yielded only reports of medications that can produce "pityriasis rosea-like" reactions and were not related to medicament toxicity when treating pityriasis rosea (PR).

Included studies

Fourteen randomised trials met the inclusion criteria of this review (Zhu 1992; Lazaro-Medina 1996; Villarama 2002; Akhyani 2003; Amer 2006; Ehsani 2010; Rassai 2011; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Jairath 2015; Singh 2016; Sonthalia 2018). One of these studies met the inclusion criteria but did not report on outcomes at week 2 (Jairath 2015), thus it was only described since it was the only study available on the modality of ultraviolet therapy and was found to be relevant for future research.

The main characteristics of the included studies are detailed in the Characteristics of included studies table. The studies that were included in the previous review are Lazaro-Medina 1996, Villarama 2002, and Zhu 1992. One study, Jairath 2015, was identified by a secondary search performed by one review author (JCR). Thirteen of the 14 studies have been published, whilst one study remains unpublished (Villarama 2002). The data from one study were extracted from an abstract in Chinese that was translated into English, yet we failed to obtain full text of the study from the authors, despite repeated attempts (Zhu 1992). Another trial was published in Persian, and the abstract was translated into English (Akhyani 2003). Specific questions on the methods and results of this trial were also provided from a native of Iran.

One study did not report on some of the outcomes at week 2 (Singh 2016), but the author was contacted and these data were provided. One study was missing information on pruritus, and clarification on the methods used for diagnosis and recruitment was needed; the authors were contacted and the information provided (Das 2015). Another trial was missing information on rash improvement, itch, and dropouts, but we were able to obtain this information from the authors (Pandhi 2014). One trial did not provide information on complete resolution of itch, scores on the Pityriasis Rosea Severity Score (PRSS), or standard deviations on rash improvement (Sonthalia 2018), but we were able to obtain part of this missing information from the author. Finally, two more trials had unclear information on the methodology, and the authors were contacted for clarification (Ahmed 2014; Ganguly 2014).

Design

All included studies were parallel RCTs, where each participant was randomised to the intervention or comparator group.

Setting and diagnosis

Six of the included studies were conducted in India, three in Iran, two in the Philippines, and one each in Pakistan, the USA, and China. Thirteen trials were performed in dermatology departments and one in a paediatric ward (Amer 2006). The methods of diagnosis differed slightly amongst the trials. In eight trials, the diagnosis of PR was made by one to three dermatologists (Akhyani 2003; Ehsani 2010; Ahmed 2014; Pandhi 2014; Das 2015; Jairath 2015; Singh 2016; Sonthalia 2018). In one trial dermoscopy was additionally performed (Sonthalia 2018). Five trials were conducted in dermatology departments (Zhu 1992; Lazaro-Medina 1996; Villarama 2002; Rassai 2011; Ganguly 2014), although it was not explicitly stated whether the diagnosis of PR was made by dermatologists. In three trials the clinical diagnosis of PR was confirmed through a biopsy (Lazaro-Medina 1996; Ganguly 2014; Jairath 2015). Paediatricians made the diagnosis in a single trial (Amer 2006). Consequently, there is a high degree of certainty for all but one trial that the participants had PR (Amer 2006). Although most trials did not specifically exclude drug-induced PR, six trials listed prior use of drugs as exclusion criteria (Villarama 2002; Rassai 2011; Ahmed 2014; Ganguly 2014; Singh 2016; Sonthalia 2018); therefore, it can be assumed that none of these trials included participants with drug-induced PR.

Participants

The included studies involved a total of 761 participants. The age range of participants was 2 to 60 years. Except for one study where only male patients were recruited (Amer 2006), the included studies involved both male and female participants. Three studies failed to report participant age and sex (Zhu 1992; Rassai 2011; Ganguly 2014). Of the trials that reported gender, 307 participants were male and 251 female. A detailed description of participants in each of the studies is provided in the Characteristics of included studies table. The sample sizes of the included studies ranged from 23 to 100. A total of 265 participants were included in studies that compared different macrolide antibiotics versus placebo or vitamins. Acyclovir was compared with vitamins, placebo, no treatment, or standard of care in a total sample of 188 participants (Rassai 2011; Ganguly 2014; Das 2015; Singh 2016). Erythromycin was compared with acyclovir in an additional 30 participants (Ehsani 2010). Narrowband ultraviolet B phototherapy was compared with topical emollient in 100 participants (Jairath 2015). Oral corticosteroids were compared with placebo in a study with 70 participants, Sonthalia 2018, and with antihistamines in a study with 85 participants, Lazaro-Medina 1996. A single study with 23 participants investigated the effects of the Chinese medicine glycyrrhizin (Zhu 1992).

All trials documented the extent or severity of the rash, or both, but with diverse measures. Also, participants were not divided into categories based on disease severity. A disease-specific severity index, the Pityriasis Rosea Severity Score (PRSS), which incorporates the extent of the disease, along with erythema, infiltration, and scaling, was used in only three studies (Pandhi 2014; Jairath 2015; Sonthalia 2018). With a theoretical maximal score of 54, baseline PRSS scores in the intervention and control groups were 25.64 ± 14.21 and 23.04 ± 15.09 in Jairath 2015; 18.06 ± 5.62 and 20.23 ± 5.16 in Pandhi 2014; and 18.51 ± 5.32 and 19.45 ± 5.88 in Sonthalia 2018. Six trials used the number of lesions as a measure of disease severity (Lazaro-Medina 1996; Villarama 2002; Ehsani 2010; Rassai 2011; Ahmed 2014; Ganguly 2014), although most of these studies did not specify the absolute lesion count and only reported on (partial or complete) disappearance of existing lesions or the appearance of new lesions. One study used a lesional score with a theoretical maximum of 5, calculated by addition of erythema score, scaling score, and number of lesions score (Das 2015), and reported baseline values of 4.08 ± 0.79 and 4.08 ± 0.90 in the intervention and control groups, respectively. Another study used the Pityriasis Rosea Area and Severity Index (PRASI) ranging from 0 to 48 and reported baseline median scores of 3.5 and 5.4 in the intervention and control groups, respectively (Singh 2016).

Seven studies reported the presence or absence of itch at baseline. Itch accompanied the rash in the following percentages of participants: 46.7% (Ehsani 2010; Ahmed 2014), 77.8% (Singh 2016),

81.6% (Amer 2006), 83.5% (Lazaro-Medina 1996), or all participants (Das 2015; Sonthalia 2018). Three studies assessed intensity of itch on a 0-to-3 scale, with comparable baseline itch severity values in the intervention and control arms: 2.17 ± 0.83 and 2.25 ± 0.75 in Das 2015; 2.00 ± 0.82 and 2.04 ± 0.82 in Jairath 2015; and 1.36 ± 1.01 and 1.15 ± 0.9 in Singh 2016. Four studies assessed itch with a visual analogue scale (VAS) ranging from 0 to 10, and baseline values in the intervention and control arms were 8.25 ± 1.06 and 8.42 ± 1.08 in Das 2015; 1.31 ± 1.02 and 1.4 ± 1.1 in Sonthalia 2018; and 1.31 ± 1.105 and 1.23 ± 1.239 in Pandhi 2014, whilst Villarama 2002 only reported on the difference in scores before and after treatment, without specifying absolute values.

Interventions

The treatments and their duration were clearly defined in all 14 included studies (see Characteristics of included studies). As most of the included studies investigated different interventions and different outcome measures, pooling of data for analysis was only feasible for a few comparisons in the 13 trials that we were able to analyse.

Four studies documented the use of medications before inclusion of participants into the study (Zhu 1992; Lazaro-Medina 1996; Villarama 2002; Ganguly 2014). Six studies excluded patients who had taken any medication after the onset of the rash (Villarama 2002; Rassai 2011; Ahmed 2014; Ganguly 2014; Singh 2016; Sonthalia 2018). The remaining trials did not comprehensively document the use of previous medications after the appearance of rash.

Six studies analysed the use of macrolide antibiotics. In a single study that compared clarithromycin to placebo (Ahmed 2014), clarithromycin tablets were used for a week in a dose of 500 mg twice daily for adults and 250 mg twice daily for children aged 10 to 12 years. Two studies compared oral erythromycin to placebo: erythromycin was used in a daily dose of 1 g for one week, Akhyani 2003, or 250 mg for two weeks, Villarama 2002. Two studies evaluated the effects of a dose of 12 mg/kg/day of azithromycin tablets for 5 days versus placebo, Amer 2006, and vitamins, Pandhi 2014. One study compared oral erythromycin in a dose of 400 mg 4 times/day for 10 days to the antiviral agent acyclovir administered orally in a dose of 8000 mg 5 times/day for 10 days (Ehsani 2010).

Three studies compared acyclovir to placebo or no treatment (Rassai 2011; Ganguly 2014; Singh 2016). Oral acyclovir was administered in a dose of 800 mg 5 times/day, Ganguly 2014; Singh 2016, or 400 mg 5 times/day, Rassai 2011, for 7 days in adults, and in a dose of 20 mg/kg 4 times/day for 7 days in children, Ganguly 2014. One study compared acyclovir tablets in a dose of 400 mg 3 times/day for 7 days along with standard of care (calamine lotion and cetirizine 10 mg tablets once daily at bedtime) versus standard of care alone (Das 2015).

One study compared three interventions: oral antihistamine dexchlorpheniramine (4 mg 2 times/day for 2 weeks, then once a day for the following 2 weeks) versus oral corticosteroid betamethasone (500 mcg, 2 times/day for 2 weeks, then once a day for the following 2 weeks) versus combined therapy (betamethasone 250 mcg and dexchlorpheniramine 2 mg, both 2 times/day for 2 weeks, then once a day for the following 2 weeks) (Lazaro-Medina 1996). One study compared low-dose oral prednisolone (20 mg/day for 5 days, 15 mg/day for the next 5 days, and 10 mg/day for the last 5 days) to placebo (Sonthalia 2018).

The effects of narrowband ultraviolet B phototherapy were compared with placebo in one trial that did not report on outcomes at week 2 (Jairath 2015). Phototherapy was applied in a fixed dose of 250 mJ/cm^2 three times a week on non-consecutive days for four weeks (total dose of 3 J/cm^2).

One study investigated the effects of the Chinese medicine potenline (glycyrrhizin, 80 mL in 500 mL of 10% glucose intravenous solution, administered once daily) versus procaine (300 mg to 600 mg in 500 mL of 10% glucose intravenous solution, administered once daily) (Zhu 1992). The duration of treatment was unclear.

Outcomes

Objectives and outcome measures were clearly defined in 13 studies. In the study by Zhu 1992, the disappearance of symptoms and rash were assessed together. Symptoms were not specified as itch. We had to assume that symptoms were limited to itch only.

None of the included studies assessed the following participant-reported outcomes: our primary outcome of proportion of participants with good or excellent rash improvement within two weeks, as rated by the participant, and our secondary outcome of improvement in quality of life as rated by the participant by the use of questionnaires or other methods.

Seven studies reported the proportion of participants with resolution of itch within two weeks, either in the original trial reports or upon email contact with the study authors (Lazaro-Medina 1996; Ehsani 2010; Ahmed 2014; Pandhi 2014; Das 2015; Singh 2016; Sonthalia 2018).

Six studies assessed reduction in itch score, as rated by the participant, either on a 0-to-3 scale (i.e. absent, mild, moderate, severe) (Das 2015; Jairath 2015; Singh 2016), or by means of a 0-to-10 VAS (Villarama 2002; Pandhi 2014; Das 2015; Sonthalia 2018).

Eleven studies reported the proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner. Most of these studies assessed this outcome as partial or complete response to treatment, with complete response meaning all lesions had started healing in less than two weeks without the appearance of any fresh lesion, and partial response when lesions had regressed partially, or few new lesions had appeared in two weeks, or similar. In two studies that used the PRSS as a severity index, improvement was graded as the percentage reduction as follows: good, 26% to 50%; very good, 51% to 75%; and > 75%, excellent (Pandhi 2014; Sonthalia 2018).

Twelve studies assessed adverse events. In the available translated details of Akhyani 2003 and Zhu 1992, side effects were not reported as one of the assessed outcomes. Ahmed 2014 specified upon email contact that “adverse effects were not directly asked [sic] in order to prevent disclosure of drug and placebo groups”, but that there were no serious adverse events requiring withdrawal.

Length of follow-up

Length of follow-up in the included studies varied from two weeks, Ganguly 2014, to as long as one year, Ehsani 2010, with one study not reporting the length of follow-up (Zhu 1992). In four studies participants were followed up for four weeks (Amer 2006; Rassai

2011; Das 2015; Jairath 2015). In another four studies participants were followed up for six weeks (Villarama 2002; Akhyani 2003; Ahmed 2014; Pandhi 2014). In two studies participants were followed up for 12 weeks after the beginning of the treatment (Lazaro-Medina 1996; Sonthalia 2018). In one trial participants were followed until rash resolution (approximately one month) (Singh 2016). Study duration ranged from 5 to 26 months.

Funding sources

Funding sources were not reported for the majority of the included studies (Zhu 1992; Villarama 2002; Akhyani 2003; Ehsani 2010; Rassai 2011; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Jairath 2015). One study was independently funded (Singh 2016); a pharmaceutical company provided the study medication. However, the study of Amer 2006 was supported by a grant from Pfizer Inc, and the study by Lazaro-Medina 1996 was supported by Schering-Plough.

Language of publication

Eleven trials were published in English (Lazaro-Medina 1996; Amer 2006; Ehsani 2010; Rassai 2011; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Jairath 2015; Singh 2016; Sonthalia 2018); one in Persian (Akhyani 2003); and one in Chinese (Zhu 1992). One study is still unpublished, but was written in English (Villarama 2002).

Excluded studies

See Characteristics of excluded studies.

We excluded 16 studies. In the previous version of this review, 13 trials were excluded because no mention of randomisation was made. One of these studies was pseudo-randomised because participants were assigned by alternate allocation (Sharma 2000). Three more trials were excluded from our search results because they were not randomised trials (Drago 2006; Rasi 2008; Amatya 2012). One trial stated that the participants were randomised into two groups (Amatya 2012). However, given that there was no explanation of the method of randomisation in the manuscript, we contacted the author, who stated that alternate allocation was the method used; therefore, the study was not randomised. Another study clearly stated in the methods that participants were alternately assigned (Drago 2006). Finally, the last trial is a case-controlled, open-label study without randomisation (Rasi 2008).

Risk of bias in included studies

'Risk of bias' assessments for each included study are provided in Characteristics of included studies and Figure 4 and Figure 5.

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

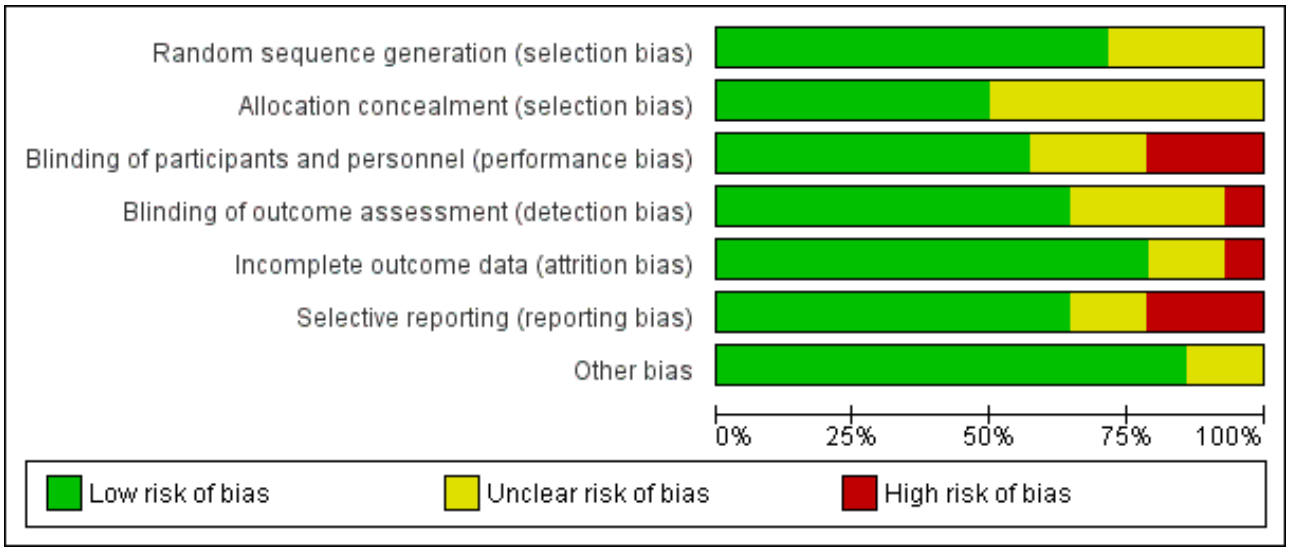
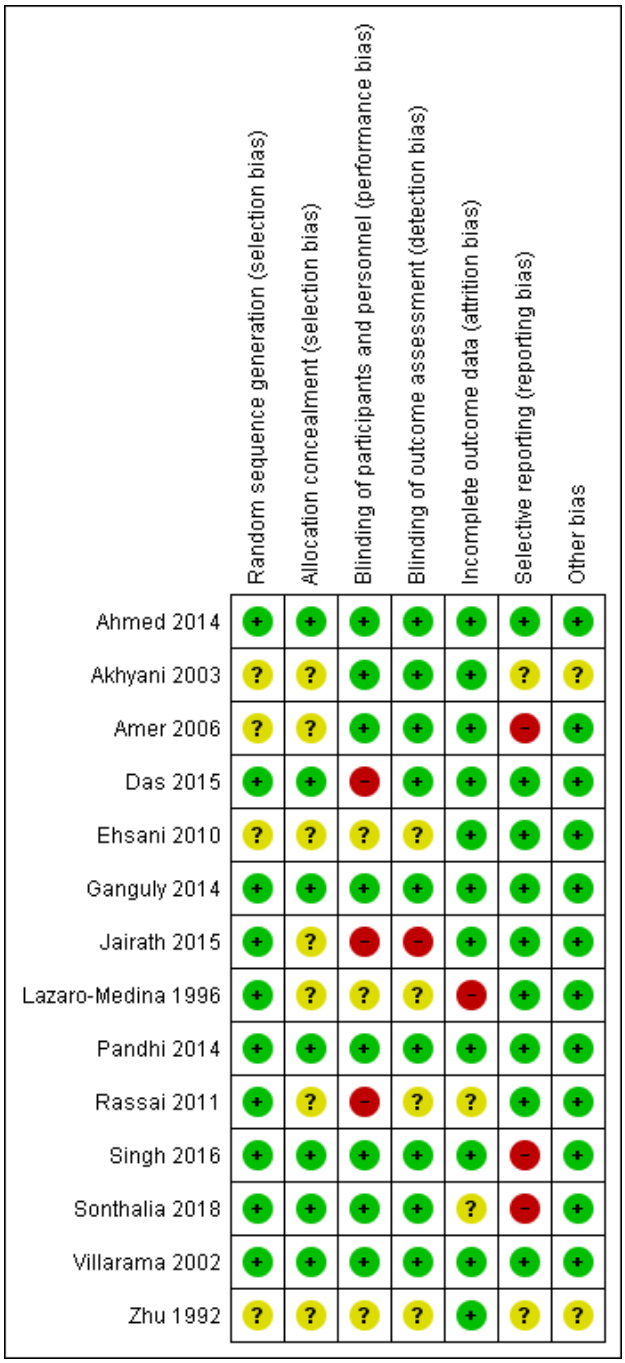


Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

We assessed risk of bias arising from method of generation of the allocation sequence to be low in 10 trials (Lazaro-Medina 1996; Villarama 2002; Rassai 2011; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Jairath 2015; Singh 2016; Sonthalia 2018). The remaining four trials were at unclear risk of bias for this domain.

Allocation concealment

We assessed risk of bias arising from method of allocation concealment to be low in seven trials (Villarama 2002; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Singh 2016; Sonthalia 2018). We judged the remaining seven trials as having an unclear risk for this domain.

Blinding

We rated risk of bias due to lack of blinding of participants and personnel as low in eight trials (Villarama 2002; Akhyani 2003; Amer 2006; Ahmed 2014; Ganguly 2014; Pandhi 2014; Singh 2016;

Sonthalia 2018); unclear in three trials (Zhu 1992; Lazaro-Medina 1996; Ehsani 2010); and high in three trials (Rassai 2011; Das 2015; Jairath 2015). Since the full text of the manuscript was not available for Zhu 1992, the information was extracted from the abstract. The authors clearly state in the abstract that this study was not blinded, but that both groups of participants received some form of intravenous therapy. Given the lack of information to determine whether or not this influenced the outcomes, we judged the risk of bias for this domain as unclear.

In nine trials, outcome assessment was clearly reported as blinded and thus detection bias was considered to be low (Villarama 2002; Akhyani 2003; Amer 2006; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Singh 2016; Sonthalia 2018). Blinding of outcome assessment was unclear in four trials (Zhu 1992; Lazaro-Medina 1996; Ehsani 2010; Rassai 2011). We assessed one trial, Jairath 2015, as at high risk of bias because the method of blinding was not specified and in all likelihood, given the tanning effect of ultraviolet radiation, blinding would have been difficult.

Incomplete outcome data

We assessed risk of attrition bias as low in 11 trials, Zhu 1992; Villarama 2002; Akhyani 2003; Amer 2006; Ehsani 2010; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Jairath 2015; Singh 2016, and unclear in two trials, Rassai 2011; Sonthalia 2018. We judged the remaining trial, Lazaro-Medina 1996, as at high risk of bias because multiple dropouts in a single group (group C) were evident, and no information as to the cause of the dropouts was provided.

Selective reporting

We rated risk of reporting bias as low in nine trials (Lazaro-Medina 1996; Villarama 2002; Ehsani 2010; Rassai 2011; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Jairath 2015); unclear in two trials (Zhu 1992; Akhyani 2003); and high in three trials (Amer 2006; Singh 2016; Sonthalia 2018). Amer 2006 failed to report on pruritus and concomitant medications used, both of which were stated in the methods. Singh 2016 failed to report a secondary outcome (50% reduction in severity) and PRASI score, and in Sonthalia 2018, there were inconsistencies in the final report of results of outcomes prespecified in the original article, and upon further contact with the author, the information provided was incomplete and we received no answer to our request for clarification.

Other potential sources of bias

We rated risk of other bias as low in 12 trials (Lazaro-Medina 1996; Villarama 2002; Amer 2006; Ehsani 2010; Rassai 2011; Ahmed 2014; Ganguly 2014; Pandhi 2014; Das 2015; Jairath 2015; Singh 2016; Sonthalia 2018), and unclear for the remaining two trials as there was insufficient information for judgement (Zhu 1992; Akhyani 2003).

Effects of interventions

See: **Summary of findings for the main comparison** Clarithromycin compared to placebo for pityriasis rosea; **Summary of findings 2** Erythromycin compared to placebo for pityriasis rosea; **Summary of findings 3** Azithromycin compared to placebo or vitamins for pityriasis rosea; **Summary of findings 4** Acyclovir compared to placebo, vitamins, or no treatment for pityriasis rosea; **Summary of findings 5** Acyclovir + calamine + cetirizine compared to calamine + cetirizine for pityriasis rosea; **Summary of findings 6** Acyclovir compared to erythromycin for pityriasis rosea

See: Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3, Summary of findings 4, Summary of findings 5, Summary of findings 6.

We analysed outcomes as described in the Types of outcome measures section. Each outcome was investigated for the pre-established interventions described in the Types of interventions section. Only those outcomes for which we found suitable data are described below. None of the included studies reported on the primary outcome of proportion of participants with good or excellent rash improvement within two weeks, as rated by the participant, or the secondary outcome of improvement in quality of life measures. We meta-analysed findings from the included studies when a drug was tested in at least two studies.

We did not perform subgroup or sensitivity analyses due to the limited number of studies identified for each specific outcome or intervention.

Comparison 1: Clarithromycin compared to placebo

We identified one study including 60 participants for this comparison (Summary of findings for the main comparison) (Ahmed 2014). Clarithromycin was given orally in a dose of 500 mg twice daily for adults and 250 mg twice daily for children for one week. The control intervention was placebo tablets.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment

No participants from either group suffered serious adverse effects requiring withdrawal (moderate-quality evidence).

Secondary outcome 1: The proportion of participants with resolution of itch within two weeks, as rated by the participant

The author of Ahmed 2014 was contacted and information on this outcome was provided. Each group had a total of 30 participants; however, not all participants had itch at baseline (16 in the clarithromycin group and 12 in the placebo group). No significant difference was found in the proportion of participants with resolution of itch at two weeks (9/16 versus 8/12; risk ratio (RR) 0.84, 95% confidence interval (CI) 0.47 to 1.52; moderate-quality evidence; Analysis 1.1)

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

No significant difference was found between clarithromycin and placebo in the proportion of participants with good or excellent rash improvement (assessed as partial or complete response to treatment) at two weeks, as rated by a medical practitioner (26/30 versus 23/30; RR 1.13, 95% CI 0.89 to 1.44; moderate-quality evidence; Analysis 1.2).

Comparison 2: Erythromycin compared to placebo

We identified two studies for this comparison (Summary of findings 2) (Villarama 2002; Akhyani 2003). Oral erythromycin was given in a total daily dose of 1 g/day for one week, in Akhyani 2003, or two weeks, in Villarama 2002.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment

One study evaluated adverse events, and no participants from either group suffered serious adverse effects (Villarama 2002).

Secondary outcome 2: Reduction in itch score within two weeks, as rated by the participant

One trial showed that erythromycin significantly reduced itch score compared with placebo (mean difference (MD) 3.95, 95% CI 3.37 to 4.53, 34 participants; P < 0.001; moderate-quality evidence; Analysis 2.1) (Villarama 2002).

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

For this outcome we found two relevant trials with a total of 86 participants (Villarama 2002; Akhyani 2003). The outcome was defined as partial or complete response (see Characteristics of included studies), but pooling of data was possible only for complete response, because these were the only results available regarding this outcome for one study. In the Villarama 2002 trial, with a total of 40 participants, there was a significant difference in the proportion of participants with complete cure in favour of erythromycin. Likewise, in the Akhyani 2003 study, complete cure was achieved by a higher proportion of participants in the erythromycin group. However, in the meta-analysis, even though there were more events in the erythromycin group, the results did not show a significant difference between groups (34/43 versus 14/43; RR 4.02, 95% CI 0.28 to 56.61; I^2 = 86%; Analysis 2.2). We assessed the quality of the evidence as low due to the small number of participants and considerable heterogeneity amongst studies. This considerable heterogeneity may be due to the differences in the treatment duration (one week in Akhyani 2003 versus two weeks in Villarama 2002), or differences in the characteristics of participants (age, race, ethnicity).

Secondary outcome 5: Minor participant-reported adverse events not requiring withdrawal of the treatment

In one trial (Villarama 2002), gastrointestinal upset was reported in both the erythromycin and placebo groups without any significant difference between groups (2/17 versus 1/17; RR 2.00, 95% CI 0.20 to 20.04; Analysis 2.3).

Comparison 3: Azithromycin compared to placebo (or vitamins)

Two studies were available for this comparison (Summary of findings 3) (Amer 2006; Pandhi 2014). In both studies, azithromycin was given orally in a dose of 12 mg/kg/day for five days. The control intervention was either placebo tablets or syrup, in Amer 2006, or multivitamin tablets, in Pandhi 2014.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment

Both studies evaluated adverse events, and no participants from either group suffered serious adverse effects (moderate-quality evidence).

Secondary outcome 1: The proportion of participants with resolution of itch within two weeks, as rated by the participant

The author of one study provided these data upon email contact (Pandhi 2014). No significant difference was found between azithromycin and placebo for this outcome (5/35 versus 6/35; RR 0.83, 95% CI 0.28 to 2.48; moderate-quality evidence; Analysis 3.1).

Secondary outcome 2: Reduction in itch score within two weeks, as rated by the participant

In the study by Pandhi 2014, the mean itch score, evaluated by means of a VAS, significantly decreased from baseline to two weeks in each of the intervention groups (from 1.31 ± 1.10 to 0.80 ± 0.80 for azithromycin and from 1.23 ± 1.24 to 0.76 ± 0.81 for placebo). Mean decrease per group was calculated from these values, and the associated standard deviation was imputed as described above. The change in itch score was similar in both groups (0.51 ± 0.79 for azithromycin versus 0.47 ± 0.89 for placebo; MD 0.04, 95% CI −0.35 to 0.43; moderate-quality evidence; Analysis 3.2).

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

Pooled data from two studies including a total of 119 participants showed no difference for this outcome between azithromycin and placebo (28/60 versus 26/59; RR 1.02, 95% CI 0.52 to 2.00; I^2 = 55%; low-quality evidence; Analysis 3.3). The statistical heterogeneity observed may have been due to the differences between the two trials in the race/ethnicity and age of the participants, or in the duration of the disease before diagnosis (Pandhi 2014 excluded patients presenting later than two weeks, whereas Amer 2006 did not). Nevertheless, both trials showed a lack of statistically significant difference in the outcome between the intervention groups. In Amer 2006, improvement was achieved by 22/25 participants in the azithromycin group and 17/24 in the placebo group (RR 1.24, 95% CI 0.93 to 1.67), and in Pandhi 2014, this was achieved by 6/35 versus 9/35, respectively (RR 0.67, 95% CI 0.27 to 1.67).

Secondary outcome 5: Minor participant-reported adverse events not requiring withdrawal of the treatment

Both studies reported mild abdominal pain (Amer 2006; Pandhi 2014), but the meta-analysis did not show a significant difference between groups (119 participants; 5/60 versus 0/59; RR 5.82, 95% CI 0.72 to 47.10; I^2 = 0%; Analysis 3.4). No significant difference between groups was found for diarrhoea in the one trial that reported this mild adverse event (2/25 versus 0/24; RR 4.81, 95% CI 0.24 to 95.25; Analysis 3.5) (Amer 2006).

Comparison 4: Acyclovir compared to placebo (or vitamins) or no treatment

One trial compared acyclovir (400 mg 5 times/day for 1 week) against no treatment (Rassai 2011); one trial compared acyclovir (800 mg 5 times/day for 1 week) against placebo (Singh 2016); and a third trial also evaluated acyclovir 800 mg 5 times/day for 1 week but used vitamin C tablets as the control intervention (Ganguly 2014). See Summary of findings 4. We could not analyse the effect of different dose regimens given the limited number of studies and the small sample size of the studies.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment

All three studies evaluated adverse events, and no participants from either group suffered serious adverse effects requiring withdrawal of the treatment (moderate-quality evidence).

Secondary outcome 1: The proportion of participants with resolution of itch within two weeks, as rated by the participant

The author of one study provided information on this outcome upon email contact (Singh 2016). Three out of 11 participants in the acyclovir group and 8 out of 10 in the placebo group experienced complete resolution of itch after two weeks. This difference was significant in favour of the placebo (RR 0.34, 95% CI 0.12 to 0.94; P = 0.04; moderate-quality evidence; Analysis 4.1)

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

Three trials assessed this outcome (Rassai 2011; Ganguly 2014; Singh 2016). One study divided the rash response into separate evaluation of erythema and scaling (Rassai 2011), and the other two studies used only a decrease or absence of erythema as a measure of response.

We performed a meta-analysis with the data from two trials (Ganguly 2014; Singh 2016), and using only reduction in erythema as a corresponding indicator of improvement in the Rassai 2011 trial. The consumer author and the expert dermatologists authors agreed that erythema was much more important than scaling in defining improvement. The results showed a significant difference in favour of acyclovir at week 2 (48/72 versus 19/69; RR 2.45, 95% CI 1.33 to 4.53; P = 0.004; I^2 = 39%; moderate-quality evidence; Analysis 4.2) (Summary of findings 4). Singh 2016 may have been inadequately powered, had dissimilar intervention groups with regards to age, and was more strict in the definition of outcome measures (reported data only for complete cure), which could explain the moderate heterogeneity observed in the meta-analysis.

The proportion of participants who showed a reduction in scaling of the lesions was significantly higher with acyclovir at two weeks (28/28 versus 17/26; RR 1.52, 95% CI 1.14 to 2.01; P = 0.004; Analysis 4.3) (Rassai 2011).

Secondary outcome 5: Minor participant-reported adverse events not requiring withdrawal of the treatment

In the Singh 2016 trial, one participant in the placebo group experienced abdominal pain and diarrhoea rated as mild and not requiring treatment, whilst no side effects were detected in any of the groups in the remaining two trials. This adverse event did not reach significance (0/72 versus 1/69; RR 0.31, 95% CI 0.01 to 7.02; Analysis 4.4).

Comparison 5. Acyclovir plus calamine and cetirizine compared to calamine plus cetirizine

One trial compared the combination of acyclovir tablets (400 mg 3 times/day for 7 days), calamine lotion, and cetirizine tablets (10 mg) versus calamine lotion and cetirizine tablets alone (considered as standard of care by the trialists) (Das 2015). See Summary of findings 5.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment

No serious adverse events requiring withdrawal were reported in either group (low-quality evidence).

Secondary outcome 1: The proportion of participants with resolution of itch within two weeks, as rated by the participant

We contacted the author of Das 2015 who provided information on this outcome. Resolution of itch at two weeks of follow-up was experienced by 9 out of 12 participants in the group that received acyclovir in addition to standard of care compared with only 2 out of 12 participants that received standard of care alone. This difference was significant in favour of acyclovir added to the standard of care (RR 4.50, 95% CI 1.22 to 16.62; Analysis 5.1), but we rated the quality of the evidence as low due to the small number of participants and lack of blinding (Summary of findings 5).

Secondary outcome 2: Reduction in itch score within two weeks, as rated by the participant

In Das 2015, the mean itch score, evaluated on a scale from 0 to 10, significantly decreased from baseline to week 2 in the group receiving acyclovir plus standard of care (from 2.17 ± 0.83 to 0.33 ± 0.65), but not in the group receiving standard of care alone (from 2.25 ± 0.75 to 1.67 ± 0.98). The mean decrease per group was calculated from these values, and the associated standard deviation was imputed as described above. The mean change in itch score was significantly larger when acyclovir was added to standard of care (1.84 ± 0.60 versus 0.58 ± 0.70; MD 1.26, 95% CI 0.74 to 1.78; Analysis 5.2). As for the previous outcome, we rated the quality of the evidence as low due to the small number of participants and lack of blinding (Summary of findings 5).

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

Das 2015 did not report on this precise outcome. However, it is worth noting that this study did evaluate participants for reduction in lesional score (a measure of rash severity), which was calculated by the addition of erythema score (0 if absent, 1 if present), scaling score (0 if absent, 1 if present), and number of lesions score (< 30 lesions given a score of 1; 30 to 100 lesions given a score of 2; and > 100 lesions given a score of 3). Similar to the above-mentioned itch score, the mean lesional score significantly decreased from baseline to week 2 in the group receiving acyclovir plus standard of care (from 8.25 ± 1.06 to 2.17 ± 0.58), but not in the group receiving standard of care alone (from 8.42 ± 1.08 to 5.58 ± 0.51). The mean decrease per group was calculated from these values, and the associated standard deviation was imputed as described above. The mean change in lesional score was significantly greater when acyclovir was added to standard of care (6.08 ± 0.77 versus 2.84 ± 0.81; MD 3.24, 95% CI 2.61 to 3.87; Analysis 5.3). We rated the quality of the evidence as moderate due to the small number of participants.

Secondary outcome 5: Minor participant-reported adverse events not requiring withdrawal of the treatment

No significant differences were found between groups in any of the reported adverse events in Das 2015: headache (3/12 versus 0/12; RR 7.00, 95% CI 0.40 to 122.44; Analysis 5.4); increased sleep (2/12 versus 1/12; RR 2.00, 95% CI 0.21 to 19.23; Analysis 5.5); nausea and

vomiting (2/12 versus 0/12; RR 5.00, 95% CI 0.27 to 94.34; Analysis 5.6); and dysgeusia (1/12 versus 0/12; RR 3.00, 95% CI 0.13 to 67.06; Analysis 5.7). No pooling of minor side effects was possible because the authors did not specify if any of the participants experienced more than one side effect.

Comparison 6. Acyclovir compared to erythromycin

This comparison was assessed in a single trial (Ehsani 2010). Acyclovir was given in dose of 800 mg 5 times/day and erythromycin in a dose of 400 mg 4 times/day, for a total of 10 days. See Summary of findings 6.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment.

No serious adverse events requiring withdrawal were reported in either group.

Secondary outcome 1: The proportion of participants with resolution of itch within two weeks, as rated by the participant

In a single study comparing acyclovir against erythromycin, 8/15 participants in the acyclovir group started with itch compared with 6/15 participants in the erythromycin group. Although all participants in the acyclovir group had resolution of itch compared with none of the participants in the erythromycin group, this difference did not reach statistical significance (8/8 versus 0/6; RR 13.22, 95% CI 0.91 to 192.02; Analysis 6.1). Due to the very small sample size, small number of events, and unclear risk of bias in several categories, we assessed this evidence as of low quality.

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

This outcome was assessed, but no participants in either group showed complete rash response at week 2 of follow-up.

Secondary outcome 5: Minor participant-reported adverse events not requiring withdrawal of the treatment

No side effects in either group are mentioned in the study.

Comparison 7: Prednisolone compared to placebo

A single trial with 70 randomised participants evaluated the comparison of low-dose prednisolone tapered over 2 weeks versus placebo (Sonthalia 2018). Oral prednisolone was given as a single dose of 20 mg/day for 5 days, followed by 15 mg/day for the next 5 days, and 10 mg/day for the last 5 days. Concomitant symptomatic treatment with antipruritic lotion (calamine with liquid paraffin) was allowed during the study.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment

No serious adverse events requiring withdrawal were detected in either group.

Secondary outcome 1: The proportion of participants with resolution of itch within two weeks, as rated by the participant

We contacted the author of Sonthalia 2018, and information on this outcome was provided. Resolution of itch at two weeks of follow-up was experienced by 32/34 participants in the prednisolone group and 11/34 participants in the placebo group. This difference was significant in favour of prednisolone (RR 2.91, 95% CI 1.78 to 4.76; low-quality evidence; Analysis 7.1).

Secondary outcome 2: Reduction in itch score within two weeks, as rated by the participant

The mean itch score, evaluated on a scale from 0 to 10, significantly decreased from baseline to week 2 in each of the intervention arms (from 1.31 ± 1.02 to 0.41 ± 0.69 for prednisolone and from 1.40 ± 1.1 to 0.81 ± 0.71 for placebo). Mean decrease per group was calculated from these values, and the associated standard deviation was imputed as described above. The mean change in itch score did not differ between groups (MD 0.31, 95% CI −0.05 to 0.67; low-quality evidence; Analysis 7.2).

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

The author of Sonthalia 2018 provided this information upon email contact. Good-to-excellent rash improvement at two weeks of follow-up was noted in 34/35 participants in the prednisolone group and 21/35 participants in the placebo group. This difference was significant in favour of prednisolone (RR 1.62, 95% CI 1.23 to 2.13; low-quality evidence; Analysis 7.3).

Secondary outcome 5: Minor participant-reported adverse events not requiring withdrawal of the treatment

No significant differences were found between groups for any of the reported adverse events in Sonthalia 2018. In the treatment group, two participants complained of mild gastric hyperacidity (Analysis 7.4), and one participant complained of transient anxiety and palpitations (Analysis 7.5). In the placebo group, one participant complained of belching (Analysis 7.6), and another participant reported the development of a stye (Analysis 7.7).

In addition to the outcomes described, the authors of Sonthalia 2018 evaluated relapse rate at 12 weeks, detecting it in six participants (17%) in the prednisolone group and only one participant (3%) in the placebo group (RR 6.00, 95% CI 0.76 to 47.29; low-quality evidence; Analysis 7.8).

Comparison 8. Oral dexchlorpheniramine versus oral betamethasone versus combination of oral dexchlorpheniramine and oral betamethasone

A single trial evaluated the comparison of oral dexchlorpheniramine 4 mg (alone) versus oral betamethasone 500 mcg (alone) versus a combination of oral dexchlorpheniramine 2 mg plus oral betamethasone 250 mcg (Lazaro-Medina 1996). The study included 27 to 31 participants per group and had a high proportion of dropouts that were unbalanced between groups, along with unclear risk of bias in several other categories (see Characteristics of included studies). We therefore assessed the overall quality of the evidence for the outcomes described below for this comparison as very low.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment

Adverse events were assessed, but no serious adverse events requiring withdrawal were reported in any group.

Secondary outcome 1: The proportion of participants with resolution of itch within two weeks, as rated by the participant

No significant difference was found for this outcome when comparing oral dexchlorpheniramine versus oral betamethasone (11/25 versus 14/29; RR 0.91, 95% CI 0.51 to 1.63; Analysis 8.1) or oral dexchlorpheniramine versus a combination of oral dexchlorpheniramine and oral betamethasone (11/25 versus 9/17; RR 0.83, 95% CI 0.44 to 1.56; Analysis 9.1) or oral betamethasone versus a combination of oral dexchlorpheniramine and oral betamethasone (14/29 versus 9/17; RR 0.91, 95% CI 0.51 to 1.64; Analysis 10.1).

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

No significant difference was found for this outcome when comparing oral dexchlorpheniramine alone versus oral betamethasone alone (12/25 versus 21/29; RR 0.66, 95% CI 0.42 to 1.06; Analysis 8.2). However, a significant difference was found for this outcome favouring dexchlorpheniramine alone versus the combination of betamethasone and dexchlorpheniramine (12/25 versus 1/17; RR 8.16, 95% CI 1.17 to 57.05; P = 0.03; Analysis 9.2). A significant difference was also found favouring betamethasone alone versus betamethasone plus dexchlorpheniramine (21/29 versus 1/17; RR 12.31, 95% CI 1.81 to 83.52; P = 0.01; Analysis 10.2).

Comparison 9. Glycyrrhizin (potenline) compared to procaine

We identified one small trial for this comparison (Zhu 1992).

Secondary outcome 3: The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner

There was no significant difference between groups for this outcome (12/12 versus 8/11; RR 1.36, 95% CI 0.93 to 1.98; Analysis 11.1). Due to unclear risk of bias across different categories and very small sample size, we assessed this evidence as of very low quality.

Comparison 10. Ultraviolet light compared to emollient

One trial assessed the comparison of narrowband ultraviolet B phototherapy (fixed dose of 250 J/cm^2 3 times/week for 4 weeks) with application of a topical emollient (Jairath 2015), but the outcomes were only reported at four weeks. As noted above, PR may improve after two weeks on its own, thus we excluded the trial from the analysis of efficacy outcomes.

Primary outcome 2: Serious adverse events, i.e. serious enough to require withdrawal of the treatment

No serious adverse events requiring withdrawal were reported in either group.

Secondary outcome 5: Minor participant-reported adverse events not requiring withdrawal of the treatment

At four weeks of follow-up, that is after completion of the treatment, the study authors noted hyperpigmentation in 62% (31/50 versus 0/50; RR 63.00, 95% CI 3.96 to 1002.01; P = 0.003; Analysis 12.1) and hypopigmentation in 16% of participants in the treatment group (8/50 versus 0/50; RR 17.00, 95% CI 1.01 to 286.82; P = 0.05; Analysis 12.2). Also, three participants in the treatment group complained of a burning sensation (3/50 versus 0/50; RR 7.00, 95% CI 0.37 to 132.10; Analysis 12.3). It is unclear whether these side effects first occurred during the treatment of after the treatment had already been completed.

DISCUSSION

Pityriasis rosea was first accurately described by the French dermatologist Camille Melchior Gibert in 1860 (Percival 1932). Many trials have been conducted to identify the cause of PR, but the number of controlled trials of its treatment remains rather small. The number of patients who undergo spontaneous remission and do not seek medical attention is unknown. Given that PR is a rather benign condition, in some patients where the rash is asymptomatic or does not affect quality of life, awaiting spontaneous remission may be acceptable. Unfortunately, those who seek medical attention do so because of the severity of the rash itself or due to the discomfort caused by pruritus. In PR there seems to be no correlation between the extensiveness of the rash, the severity of itch, and their impact on quality of life (Chuh 2005a). Some people with extensive rash might not experience any itch at all.

Summary of main results

We identified 11 new trials that met the inclusion criteria in this review update. One of these trials failed to report outcomes at week 2 and was therefore not analysed (Jairath 2015). In general, risk of selection bias was unclear in about a third of studies (random sequence generation) to over a half of studies (allocation concealment), and low in the rest of the studies. Risk of performance bias and reporting bias was high for 21% of the studies. Other judgements related to risk of bias were for the most part low risk of bias.

Several treatment modalities were studied in the current review, both topical and systemic. Topical treatments included calamine and emollient lotion. Systemic treatment included oral antibiotics such as azithromycin, clarithromycin, and erythromycin; the antiviral drug acyclovir; oral antihistamines dexchlorpheniramine and cetirizine; oral corticosteroids prednisolone and betamethasone; intravenously administered glycyrrhizin and procaine; and ultraviolet B phototherapy. Pooling of data for analysis was feasible for only three comparisons: erythromycin compared to placebo, azithromycin compared to placebo, and acyclovir compared to placebo, and for only a few outcomes within each comparison. Meta-analyses comprised two or maximum three trials.

Unless otherwise stated, all effectiveness outcomes were reported by the participants and assessed within two weeks of treatment.

Clarithromycin was investigated in a single trial, which found that it probably has no additional beneficial effect compared to placebo in terms of achieving resolution of itch or good or excellent rash improvement as rated by a medical practitioner (moderate-quality evidence). Reduction in itch score was not measured. See Summary of findings for the main comparison.

Based on the meta-analysis of two studies, we are uncertain whether erythromycin has a beneficial effect compared with placebo in terms of increasing the proportion of participants with good or excellent rash improvement (low-quality evidence). This meta-analysis also had considerable heterogeneity, possibly due

to the differences in the treatment duration (one week versus two weeks) or differences in participant characteristics (age, race and ethnicity). The proportion of participants with resolution of itch was not measured, but the reduction in itch score was measured in one study and is probably higher with erythromycin (moderate-quality evidence). See Summary of findings 2.

Azithromycin probably has no additional beneficial effect on the resolution of itch or the reduction in itch score when compared to placebo (one trial, moderate-quality evidence). Moreover, meta-analysis of two trials showed that there may be no difference between these treatments in the proportion of participants with good or excellent rash improvement, as rated by a medical practitioner (low-quality evidence). The pooled data showed moderate heterogeneity, possibly due to differences in the race/ethnicity and age of the participants, or in the duration of the disease before diagnosis. Nevertheless, both trials showed lack of difference between the intervention groups for this outcome. See Summary of findings 3.

Regarding medical practitioner-rated good or excellent rash improvement, pooled data from three trials showed that there is probably a larger improvement in favour of acyclovir than placebo, vitamins, or no treatment. Although the pooled data showed moderate heterogeneity, we assessed the quality of the evidence as moderate. One small trial indicated that the proportion of participants with resolution of itch is probably higher with placebo than with acyclovir (moderate-quality evidence), but reduction in itch score was not measured. See Summary of findings 4.

Based on a single trial, it may be beneficial to add acyclovir to standard care (calamine lotion and oral cetirizine) to reduce itch severity and to achieve itch resolution (low-quality evidence). The proportion of participants with good or excellent rash improvement within two weeks, as rated by a medical practitioner, was not measured in this trial. However, this study used a scoring system for evaluating rash severity that included absence or presence of erythema and scaling as well as the number of lesions, and showed a difference in favour of acyclovir in reducing the rash lesional score. The scoring system used in this trial seems objective and the assessors of the outcome were blinded (moderate-quality evidence); therefore, we included these results in the footnotes of Summary of findings 5.

It is important to note that the trials comparing acyclovir either to placebo or to other interventions used different dose regimens and different interventions as control, which made it impossible to compare different doses of acyclovir with regard to their efficacy; however, this may have an impact on the clinical outcomes. No studies compared different dose regimens of acyclovir.

None of the studies included in this review reported serious adverse events. The evidence was of low quality for the comparison of acyclovir plus standard care compared to standard care alone; it was moderate quality for the comparisons of clarithromycin versus placebo, erythromycin versus placebo, azithromycin versus placebo (or vitamins), and acyclovir versus placebo (or vitamins) or no treatment.

The single trial comparing oral clarithromycin versus placebo did not measure minor participant-reported adverse events not requiring withdrawal of the treatment. In the other key comparisons, the rates were very low with each treatment (< 3%), and there were no significant differences between groups. These results were mainly based on single studies with a small sample size. Reported minor adverse events included gastrointestinal upset, mild abdominal pain, diarrhoea, and headache (low- to moderate-quality evidence).

None of the included studies measured our primary outcome of proportion of participants with good or excellent rash improvement within two weeks, as rated by the participant, or our secondary outcome of improvement in quality of life as rated by the participant by the use of questionnaires or other methods. Uncertainty remains about the effects of treatments that have not been appropriately assessed through controlled trials, some of which are even used as standard treatment nowadays, such as emollients, topical antihistamine creams, topical corticosteroid creams, or ultraviolet B phototherapy.

Overall completeness and applicability of evidence

All but one of the clinical trials were performed in dermatology departments (one was performed in a paediatric ward) where the diagnosis of PR was made by one or more dermatologists and in some cases even confirmed by biopsy. Consequently, there is a high degree of certainty that the participants in these trials indeed had PR. Diagnostic criteria of PR have been suggested previously (Chuh 2003b), and validated in Chinese and Indian patients (Chuh 2003a), but only five trials specifically mention the use of these criteria (Villarama 2002; Amer 2006; Rassai 2011; Pandhi 2014; Singh 2016).

Lesional biopsy for histopathology was performed for all participants in three studies (Lazaro-Medina 1996; Ganguly 2014; Jairath 2015). Lesional histopathological changes in PR are non-specific, and can be used to substantiate the diagnosis and exclude important differential diagnoses.

Although participant age ranged from 2 to 60 years, most participants in the included trials were young adults, adequately representing the age group most commonly affected by PR (see Characteristics of included studies tables).

Several treatment modalities commonly used by dermatologists in practice to treat PR, such as topical corticosteroids of varying potencies, emollients, oral antihistamines, or ultraviolet radiation (UVB phototherapy), were not covered (or adequately evaluated) by studies included in this review. Furthermore, although this review identified some low- to moderate-quality evidence in favour of acyclovir when compared to placebo, vitamins, no treatment, or standard of care, different dose regimens of the drug were used in the various studies and were not compared in any. Consequently, the available evidence is insufficient to permit a conclusion on the ideal dose regimen of acyclovir in the management of PR. No studies addressed the use of other antivirals such as valacyclovir or famciclovir, drugs used in the treatment of other herpetic infections.

None of the included trials assessed the proportion of participants with rash improvement within two weeks, as rated by the participant, or the impact of the disease on the quality of life measures.

Amongst the 14 studies included in this review, itch was evaluated in nine studies (Lazaro-Medina 1996; Villarama 2002; Ehsani 2010; Ahmed 2014; Pandhi 2014; Das 2015; Jairath 2015; Singh 2016; Sonthalia 2018). The study by Zhu 1992

lumped symptoms (itch) and signs (rash) together and evaluated them as a single outcome measurement. The key outcome of complete resolution of itch within two weeks was evaluated in seven trials assessing azithromycin versus placebo (Pandhi 2014), clarithromycin versus placebo (Ahmed 2014), acyclovir versus placebo (Singh 2016), acyclovir added to standard of care versus standard of care alone (Das 2015), acyclovir versus erythromycin (Ehsani 2010), prednisolone versus placebo (Sonthalia 2018), and dexchlorpheniramine versus betamethasone versus their combination (Lazaro-Medina 1996).

Six trials assessed reduction of itch scores at week 2 as rated by the participant.

Regarding the outcome of rash improvement within two weeks as rated by a medical practitioner, most trials reported this secondary outcome as their main outcome, but used different measures to assess it. There was some heterogeneity amongst studies in the definition of good or excellent rash improvement, that is the definitions of complete, partial, or no response.

Except for the studies of Akhyani 2003 and Zhu 1992, for which there was insufficient information about adverse events, and the Ahmed 2014 study, in which participants were not specifically asked about adverse effects, the included studies seem to have assessed adverse events adequately.

Quality of the evidence

In general, the amount of comparative trials of any intervention for PR is small. The number of participants in the 14 studies included in this review varied from 23 to 100. The existing body of evidence does not permit a robust conclusion regarding the main interventions and outcomes assessed in the current review. Nine different topical and systemic interventions were included in this review, most of them based on a single trial.

Risk of bias (Figure 4 and Figure 5) was low for random sequence generation for all trials except four, for which it was unclear. Allocation concealment was unclear for seven trials and low for seven trials. Blinding of participants and personnel was assessed as at high risk of bias in three trials, unclear risk in three trials, and low risk in the remaining trials. Blinding of outcome assessment was assessed as at low risk of bias in nine trials, unclear risk in four trials, and high risk in one trial. Attrition bias was assessed as at low risk of bias in all but two trials at unclear risk and one trial at high risk. Reporting bias was low for most studies, except for two trials at unclear risk and three trials at high risk.

We assessed the quality of the evidence as either moderate or low. We downgraded outcomes by one or two levels for the following reasons: small number of participants in each study (imprecision), small number of events (imprecision), scarce number of trials (imprecision), risk of bias (study limitations), or heterogeneity amongst studies (inconsistency). Reasons for downgrading the evidence for each comparison and outcome are noted in the corresponding 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6).

Potential biases in the review process

After thoroughly searching all relevant/available databases, trials registers, conference proceedings, and literature, and after attempting to obtain published or unpublished clinical trials from the pharmaceutical industry, we performed the process of data collection and analysis. This included five review authors who independently analysed, selected, and extracted data for inclusion in this version of the systematic review. All the criteria for assessment had been clearly defined prior to the data entry. In each step of the process, at least two review authors participated independently, and all discrepancies were carefully weighted and discussed until consensus was obtained. Hence, there is low risk of bias related to the process of searching, study selection, data collection, extraction, and analysis.

Agreements and disagreements with other studies or reviews

The original version of the review published in 2007, Chuh 2007, included only three RCTs. Based on the results of these trials, no recommendation regarding the cost-effectiveness of interventions could be made due to the lack of evidence for efficacy of most treatment modalities. The only exception was erythromycin, although the evidence for this treatment came from a single, small trial. However, for the purpose of this update, we identified 11 new studies for inclusion. Unlike the original version of the review, this updated version found evidence that acyclovir, despite moderate heterogeneity of the results, probably improves rash and itch in PR. However, there remains a need for larger RCTs to confirm these results.

Two other recently published systematic reviews focusing on acyclovir are only partially in agreement with the findings of this review. The authors of Chang 2019 are more affirmative about the effects of acyclovir; however, two of the included studies are non-randomised trials (Amatya 2012 and Drago 2006; see Characteristics of excluded studies). Furthermore, unlike in our review, they pooled data from Ehsani 2010 in which acyclovir was compared with erythromycin, together with data from trials in which acyclovir was compared with no treatment or placebo. On the other hand, the choice of outcomes was such that unfavourable data from Singh 2016 were not pooled in the meta-analysis. The conclusion reached by the Rodriguez-Zuniga 2018 review that acyclovir is superior to placebo in terms of rash improvement is comparable with that of our review. The main difference between these reviews and our review was their inclusion of both randomised and quasi-randomised trials, and selection of various time points for the outcome assessments.

AUTHORS' CONCLUSIONS

Implications for practice

Pityriasis rosea (PR) is a self-limiting condition, and spontaneous recovery is expected in 2 to 12 weeks without active treatment. It is unusual for the face to be affected, and many people with PR do not itch at all. The severity of itch and its effect on quality of life are not necessarily correlated with the extent of the rash. When choosing treatment options, the severity of itch, the extent and distribution of the rash, and potential adverse effects of the treatment all need to be taken into consideration. In most cases, the option of no

treatment, and providing reassurance, may be a valid alternative given the benign nature of PR.

The treatments currently used for PR are for the most part not supported by well-designed clinical trials, and many different types of treatment are used. Regarding the most commonly used treatment options in the management of people with PR, this review provides no information about which emollients or which potency topical corticosteroids might be preferred for the topical treatment of PR, and we found inadequate evidence about whether oral antihistamines or phototherapy provides any clinical benefit compared to no treatment. There is little, low- to moderate-quality evidence on the favourable effects of acyclovir for the treatment of PR. However, this evidence comes from trials with different dose regimens of acyclovir; therefore, it is unclear which doses of acyclovir perform best. Since the causative agent(s) of PR have not yet been definitively identified, and the disease usually follows a benign, self-limiting course, until sufficient evidence is obtained regarding the origin of the disease, the treatment remains symptomatic.

The current review update suggests that acyclovir probably improves the rash in PR better than placebo, vitamins, or no treatment, or when added to combined treatment regimens. However, evidence for the effect of acyclovir on itch was inconclusive. All of the trials assessing acyclovir were small, and further adequately powered studies with similar methodology are needed to corroborate these findings. The optimal dose of acyclovir remains unknown.

Regarding the use of various macrolide antibiotics, none of those reviewed (i.e. erythromycin, azithromycin, or clarithromycin) showed any conclusive beneficial effect on rash. Based on a single trial, erythromycin is probably more beneficial in reducing the severity of itching than placebo. There is probably no difference between azithromycin and placebo (or vitamins) in resolution of itch or reduction in itch score. Similarly, there is probably no difference in resolution of itch between clarithromycin and placebo.

None of the included studies in this review reported serious adverse events (based on low- to moderate-quality evidence).

The single trial assessing oral clarithromycin versus placebo did not measure minor participant-reported adverse events not requiring withdrawal of the treatment. In the other key comparisons, the rates were very low with each treatment (< 3%), and there were no significant differences between groups (low- to moderate-quality evidence). Reported minor adverse events included gastrointestinal upset, mild abdominal pain, diarrhoea, and headache.

The evidence of efficacy of other treatments is insufficient to draw meaningful conclusions, but the absence of evidence of efficacy for many treatments in PR does not necessarily imply that they are not effective.

Implications for research

We recommend well-designed, adequately powered (using a sample size calculation) randomised controlled trials to investigate treatments for PR that are commonly used by dermatologists. These interventions include topical corticosteroids versus placebo, emollients versus placebo, ultraviolet radiation, and antihistamines for people with PR who are symptomatic. Trials should adhere to the CONSORT guidelines (Schulz 2010).

We advocate that further research should be conducted to validate a set of diagnostic criteria for PR, which future clinical trials might then adopt. Pityriasis rosea may present with atypical features, and therefore the use of validated diagnostic criteria might aid in standardising the inclusion of participants in future clinical trials and allow the results to be compared. For participants with a typical PR eruption, we do not think that biopsies for confirmation are necessary. Insisting on lesional biopsy for all participants might also lead to a lower recruitment rate in randomised controlled trials and other types of research for PR, thus causing a potential threat to external validity.

As there is no universally accepted active intervention for PR, we suggest that future clinical trials for PR should include placebo as a control, rather than merely comparing several potentially active interventions against one another.

The time frame for assessing outcomes should preferably be within two weeks, as spontaneous remission cannot be excluded after two weeks. If the time frame for assessing outcomes is beyond two weeks, the study should be adequately powered to compare treatment versus placebo in order to demonstrate meaningful reductions in average time course to resolution of rash or symptoms.

None of the included studies measured our primary outcome of proportion of participants with rash improvement within two weeks as rated by the participant, but most studies measured rash improvement by a medical practitioner. However, different measures were used to assess this. Future studies should include an assessment of rash improvement measured by the participant and using a standardised outcome measure. Future trials should consult the Cochrane Skin Outcomes Set Initiative (CSG-COUSIN) to check for any core outcome measures.

Furthermore, trials should consider always clarifying the beginning of the rash as the starting point of the disease. We advocate that, apart from baseline assessment of the extensiveness of the rash, the baseline assessment of symptoms (mainly itch) and effects on quality of life should be well documented in any future clinical trials on PR. We also advocate that validated quality of life indexes (e.g. standardised questionnaires) should be adopted as measures of this outcome. Without relevant information regarding the impact of the treatment on quality of life, complete judgement regarding the clinical importance and cost-effectiveness of interventions is not possible due primarily to the benign and self-limiting course of the disease.

Researchers should be alert to the fact that many people with PR have little or no itch. A diagnostic label in Latin may be given, but the condition may not bother the person at all. The potential adverse effects of any intervention should be balanced against potential benefit, if any, for this group of people.

None of the trials reported any severe side effects, and mild side effects did not differ between study groups in any of the included trials. These adverse events were measured in the short term; long-term effects should also be taken into consideration.

As shown, there is moderate-quality evidence for a beneficial effect of acyclovir in good or excellent rash improvement in PR (compared against placebo). Studies confirming this effect should therefore be conducted to establish whether or not this treatment could become standard of care. Since there is no ideal dose regimen of acyclovir for PR, studies evaluating different dose regimens are needed. Given the incidence of the disease, large studies evaluating dose-response may not be possible, so even comparing dose regimens of 4 g per day to regimens of 2 g or less per day could provide a first step in clarifying whether low- versus high-dose acyclovir provides a better clinical response. Since evidence suggests the implication of several members of the Herpesviridae family in PR, trials evaluating other antivirals such as valacyclovir or famciclovir could be justified, although the cost of such treatments is usually higher. Uncertainty remains about the effects of treatments that have not been appropriately assessed through controlled trials, some of which are even used as standard treatment nowadays, such as emollients, topical antihistamine creams, topical corticosteroid creams, and ultraviolet B phototherapy.

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REFERENCES

References to studies included in this review

Ahmed 2014 *{published data only}*

Ahmed N, Iftikhar N, Bashir U, Rizvi SD, Sheikh ZI, Manzur A. Efficacy of Clarithromycin in Pityriasis rosea. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP* 2014;**24**(11):802-5. [CENTRAL: CN-01254667; PUBMED: 25404436]

Akhyani 2003 *{published data only}*

Akhyani M, Mortazavi H, Izadi, Ehsani AH. The efficacy of oral erythromycin in the treatment of patients with pityriasis rosea: A randomized double blind, placebo controlled clinical trial. *Iranian Journal of Dermatology* 2003;**7**(25):3. [www.iranjd.ir/english/abstract.asp?articleID=1197]

Amer 2006 *{published data only}*

Amer A, Fischer H. Azithromycin does not cure pityriasis rosea. *Pediatrics* 2006;**117**(5):1702-5. [CENTRAL: CN-00564928; PUBMED: 16651327]

Das 2015 *{published data only}*

* Das A, Sil A, Das NK, Roy K, Das AK, Bandyopadhyay D. Acyclovir in pityriasis rosea: an observer-blind, randomized, controlled trial of effectiveness, safety and tolerability. *Indian Dermatology Online Journal* 2015;**6**(3):181-4. [CENTRAL: CN-01445605; PUBMED: 26009712]

Ehsani 2010 *{published data only}*

Ehsani A, Esmaily N, Noormohammadpour P, Toosi S, Hosseinpour A, Hosseini M, et al. The comparison between the efficacy of high dose acyclovir and erythromycin on the period and signs of pitiriasis rosea. *Indian Journal of Dermatology* 2010;**55**(3):246-8. [CENTRAL: CN-00796204; PUBMED: 21063515]

Ganguly 2014 *{published data only}*

Ganguly S. A randomized, double-blind, placebo-controlled study of efficacy of oral acyclovir in the treatment of pityriasis rosea. *Journal of Clinical and Diagnostic Research* 2014;**8**(5):YC01-4. [CENTRAL: CN-00992962; PUBMED: 24995231]

Jairath 2015 *{published data only}*

Jairath V, et al. Narrowband UVB phototherapy in pityriasis rosea. *Indian Dermatology Online Journal* 2015;**6**(5):326-9. [CENTRAL: CN-01445613; PUBMED: 26500862]

Lazaro-Medina 1996 *{published data only}*

Lazaro-Medina A, Villena-Amurao C, Dy-Chua NS, Sit-Toledo MSW, Villanueva B. A clinicohistopathologic study of a randomized double-blind clinical trial using oral dexchlorpheniramine 4 mg, betamethasone 500 mcg and betamethasone 250 mcg with dexchlorpheniramine 2 mg in the treatment of pityriasis rosea: a preliminary report. *Journal of the Philippine Dermatological Society* 1996;**5**:3-7. [CENTRAL: CN-00602242]

Pandhi 2014 *{published data only}*

Pandhi D, Singal A, Vema P, Sharma R. The efficacy of azithromycin in pityriasis rosea: A randomized, double-blind, placebo-controlled trial. *Indian Journal of Dermatology, Venerology and Leprology* 2014;**80**(1):36-40. [CENTRAL: CN-00982445; PUBMED: 24448121]

Rassai 2011 *{published data only}*

Rassai S, Feily A, Sina N, Abtahian S. Low dose of acyclovir may be an effective treatment against pityriasis rosea: a random investigator-blind clinical trial on 64 patients. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2011;**25**(1):24-6. [PUBMED: 20477925]

Singh 2016 *{published and unpublished data}*

Singh S, Anurag, Tiwary NK. Acyclovir is not effective in pityriasis rosea: Results of a randomized, triple blind, placebo-controlled trial. *Indian Journal of Dermatology, Venereology and Leprology* 2016;**82**(5):505-9. [CENTRAL: CN-01211602; DOI: 10.4103/0378-6323.182791]

Sonthalia 2018 *{published data only}*

Sonthalia S, Kumar A, Zawar V, Priya A, Yadav P, Srivastava S, Gupta A. Double-blind randomized placebo-controlled trial to evaluate the efficacy and safety of short-course low-dose oral prednisolone in pityriasis rosea. *Journal of Dermatological Treatment* 2018;**29**(6):617-22. [PUBMED: 29363373]

Villarama 2002 *{unpublished data only}*

Villarama C, Lansang P. The efficacy of erythromycin stearate in pityriasis rosea: a randomized, double-blind, placebo-controlled trial. 10th Philippine Dermatological Society Resident's Research Forum. Phillipines: Phillipine Dermatological Society, 27th November 2002:1-17.

Zhu 1992 *{published data only}*

Zhu QY. The observation of curative effects of glycyrrhizin in treating pityriasis rosea. *Journal of Clinical Dermatology* 1992;**21**(1):43. [CENTRAL: CN-00455018]

References to studies excluded from this review

Amatya 2012 *{published data only}*

Amatya A, Rajouria EA, Karn DK. Comparative study of effectiveness of oral acyclovir with oral erythromycin in the treatment of Pityriasis rosea. *Kathmandu University Medical Journal* 2012;**10**(37):57-61. [CENTRAL: CN-00878938; PUBMED: 22971864]

Arndt 1983 *{published data only}*

* Arndt KA, Paul BS, Stern RS, Parrish JA. Treatment of pityriasis rosea with UV radiation. *Archives of Dermatology* 1983;**119**(5):381-2. [CENTRAL: CN-00263403; PUBMED: 6847217]

Chen 1994 *{published data only}*

* Chen ZY. UV-N type phototherapy instrument for pityriasis rosea. *Chinese Journal of Dermatovenereology* 1994;**8**(2):121. [CENTRAL: CN-00797091]

Drago 2006 *{published data only}*

Drago F, Vecchio F, Rebora A. Use of high-dose acyclovir in pityriasis rosea. *Journal of American Academy of Dermatology* 2006;**54**(1):82-5. [CENTRAL: CN-00561883; PUBMED: 16384760]

Grobe 1984 *{published data only}*

* Grobe JW. Virostatic effect in the treatment of pityriasis rosea irritata with moroxydine-HCI. *Dermatosen in Beruf und Umwelt* 1984;**32**(1):25. [PUBMED: 6705693]

Gutowski 1950 *{published data only}*

* Gutowski W. Trial treatment of Gibert's pityriasis rosea with bismuth and penicillin. *Polski tygodnik lekarski* 1950;**5**(51-52):1774-6. [PUBMED: 14816144]

Kalbarczyk 1957 *{published data only}*

* Kalbarczyk K, Gutowski W. Prednisone in the treatment of Gibert's pityriasis. *Wiadomości lekarskie* 1972;**25**(7):627-8. [PUBMED: 5047081]

Karpouzis 2003 *{published data only}*

* Karpouzis A, et al. Clarithromycin in pityriasis rosea: a clinical study. *Journal of the European Academy of Dermatology and Venereology* 2003;**17**(Suppl 3):157. [CENTRAL: CN-00478603]

Leenutaphong 1995 *{published data only}*

* Leenutaphong V, Jiamton S. UVB phototherapy for pityriasis rosea: a bilateral comparison study. *Journal of the American Academy of Dermatology* 1995;**33**(6):996-9. [CENTRAL: CN-00121183; PUBMED: 7490372]

Merchant 1974 *{published data only}*

* Merchant M, Hammond R. Controlled study of ultraviolet light for pityriasis rosea. *Cutis* 1974;**14**(4):548-9. [CENTRAL: CN-00269370]

Rasi 2008 *{published data only}*

Rasi A, Tajziehchi L, Savabi-Nasab S. Oral erythromycin is ineffective in the treatment of pityriasis rosea. *Jornal of Drugs in Dermatology* 2008;**7**(1):35-8. [CENTRAL: CN-00629806; PUBMED: 18246696]

Roxas *{unpublished data only}*

Roxas MZL, Reyes RPS. Erythromycin in pityriasis rosea: a placebo-controlled clinical trial in East Avenue Medical Center. From the authors.

Salin 1957 *{published data only}*

* Salin RW, Curtis AC, Wheeler A. The treatment of pityriasis rosea with convalescent plasma, gamma globulin, and pooled plasma. *American Medical Association Archives in Dermatology* 1957;**76**(5):659-62. [PUBMED: 13468800]

Sharma 2000 *{published data only}*

* Sharma PK, Yadav TP, Gautam RK, Taneja N, Satyanarayana L. Erythromycin in pityriasis rosea: A double-blind, placebo-controlled clinical trial. *Journal of the American Academy of Dermatology* 2000;**42**(2 Pt 1):241-4. [CENTRAL: CN-00266080; PUBMED: 10642679]

Valkova 2004 *{published data only}*

* Valkova S, Trashlieva M, Christova P. UVB phototherapy for pityriasis rosea. *Journal of the European Academy of Dermatology and Venereology* 2004;**18**(1):111-2. [PUBMED: 14678553]

Yamashita 1988 *{published data only}*

Yamashita Y. A well controlled comparative clinical study of the effect of difluprednate DFBA myser ointment on pityriasis rosea Gibert. *Hifu* 1988;**30**(5):669-75.

Additional references

Ahmed 1986

Ahmed MA. Pityriasis rosea in the Sudan. *International Journal of Dermatology* 1986;**25**:184-5. [PUBMED: 3699964]

Amer 2007

Amer A, Fischer H, Li X. The natural history of pityriasis rosea in black American children: how correct is the "classic" description?. *Archives of Pediatrics and Adolescent Medicine* 2007;**161**(5):503-6. [PUBMED: 17485628]

Bas 2015

Bas Y, Kalkan G, Seckin HY. Palmar initial lesion in pityriasis rosea. *Journal of the Pakistan Medical Association* 2015;**65**(1):95-7. [PUBMED: 25831687]

Bozdag 2005

Bozdag KE, Güven FO, Zeytinoglu A, Erensoy S, Karaman A, Bilgiç A. Investigation of herpes simplex virus DNA in pityriasis rosea by polymerase chain reaction. *International Journal of Dermatology* 2005;**44**(6):477-8. [PUBMED: 15941434]

Broccolo 2005

Broccolo F, Drago F, Careddu AM, Foglieni C, Turbino L, Cocuzza CE, et al. Additional evidence that pityriasis rosea is associated with reactivation of human herpesvirus-6 and -7. *Journal of Investigative Dermatology* 2005;**124**(6):1234-40. [PUBMED: 15955099]

Canpolat Kirac 2009

Canpolat Kirac B, Adisen E, Bozdayi G, Yucel A, Fidan I, Aksakal N, et al. The role of human herpesvirus 6, human herpesvirus 7, Epstein-Barr virus and cytomegalovirus in the aetiology of pityriasis rosea. *Journal of the European Academy of Dermatology and Venereology* 2009;**23**(1):16-21. [PUBMED: 18713231]

Castanedo 2003

Castanedo-Cazares JP, Lepe V, Moncada B. Should we still use phototherapy for pityriasis rosea?. *Photodermatology, Photoimmunology and Photomedicine* 2003;**19**:160-1. [PUBMED: 12914603]

Chang 2019

Chang HC, Sung CW, Lin MH. The efficacy of oral acyclovir during early course of pityriasis rosea: a systematic review and meta-analysis. *Journal of Dermatological Treatment* 2019;**30**(3):288-93. [PUBMED: 30109959]

Chen 2011

Chen JF, Chiang CP, Chen YF, Wang WM. Pityriasis rosea following influenza (H1N1) vaccination. *Journal of the Chinese Medical Association* 2011;**74**(6):280-2. [PUBMED: 21621174]

Cheong 1989

Cheong WK, Wong KS. An epidemiological study of pityriasis rosea in Middle Road Hospital. *Singapore Medical Journal* 1989;**30**:60-2. [PUBMED: 2595391]

Chuah 2014

Chuah SY, Chia HY, Tan HH. Recurrent and persistent pityriasis rosea: an atypical case presentation. *Singapore Medical Journal* 2014;**55**(1):e4-6. [PUBMED: 24452984]

Chuang 1982

Chuang TY, Ilstrup DM, Perry HO, Kurland LT. Pityriasis rosea in Rochester, Minnesota, 1969 to 1978. *Journal of the American Academy of Dermatology* 1982;**7**:80-9. [PUBMED: 6980904]

Chuh 2001

Chuh AAT, Chiu SSS, Peiris JSM. Human herpesvirus 6 and 7 DNA in peripheral blood leukocytes and plasma in patients with pityriasis rosea by polymerase chain reaction - a prospective case control study. *Acta Dermato-Venereologica* 2001;**81**:289-90. [PUBMED: 11720179]

Chuh 2003a

Chuh A, Lee A, Molinari N. Case clustering in pityriasis rosea - a multi-center epidemiological study in primary care settings in Hong Kong. *Archives of Dermatology* 2003;**139**:489-93. [PUBMED: 12707096]

Chuh 2003b

Chuh AAT. Diagnostic criteria for pityriasis rosea - a prospective case control study for assessment of validity. *Journal of the European Academy of Dermatology and Venereology* 2003;**17**:101-3. [PUBMED: 12602987]

Chuh 2003c

Chuh AAT. Quality of life in children with pityriasis rosea - a prospective case control study. *Pediatric Dermatology* 2003;**20**:474-8. [PUBMED: 14651563]

Chuh 2005a

Chuh AAT, Chan HHL. The effect on quality of life in patients with pityriasis rosea - is it associated with rash severity?. *International Journal of Dermatology* 2005;**44**:372-7. [PUBMED: 15869534]

Chuh 2005b

Chuh A, Molinari N, Sciallis G, Harman M, Akdeniz S, Nanda A. Temporal case clustering in pityriasis rosea - a regression analysis on 1379 patients in Minnesota, Kuwait and Diyarbakyr, Turkey. *Archives of Dermatology* 2005;**141**(6):767-71. [PUBMED: 15967925]

Chuh 2006

Chuh AA, Chan PK, Lee A. The detection of human herpesvirus 8 DNA in plasma and peripheral blood mononuclear cells in adult patients with pityriasis rosea. *Journal of the European Academy of Dermatology and Venereology* 2006;**20**:667-71. [PUBMED: 16836493]

Deng 2007

Deng Y, Li H, Chen X. Palmoplantar pityriasis rosea: two case reports. *Journal of the European Academy of Dermatology and Venereology* 2007;**21**(3):406-7. [PUBMED: 17309476]

Dias 2011

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. National Institute for Health and Clinical Excellence. National Institute for Health and Clinical Excellence, 2011.

Drago 1997a

Drago F, Ranieri E, Malaguti F, Losi E, Rebora A. Human herpesvirus 7 in pityriasis rosea. *Lancet* 1997;**349**:1367-8. [PUBMED: 9149704]

Drago 1997b

Drago F, Ranieri E, Malaguti F, Battifoglio ML, Losi E, Rebora A. Human herpesvirus 7 in patients with pityriasis rosea. Electron microscopy investigations and polymerase chain reaction in mononuclear cells, plasma and skin. *Dermatology* 1997;**195**:374-8. [PUBMED: 9529560]

Drago 2002

Drago F, Malaguti F, Ranieri E, Losi E, Rebora A. Human herpes virus-like particles in pityriasis rosea lesions: an electron microscopy study. *Journal of Cutaneous Pathology* 2002;**29**(6):359-61. [PUBMED: 12135467]

Drago 2008

Drago F, Broccolo F, Zaccaria E, Malnati M, Cocuzza C, Lusso P, et al. Pregnancy outcome in patients with pityriasis rosea. *Journal of the American Academy of Dermatology* 2008;**58**(5 Suppl 1):S78-83. [PUBMED: 18489054]

Drago 2009a

Drago F, Broccolo F, Rebora A. Pityriasis rosea: an update with a critical appraisal of its possible herpesviral etiology. *Journal of the American Academy of Dermatology* 2009;**61**(2):303-18. [PUBMED: 19615540]

Drago 2009b

Drago F, Rebora A. Treatments for pityriasis rosea. *Skin Therapy Letter* 2009;**14**(3):6-7. [PUBMED: 19585058]

Drago 2014a

Drago F, Ciccarese G, Rebora A, Parodi A. Relapsing pityriasis rosea. *Dermatology* 2014;**229**(4):316-8. [PUBMED: 25412725]

Drago 2014b

Drago F, Ciccarese G, Rebora A, Parodi A. Pityriasis rosea and pityriasis rosea-like eruption: can they be distinguished?. *Journal of Dermatology* 2014;**41**(9):864-5. [PUBMED: 25182298]

Drago 2014c

Drago F, Ciccarese G, Javor S, Parodi A. Vaccine-induced pityriasis rosea and pityriasis rosea-like eruptions: a review of the literature. *Journal of the European Academy of Dermatology and Venereology* 2016;**30**(3):544-5. [DOI: 10.1111/jdv.12942.; PUBMED: 25545307]

Drago 2014d

Drago F, Broccolo F, Javor S, Drago F, Rebora A, Parodi A. Evidence of human herpesvirus-6 and -7 reactivation in miscarrying women with pityriasis rosea. *Journal of the American Academy of Dermatology* 2014;**71**(1):198-9. [PUBMED: 24947696]

Drago 2015a

Drago F, Broccolo F, Ciccarese G, Rebora A, Parodi A. Persistent pityriasis rosea: an unusual form of pityriasis rosea with persistent active HHV-6 and HHV-7 infection. *Dermatology* 2015;**230**(1):23-6. [PUBMED: 25612842]

Drago 2015b

Drago F, Ciccarese G, Broccolo F, Cozzani E, Parodi A. Pityriasis Rosea in Children: Clinical Features and Laboratory Investigations. *Dermatology* 2015;**231**(1):9-14. [PUBMED: 25997658]

Drago 2015c

Drago F, Ciccarese G, Rebora A, Parodi A. Pityriasis rosea following human papillomavirus vaccination. *Brazilian Journal of Infectious Diseases* 2015;**19**(2):224-5. [PUBMED: 25527111]

GRADE Handbook

Schünemann H, Brożek J, Guyatt G, Oxman A, eds. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, 2013.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed prior to 30 May 2018. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Harman 1998

Harman M, Aytekin S, Akdeniz S, Inaloz HS. An epidemiological study of pityriasis rosea in the Eastern Anatolia. *European Journal of Epidemiology* 1998;**14**:495-7. [PUBMED: 9744683]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Jacyk 1980

Jacyk WK. Pityriasis rosea in Nigerians. *International Journal of Dermatology* 1980;**19**:397-9. [PUBMED: 7419321]

Karabulut 2002

Karabulut AA, Kocak M, Yilmaz N, Eksioglu M. Detection of human herpesvirus 7 in pityriasis rosea by nested PCR. *International Journal of Dermatology* 2002;**41**:563-7. [PUBMED: 12358824]

Kaymak 2008

Kaymak Y, Taner E. Anxiety and depression in patients with pityriasis rosea compared to patients with tinea versicolor. *Dermatology Nursing* 2008;**20**(5):367-70,377. [PUBMED: 19051783]

Kempf 1999

Kempf W, Adams V, Kleinhans M, Burg G, Panizzon RG, Campadelli-Fiume G, et al. Pityriasis rosea is not associated with human herpesvirus 7. *Archives of Dermatology* 1999;**135**(9):1070-2. [PUBMED: 10490111]

Klauder 1924

Klauder JV. Pityriasis rosea with particular reference to its unusual manifestations. *Journal of the American Medical Association* 1924;**82**:178-83.

Kosuge 2000

Kosuge H, Tanaka-Taya K, Miyoshi H, Amo K, Harada R, Ebihara T, et al. Epidemiological study of human herpesvirus-6 and human herpesvirus 7 in pityriasis rosea. *British Journal of Dermatology* 2000;**143**(4):795-8. [PUBMED: 11069458]

Kyriakis 2006

Kyriakis KP, Palamaras I, Terzoudi S, Pagana G, Emmanuelides S, Michailides C. Epidemiologic characteristics of pityriasis rosea in Athens Greece. *Dermatology Online Journal* 2006;**12**(1):24. [PUBMED: 16638392]

Legat 2018

Legat FJ. The Antipruritic Effect of Phototherapy. *Frontiers in Medicine* 2018;**30**(5):333. [DOI: 10.3389/fmed.2018.00333; PUBMED: 30560129]

Messenger 1982

Messenger AG, Knox EG, Summerly R, Muston HL, Ilderton E. Case clustering in pityriasis rosea: support for role of an infective agent. *British Medical Journal (Clinical Research Edition)* 1982;**284**:371-3. [PUBMED: 6800463]

Nanda 1999

Nanda A, Al-Hasawi F, Alsaleh QA. A prospective survey of pediatric dermatology clinic patients in Kuwait: an analysis of 10,000 cases. *Pediatric Dermatology* 1999;**16**:6-11. [PUBMED: 10027990]

Offidani 2000

Offidani A, Pritelli E, Simonetti O, Cellini A, Giornetta L, Bossi G. Pityriasis rosea associated with herpesvirus 7 DNA. *Journal of the European Academy of Dermatology and Venereology* 2000;**14**:313-4. [PUBMED: 11204526]

Olumide 1987

Olumide Y. Pityriasis rosea in Lagos. *International Journal of Dermatology* 1987;**26**:234-6. [PUBMED: 3596885]

Ozyürek 2014

Ozyürek GD, Alan S, Cenesizoğlu E. Evaluation of clinico-epidemiological and histopathological features of pityriasis rosea. *Postępy Dermatologii i Alergologii* 2014;**31**(4):216-21. [PUBMED: 25254006]

Pariser 1987

Pariser RJ, Pariser DM. Primary care physicians' errors in handling cutaneous disorders. *Journal of the American Academy of Dermatology* 1987;**17**:239-45. [PUBMED: 3624563]

Percival 1932

Percival GH. Pityriasis rosea. *British Journal of Dermatology* 1932;**44**:241-53.

Polat 2012

Polat M, Yildirim Y, Makara A. Palmar herald patch in pityriasis rosea. *Australasian Journal of Dermatology* 2012;**53**(3):e64-5. [PUBMED: 22881477]

Prantsidis 2009

Prantsidis A, Rigopoulos D, Papatheodorou G, Menounos P, Gregoriou S, Alexiou-Mousatou I, et al. Detection of human herpesvirus 8 in the skin of patients with pityriasis rosea. *Acta Dermato-venereologica* 2009;**89**(6):604-6. [PUBMED: 19997691]

Rerknimitr 2017

Rerknimitr P, Otsuka A, Nakashima C, Kabashima K. The etiopathogenesis of atopic dermatitis: barrier disruption, immunological derangement, and pruritus. *Inflammation and Regeneration* 2017;**37**:14. [DOI: 10.1186/s41232-017-0044-7; PUBMED: 29259713]

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rivard 2005

Rivard J, Lim HW. Ultraviolet phototherapy for pruritus. *Dermatologic Therapy* 2005;**18**(4):344-54. [PUBMED: 16297008]

Robati 2009

Robati RM, Toossi P. Plantar herald patch in pityriasis rosea. *Clinical and Experimental Dermatology* 2009;**34**(2):269-70. [PUBMED: 19187313]

Rodriguez-Zuniga 2018

Rodriguez-Zuniga M, Torres N, Garcia-Perdomo H. Effectiveness of acyclovir in the treatment of pityriasis rosea. A systematic review and meta-analysis. *Anais Brasileiros de Dermatologia* 2018;**93**(5):686-95. [PUBMED: 30156618]

Sankararaman 2014

Sankararaman S, Velayuthan S. Multiple recurrences in pityriasis rosea - a case report with review of the literature. *Indian Journal of Dermatology* 2014;**59**(3):316. [PUBMED: 24891682]

Scheinfeld 2003

Scheinfeld NS, Tutrone WD, Torres O, Weinberg JM. Macrolides in dermatology. *Clinics in Dermatology* 2003;**21**(1):40-9. [PUBMED: 12609587]

Schulz 2010

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c332.

Sharma 2008

Sharma L, Srivastava K. Clinicoepidemiological study of pityriasis rosea. *Indian Journal of Dermatology, Venereology and Leprology* 2008;**74**(6):647-9. [PUBMED: 19171994]

Tay 1999

Tay YK, Goh CL. One-year review of pityriasis rosea at the National Skin Centre, Singapore. *Annals of the Academy of Medicine of Singapore* 1999;**28**:829-31. [PUBMED: 10672397]

Vag 2004

Vág T, Sonkoly E, Kárpáti S, Kemény B, Ongrádi J. Avidity of antibodies to human herpesvirus 7 suggested primary infection in young adults with pityriasis rosea. *Journal of the European Academy of Dermatology and Venereology* 2004;**18**:738-40. [PUBMED: 15482314]

van Zuuren 2017

Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. *Cochrane Database of Systematic Reviews* 2017, Issue 2. [DOI: 10.1002/14651858.CD012119.pub2]

Watanabe 1999

Watanabe T, Sugaya M, Nakamura K, Tamaki K. Human herpesvirus 7 and pityriasis rosea. *Journal of Investigative Dermatology* 1999;**113**:288-9. [PUBMED: 10469323]

Watanabe 2002

Watanabe T, Kawamura T, Jacob SE, Aquilino EA, Orenstein JM, Black JB, et al. Pityriasis rosea is associated with systemic active infection with both human herpesvirus-7 and human herpesvirus-6. *Journal of Investigative Dermatology* 2002;**119**(4):793-7. [PUBMED: 12406322]

Wong 2001

Wong WR, Tsai CY, Shih SR, Chan HL. Association of pityriasis rosea with human herpesvirus-6 and human herpesvirus-7 in Taipei. *Journal of the Formosan Medical Association* 2001;**100**:478-83. [PUBMED: 11579614]

Yasukawa 1999

Yasukawa M, Sada E, Machino H, Fugita S. Reactivation of human herpesvirus 6 in pityriasis rosea. *British Journal of Dermatology* 1999;**140**:169-70. [PUBMED: 10215792]

Yildirim 2004

Yildirim M, Aridogan BC, Baysal V, Inaloz HS. The role of human herpes virus 6 and 7 in the pathogenesis of pityriasis rosea. *International Journal of Clinical Practice* 2004;**58**:119-21. [PUBMED: 15055857]

Yoshida 1998

Yoshida M, Yamada M, Tsukazaki T, Chatterjee S, Lakeman FD, Nii S, et al. Comparison of antiviral compounds against human

herpesvirus 6 and 7. *Antiviral Research* 1998;**40**(1-2):73-84. [PUBMED: 9864048]

Yoshida 1999

Yoshida M. Detection of human herpesvirus 7 in patients with pityriasis rosea and healthy individuals. *Dermatology* 1999;**199**:197. [PUBMED: 10559605]

Zawar 2009

Zawar V, Kumar R. Multiple recurrences of pityriasis rosea of Vidal: a novel presentation. *Clinical and Experimental Dermatology* 2009;**34**(5):e114-6. [PUBMED: 19508465]

Zawar 2010a

Zawar V. Pityriasis amiantacea-like eruptions in scalp: a novel manifestation of pityriasis rosea in a child. *International Journal of Trichology* 2010;**2**(2):113-5. [PUBMED: 21712901]

Zawar 2010b

Zawar V, Jerajani H, Pol R. Current trends in pityriasis rosea. *Expert Review of Dermatology* 2010;**5**(3):325-33. [DOI: 10.1586/edm.10.28]

References to other published versions of this review

Chuh 2007

Chuh AAT, Dofitas BL, Comisel G, Reveiz L, Sharma V, Garner SE, et al. Interventions for pityriasis rosea. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD005068.pub2; PUBMED: 17443568]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmed 2014

Methods	This was a randomised, double-blind, controlled trial that lasted for 13 months (July 2008 to July 2009).
Participants	**Setting:** Dermatology department of the Military Hospital in Rawalpindi, Pakistan **Inclusion criteria of the trial:** • patients aged 10 years and above, diagnosed with PR by 2 dermatologists, presenting within 2 weeks of the onset of rash **Exclusion criteria of the trial:** • renal disease (creatinine clearance less than 30 mL/minute) • diabetes • hypersensitivity to macrolides • pregnancy • prior use of antibiotics, topical or systemic steroids within 2 weeks • using bismuth, metronidazole, barbiturates, captopril, and ketotifen **Baseline characteristics:** • groups were comparable with respect to age, gender, duration of disease and number of lesions, itching, presence of herald patch, preceding history of upper respiratory tract infection, sexual contact, and similar disease in family members • VDRL was negative in all participants **Gender:** Male = 33 Female = 27 **Age (mean/SD):** Intervention = 23.3 (SD = 10.34) years Compare = 21.67 (SD = 7.42) years **Total number randomised**: 60

Ahmed 2014 *(Continued)*

	Losses to follow-up: none
Interventions	**Intervention (N = 30):** Adults received oral clarithromycin 500 mg twice daily for 1 week, children aged 10 to 12 years received 250 mg twice daily for 1 week. **Control intervention (N = 30):** Participants received similar-looking placebo pills containing glucose.
Outcomes	**Primary outcome of the trial:** Response to treatment, defined as: • complete, when all lesions started healing in less than 2 weeks without the appearance of any fresh lesion; • partial, when lesions regressed partially or few new lesions appeared in 2 weeks; • no response, when there was no regression or new lesions continued to appear even after 2 weeks. **Secondary outcome of the trial:** Resolution of itch at week 2 For all outcomes, interval of assessment was at weeks 1, 2, 4, and 6.
Funding source	Not reported
Notes	Outcomes listed here as secondary were not defined as such in the original report, but were reported in email correspondence with the study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 803): "Randomization was done by lottery method" Comment: randomisation method was considered adequate
Allocation concealment (selection bias)	Low risk	Quote (page 803): "A doctor not involved in the treatment or follow-up of the patients was responsible for randomisation and concealment... The outcomes A or B were recorded separately on individual paper cards which were then placed in opaque sealed envelopes." Comment: seems likely that allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 803): "Neither the patient nor the doctor who followed-up, knew to which group the patient belonged." Comment: participants and study personnel were blinded to group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 803): "Neither the patient nor the doctor who followed-up knew to which group the patient belonged" Comment: it seems that the doctor who followed up did the assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.

Ahmed 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported. No adverse events were reported in the paper; however, the authors provided them by email.
Other bias	Low risk	None found.

Akhyani 2003

Methods	This was a randomised, double-blind, placebo-controlled trial (of unknown total duration).
Participants	**Setting:** Dermatology department of the Razi Hospital, Tehran, Iran **Inclusion criteria of the trial:** • patients with PR (diagnosed by 3 dermatologists), presenting within 1 week of the onset of rash, who consented to treatment **Exclusion criteria of the trial:** • allergy to erythromycin • concern regarding other differential diagnoses such as syphilis, eczema, psoriasis **Baseline characteristics:** • the study included 24 female and 22 male participants aged between 11 and 36 years, but there are no data on baseline imbalances between intervention groups. **Gender:** Intervention (male + female): 23 Compare (male + female): 23 **Age (range):** 11 to 36 years **Total number randomised:** 46 **Losses to follow-up:** none
Interventions	**Intervention (N = 23)**: oral erythromycin 1 g daily for 1 week **Control intervention (N = 23)**: placebo capsules for 1 week
Outcomes	Response to treatment, defined as: • complete, when there was no residual rash, no new rash, no redness in 2 weeks; • partial, when there was decrease in new rash or improving some red spots in 2 weeks; • no response, when there was no change within 2 weeks. Interval of assessment was at weeks 1, 2, and 6.
Funding source	Not reported
Notes	The abstract of this study was available in English, but the body of the study was in Persian. The full translation was not available, but specific questions on methodology were answered by an Iranian colleague.

Akhyani 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There was no information on how the random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	There was no information on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial is reported as double-blind. Participants and researchers were blinded. Only the pharmacist was unblinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	According to the report, participants and researchers were blinded. No specification as to how the blinding was performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	Unclear risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported. However, there is no information about adverse events.
Other bias	Unclear risk	There was insufficient information for judgement.

Amer 2006

Methods	This was a double-blind, placebo-controlled trial (of unknown total duration).
Participants	**Setting:** General Pediatric Clinic, Adolescent Clinic and Emergency Department of Children's Hospital of Michigan, Detroit, USA **Inclusion criteria of the trial:** • diagnosis of typical PR agreed upon by 2 clinicians **Exclusion criteria of the trial:** • receipt of an antibiotic within 2 weeks of diagnosis of PR • history of intolerance to azithromycin or erythromycin • presence of lesions for > 3 weeks at the time of diagnosis **Baseline characteristics:** • the study included 16 male and 33 female black participants, aged between 2 and 18 years (mean age was 8 years). • there were more boys (42% vs 24%) in the placebo group. • groups were comparable with respect to mean age, duration of lesions, and presence of pruritus. **Gender:** Male = 16 Female = 33

Amer 2006 *(Continued)*

	Age (mean/SD): Intervention = 8 years Compare = 8.4 years **Total number randomised**: 49 **Losses to follow-up:** none
Interventions	**Intervention (N = 25)**: azithromycin (oral) 12 mg/kg/day for 5 days **Control intervention (N = 24)**: placebo tablets or syrup similar in number/volume, identical-appearing and similar-tasting for 5 days
Outcomes	**Primary outcome of the trial:** Rates of cure and of partial resolution, defined as: • completely resolved PR, if areas involved previously were neither scaly nor raised and no new lesions had appeared; • partial resolution, if there was a decrease in lesion number, scaliness, or thickness but with active (i.e. raised and scaly) lesions still present; • no response (treatment failure), when there was no change in participant's skin appearance. Both examining physicians had to agree on the lesion resolution status at each follow-up. Digital photographs of all lesions were taken at enrolment and each follow-up and were reviewed at the end of study to look for missed areas of disagreement. The authors also considered reporting on the following outcomes in the methods section: • presence of pruritus • presence of residual pigmentary changes • medication adverse effects Interval of assessment was at week 1, 2, and 4 for all outcomes.
Funding source	The study was supported by a grant from Pfizer Inc.
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1703): “Patients were randomly assigned” Comment: there was no information on the method of randomisation in the original report. When contacted for clarification, the study authors did not provide any additional details.
Allocation concealment (selection bias)	Unclear risk	There was no information on the method used. When contacted for clarification, the study authors did not provide any additional details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1703): “Only the study pharmacist was aware of study patients’ treatment type… Placebo patients received an appropriate volume, or number of tablets, of an identical-appearing and similar-tasting placebo” Comment: blinding of participants was done

Amer 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 1703): “Only the study pharmacist was aware of study patients’ treatment type” Quote (page 1704): "We reviewed our photographs at the end of study (before we broke the code of treatment assignment) to look for missed areas of disagreement." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	High risk	The protocol was not available and it was not registered in a prospective clinical trial. The study states that the presence of pruritus was measured at baseline and each follow-up, but this information was not included in the results. There was also no report on concomitant treatment used, although the study states that this had been recorded at each follow-up.
Other bias	Low risk	None found.

Das 2015

Methods	This was a randomised, placebo-controlled trial lasting for 5 months (May 2013 to September 2013).
Participants	**Setting:** Department of Dermatology, Medical College, Kolkata, West Bengal, India **Inclusion criteria of the trial:** • consenting adult patients (> 18 years) of either sex diagnosed with PR **Exclusion criteria of the trial:** • patients not willing to participate in the study • pregnant or lactating women • history of sensitivity to acyclovir or cetirizine • advanced disease of vital organs • suspicion of mimicking diseases (fungal infection, psoriasis, or eczema) **Baseline characteristics:** • groups were comparable with respect to age, sex, duration and severity of skin disease, and intensity of itching. **Gender:** Male = 14 Female = 10 **Age (mean/SD):** Intervention = 32.5 (SD = 10.41) years Compare = 34 (SD = 12.06) years **Total number randomised:** 24

Das 2015 *(Continued)*

	Losses to follow-up: none
Interventions	**Intervention A (N = 12):** acyclovir tablets 400 mg 3 times/day for 7 days along with standard of care (calamine lotion and cetirizine 10 mg tablets once daily at bedtime for 4 weeks) **Intervention B (N = 12):** standard of care (calamine lotion and cetirizine 10 mg tablets once daily at bedtime for 4 weeks)
Outcomes	1. Decrease in itch assessed by participants (1-to-10 VAS) 2. Decrease in lesional score (calculated by addition of erythema score, scaling score, and number of lesions score) 3. Decrease in pruritus score (scale 0 to 3) 4. Response to therapy in terms of appearance of new lesions, categorised as: a. complete response: no new lesions, disappearance of all previous lesions, with or without residual postlesional pigmentation; b. partial response: a few new lesions, regression or disappearance of some previous lesions; c. no response: no regression of lesions, appearance of new lesions. 5. Adverse events Interval of assessment was at week 1, 2, 3, and 4 for all outcomes except for outcome 4, where it was at the end of week 4 (email correspondence with study authors).
Funding source	None
Notes	Clinical Trials Registry - India (CTRI/2013/12/004240)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were allocated, using a computer-generated randomisation schedule (simple randomisation by 1:1 allocation), to one of two treatment groups" Comment: randomisation method was considered adequate
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was done by sequentially numbered opaque envelopes." Comment: it seems likely that allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomization and dispensing of medications were done by a person unrelated to the trial. The physician evaluating the effectiveness and safety parameters was thus unaware of the treatment group of the patient making the trial observer-blind." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.

Das 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	The trial was registered with Clinical Trials Registry - India (CTRI/2013/12/004240). Protocol was not available, but all prespecified outcomes were reported.
Other bias	Low risk	None found.

Ehsani 2010

Methods	This was a randomised clinical trial lasting for 12 months (May 2007 to April 2008).
Participants	**Setting:** Department of Dermatology, Razi Hospital, Tehran, Iran **Inclusion criteria of the trial:** • patients with PR, diagnosis confirmed by 2 academic dermatologists • patients presenting within the first week of their disease • extensive generalised lesions **Exclusion criteria of the trial:** • pregnant or breastfeeding women • known sensitivity to acyclovir or erythromycin • renal or hepatic impairment • suspected fungal infection, psoriasis, or eczema • secondary syphilis (positive VDRL and TPHA) **Baseline characteristics:** • the study included adult patients and children (mean age was 32.9 ± 16 years) • groups were comparable with respect to age, sex, and presence of pruritus **Gender:** Male = 15 Female = 15 **Age (range):** Intervention = 3 (< 25 years); 5 (25 to 35 years); 7 (> 35 years) Compare = 4 (< 25 years); 6 (25 to 35 years); 5 (> 35 years) **Total number randomised**: 30 **Losses to follow-up:** none
Interventions	**Intervention A (N = 15)**: erythromycin 400 mg 4 times a day for 10 days **Intervention B (N = 15)**: acyclovir 4 g daily in 5 divided doses for 10 days
Outcomes	1. Response to treatment categorised as: a. complete response: no new lesions followed by disappearance of all previous lesions, with or without residual postlesional pigmentation; b. partial response: few new lesions plus regression or disappearance of some previous lesions; c. no response: no regression of lesions, along with appearance of new lesions. 2. Proportion of participants with itch

Ehsani 2010 *(Continued)*

	Interval of assessment was at weeks 2, 4, and 8.
Funding source	None
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomised" Comment: no information was provided on how the random sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information was provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Acyclovir and erythromycin used in the study were in similar white pill forms, with the same packaging." Comment: there is insufficient information, and it is unclear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Acyclovir and erythromycin used in the study were in similar white pill forms, with the same packaging." Comment: there is insufficient information, and it is unclear who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	Low risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported.
Other bias	Low risk	None found.

Ganguly 2014

Methods	This was a randomised, double-blind, placebo-controlled trial lasting for 19 months (November 2006 to May 2008).
Participants	**Setting:** Department of Dermatology, Venereology & Leprosy, Pondicherry Institute of Medical Sciences, Pondicherry, India **Inclusion criteria of the trial:** • patients with clinical diagnosis of PR, irrespective of age and sex **Exclusion criteria of the trial:** • use of some form of systemic therapy for PR (e.g. corticosteroids, erythromycin) • major systemic illnesses including renal impairment • use of a drug known to cause PR-like eruption (allopurinol, arsenic, bismuth, barbiturate, gold, hydrochlorothiazide, organic mercurials, nimesulide, d-penicillamine, clonidine, isotretinoin, ketotifen, captopril, metronidazole, omeprazole) in the preceding 2 weeks with absence of herald patch and presence of eosinophilia

Ganguly 2014 *(Continued)*

	Baseline characteristics: • groups were comparable with respect to age, gender, and duration of disease. **Gender:** Male = unspecified Female = unspecified **Age (mean/SD):** Intervention = unspecified Compare = unspecified **Total number randomised**: 73 **Losses to follow-up:** 13 in total, balanced between groups, reason for all dropouts was failure to attend follow-up visit at week 1 or 2
Interventions	**Intervention (N = 38)**: acyclovir tablets: adults 800 mg 5 times/day, children 20 mg/kg/dose 4 times/day, for 7 days **Control intervention (N = 35)**: vitamin C tablets: adults 100 mg 5 times/day, children 50 mg 4 times/day, for 7 days **Use of concomitant treatment:** emollients and oral antihistamines were used for symptomatic treatment of itch
Outcomes	1. Regression of skin lesions, evaluated as: a. regressed; if erythema had decreased or disappeared in all lesions leaving desquamation or pigmentation; b. partially regressed; if erythema had decreased in ≥ 50% of lesions; c. unchanged; if decrease in erythema was recorded in < 50% of lesions 2. Time taken for clearance of lesions 3. Appearance of new lesions 4. Adverse events Interval of assessment was at week 1 and 2.
Funding source	Not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "simple randomisation by lottery" Comment: randomisation method considered adequate
Allocation concealment (selection bias)	Low risk	Quote (correspondence with authors): "The randomisation was done by a senior dermatologist other than the chief investigator who used the terms 'treatment A' and treatment B' on the prescription, according to the randomisation. Therefore, the chief investigator and the dermatologist assigned to give treatment were unaware of the drug prescribed to individual patients. The pharmacist dispensed tablet acyclovir in the described dose for 'treatment A' and vitamin C in the described dose for 'treatment B' in identical containers. So, the patients were also kept unaware of the therapeutic group to which they belong to (acyclovir or placebo)."

Ganguly 2014 *(Continued)*

		Comment: it seems likely that allocation was concealed via the method described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As above - participants and study personnel were unaware of group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (correspondence with authors): "The meaning of 'treatment A' and 'treatment B' was disclosed to the chief investigator after completion of the trial." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 13 dropouts, which were balanced between groups (8 in the intervention group and 5 in the control group), reasons for dropouts was the same (loss to follow-up).
Selective reporting (reporting bias)	Low risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported. No adverse events were reported in the paper; however, the authors provided them by email.
Other bias	Low risk	None reported.

Jairath 2015

Methods	This was a randomised clinical trial (of unknown total duration).
Participants	**Setting:** skin outpatient department of a tertiary care hospital in India **Inclusion criteria of the trial:** • new or relapsing cases of PR, or both **Exclusion criteria of the trial:** • patients with photosensitivity, eye disorders, history of mood swings, mania • pregnancy and lactation • positive serology for syphilis • age less than 5 years **Baseline characteristics:** • groups were comparable with respect to age, gender, duration and severity of disease, and intensity of pruritus. **Gender:** Male = 52 Female = 28 **Age (mean/SD):** Intervention = 26.5 years Compare = 28.2 years **Total number randomised:** 100

Jairath 2015 *(Continued)*

	Losses to follow-up: none
Interventions	**Intervention (N = 50):** fixed-dose narrowband UVB phototherapy of 250 mJ/cm^2 3 times a week (on non-consecutive days) for 4 weeks **Control intervention (N = 50):** topical emollient
Outcomes	1. Reduction in PR severity score (PRSS) 2. Reduction in pruritus score 3. Duration of disease 4. Adverse events Interval of assessment for outcomes 1 and 2 was at week 4.
Funding source	None
Notes	Although this study met the inclusion criteria, it was excluded from the analysis because the authors did not provide information for outcomes at week 2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "were allocated into two groups by a computer-generated randomisation chart" Comment: randomisation method was considered adequate
Allocation concealment (selection bias)	Unclear risk	There was no information on the allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors stated that the study was double-blinded, but the blinding method is not specified, and lack of blinding is likely because control group was not irradiated.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The authors stated that the study was double-blinded, but the blinding method is not specified. Also, lack of blinding is likely because the control group was not irradiated, and UVB-induced skin pigmentation would likely reveal which participants received the active treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	Low risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported.
Other bias	Low risk	None reported.

Lazaro-Medina 1996

Methods	This was a randomised, double-blind clinical trial lasting for 26 months (March 1993 to April 1995).
Participants	**Setting:** Section of Dermatology, Philippine General Hospital, Manila, the Philippines **Inclusion criteria of the trial:**

Lazaro-Medina 1996 *(Continued)*

- patients of any age and gender diagnosed with PR

Exclusion criteria of the trial:

- patients with a history of intake of oral steroids, antihistamine, or combination of the 2 within the week prior to consultation
- history of topical steroid use a week prior to consultation
- positive KOH preparation of skin scrapings
- no consent of biopsy

Baseline characteristics:

- groups were comparable with respect to age, gender, occupation status, and clinical features.

Gender:

Male = 38

Female = 47

Age (range): 20.1 to 23.6 years

Total number randomised: 85

Losses to follow-up: 14 in total during treatment period (first 4 weeks); unbalanced between groups (2 in group A, 2 in group B, 10 in group C), reasons per group unknown

Interventions	**Intervention A (N = 27):** oral dexchlorpheniramine 4 mg 2 times/day for 2 weeks, then once a day for the following 2 weeks **Intervention B (N = 31):** oral betamethasone 500 mcg 2 times/day for 2 weeks, then once a day for the following 2 weeks **Intervention C (N = 27):** oral betamethasone 250 mcg + oral dexchlorpheniramine 2 mg 2 times/day for 2 weeks, then once a day for the following 2 weeks
Outcomes	1. Change in lesion count 2. Proprotion of participants with pruritus 3. Pigmentary changes 4. Disease recurrence 5. Adverse events Interval of assessment was at 3rd day and at week 1, 2, 3, 4, 8, and 12.
Funding source	Study was supported by Schering-Plough.
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 4): "randomised table provided by the statistician" Comment: randomisation method was considered adequate
Allocation concealment (selection bias)	Unclear risk	Quote (page 4): "Upon inclusion in the study, the patient was placed in the treatment group A, B or C" Comment: insufficient information

Lazaro-Medina 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 4): "Both investigators and patients were blinded to avoid bias" Comment: insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information for judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	14/85 missing within the treatment period (4 weeks from enrolment); unbalanced between groups (2 missing in group A, 2 in group B, 10 in group C), reasons per group unknown.
Selective reporting (reporting bias)	Low risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported.
Other bias	Low risk	None found.

Pandhi 2014

Methods	This was a randomised, double-blinded, placebo-controlled trial lasting for 14 months (February 2010 to March 2011).
Participants	**Setting:** dermatology outpatient department of an urban hospital in north India **Inclusion criteria of the trial:** • clinical diagnosis of PR agreed upon by 2 dermatologists **Exclusion criteria of the trial:** • disagreement between the 2 dermatologists on the diagnosis of PR • intake of an antibiotic within 2 weeks prior to the diagnosis of PR • history of intolerance to azithromycin or erythromycin • presence of lesions for more than 2 weeks • absence of pruritus at the time of diagnosis **Baseline characteristics:** • groups were comparable with respect to age, sex, duration and severity of disease, and intensity of itch. **Gender:** Male = 36 Female = 34 **Age (mean/SD):** Intervention = 23 (SD = 8.96) years Compare = 23.6 (SD = 8.3) years **Total number randomised**: 70 **Losses to follow-up:** 3 in total, 2 in the intervention group at week 4 and 1 in control group at week 6, no reasons given

Pandhi 2014 *(Continued)*

Interventions	**Intervention (N = 35):** azithromycin tablets 12 mg/kg/day for 5 days **Control intervention (N = 35):** multivitamin tablets similar to azithromycin in colour, shape, size, and taste for 5 days
Outcomes	**Primary outcome of the trial:** 1. The mean decrease in itch using a 1-to-10 VAS **Secondary outcomes of the trial:** 1. Reduction in PR severity score (PRSS) 2. Adverse events Interval of assessment was at week 2, 4, and 6.
Funding source	None
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 37): "Randomized table provided by a statistician for the generation of the randomisation sequence was used for group allocation." Comment: randomisation method is considered adequate
Allocation concealment (selection bias)	Low risk	Quote (page 37): "A clinical nurse assigned oral azithromycin and placebo to either Group A or Group B and dispensed test medications to participants. The coded containers and the key for group allocation and computer generated random numbers list were kept in an opaque and sealed envelope in a locked cupboard, to which access was available only to the nurse." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As above; participants received placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 37): "The dermatologists not involved in randomisation conducted the subsequent clinical assessment." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 2/35 dropouts in the treatment group at week 4 and 1/35 in the placebo group at week 6. Intention-to-treat analysis was applied.
Selective reporting (reporting bias)	Low risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported.
Other bias	Low risk	None known.

Rassai 2011

Methods	This was a randomised, investigator-blind trial lasting for 5 months (October 2006 to February 2007).
Participants	**Setting:** Outpatient clinic of Department of Jondishapur University of Medical Sciences, Ahvaz, Iran **Inclusion criteria of the trial:** • clinical diagnosis of PR • age between 12 and 60 years • < 1 month from the onset of PR • no systemic or topical treatment for the existing or any other condition **Exclusion criteria of the trial:** • pregnant and breastfeeding women • known hypersensitivity to acyclovir • any serious systemic diseases **Baseline characteristics:** • the study included participants aged 10 to 60 years, mean age was 27.12 years. • mean duration of disease prior to enrolment was 18.25 days. • groups were comparable with respect to age, sex, duration and severity of disease (number of lesions). **Gender:** Male = unspecified Female = unspecified **Age (mean/SD/range):** Mean: 27.12 years Range: 10 to 60 years **Total number randomised**: 64 **Losses to follow-up:** 10 in total; numbers and reasons per group not specified
Interventions	**Intervention (N = 28):** oral acyclovir 400 mg 5 times/day for 1 week **Control intervention (N = 26):** no intervention, only follow-up **Use of concomitant treatment:** participants were prohibited from using any other medication during participation in the study.
Outcomes	1. Reduction in erythema 2. Reduction in scaling 3. Adverse events For outcomes 1 and 2, all lesions were photographed and any change in scaling and erythema was recorded. Interval of assessment was at week 1, 2, 3, and 4.
Funding source	Not reported
Notes	It was unclear how many participants per group entered the study.
Risk of bias	

Rassai 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 25): "Randomization was performed by using a simple random table." Comment: randomisation method considered adequate
Allocation concealment (selection bias)	Unclear risk	There was no mention of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of participants. There was no placebo, only follow-up for the control group.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 26): "The used medications were not revealed to their physicians." Comment: unclear if blinding of outcome assessment was achieved
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 10 dropouts (15.6%), numbers and reasons per group were not specified.
Selective reporting (reporting bias)	Low risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported.
Other bias	Low risk	None found.

Singh 2016

Methods	This was a randomised, triple-blinded, placebo-controlled trial lasting for 11 months (August 2012 to June 2013).
Participants	**Setting:** Department of Dermatology and Venereology, SS Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh (India) **Inclusion criteria of the trial:** • patients of both genders, aged 7 to 65 years • fulfilment of diagnostic criteria (Chuh 2003b) • witnessed informed consent, given by the patient or parents in case of minors • weight 40 kg or more **Exclusion criteria of the trial:** • pregnancy • lactation • inability to come for weekly follow-up visits • any treatment taken for the disease within the past 1 week • any other illness as revealed by history • history of a drug reaction to acyclovir • positive potassium hydroxide test of skin scrapings • positive VDRL test **Baseline characteristics:**

Singh 2016 *(Continued)*

- participants were aged 16 to 32 years.
- 8 female, 19 male
- median duration of illness was 15 days.
- groups were comparable for all variables except for age (gender, weight, duration and severity of disease, presence of herald patch, itch).
- placebo participants were significantly younger.
- VDRL was negative in all participants.

Gender:

Male = 19

Female = 8

Age (mean/SD):

Intervention = 24.43 (SD = 7.31) years

Compare = 18.31 (SD = 2.66) years

Total number randomised: 27

Losses to follow-up: none

Interventions	**Intervention (N = 14):** acyclovir 800 mg 5 times/day orally for 7 days **Control intervention (N = 13):** identical-looking placebo tablets 5 times/day orally for 7 days **Use of concomitant treatment:** no
Outcomes	**Primary outcome of the trial:** the number of days required for cure, after initiating treatment. The Pityriasis Rosea Area and Severity Index (PRASI) was devised for the purpose of the study. Cure was defined as complete absence of erythema (grade 0) and no or minimal scaling (grade 0 or 1). **Secondary outcomes of the trial:** 1. Participant's assessment of response to treatment (unsatisfied, satisfied, or very satisfied) 2. 50% reduction in severity 3. Adverse events 4. Resolution of itch 5. Severity of itch (graded on a 0-to-3 scale: none, mild, moderate, severe) 6. Complete resolution of rash at week 2 We received information regarding secondary outcomes 4 to 6 through email contact with the author. Participants were examined weekly.
Funding source	KLM Laboratories Pvt Ltd Mumbai provided the study medications (after the trial was planned) and had no other role in the study.
Notes	Clinical Trials Registry - India (CTRI/2012/09/002995)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to the two treatment groups using an online randomisation tool (http://www.randomizer.org/)" Comment: randomisation method considered adequate

Singh 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation concealment was done using the sealed envelope technique. Opaque envelopes were prepared for each patient by a person who was not involved in the study. These contained the randomisation codes, treatment A or treatment B. After a particular patient was enrolled into the study, the envelope was opened to know which treatment was to be allocated." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "They were randomly assigned to receive either 800 mg acyclovir or identical-looking placebo tablets, to be taken five times a day for one week. Both tablets were packaged in identical blister packs." Comment: participants, investigators, and statistician were blinded throughout the entire trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The code of treatment groups was broken after statistical analysis of the data. The investigators and statistician were unaware of the contents of treatments A and B until the data was completely analysed." Comment: participants, investigators, and statistician were blinded throughout the entire trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.
Selective reporting (reporting bias)	High risk	The trial protocol was pre-registered, and the main outcome, number of days required for cure (disappearance of skin lesions), was reported. Secondary outcome (50% reduction in severity) was not reported. PRASI score was not reported.
Other bias	Low risk	None found.

Sonthalia 2018

Methods	This was a randomised, double-blinded, placebo-controlled trial lasting 2 years (March 2011 to March 2013).
Participants	**Setting:** advanced dermatology clinic-cum-research centre in the city of Gururgram in North India **Inclusion criteria of the trial:** • clinical and dermatoscopic diagnosis of PR • onset of lesions within the past 5 days • age between 18 and 60 years **Exclusion criteria of the trial:** • patients presenting after 5 days of rash onset • pregnant and lactating women • any severe medical disorder (diabetes, hypertension, cardiac or renal disease) • positive VDRL test • positive antistreptolysin (ASLO) titre • positive KOH 10% smear for fungal scraping • any topical or oral treatment for PR in the past 7 days • contraindication to oral steroids

Sonthalia 2018 *(Continued)*

- recent intake of a drug known to precipitate PR

Baseline characteristics:

- groups were comparable with respect to age, sex, duration and severity of rash, and intensity of itch.

Gender:

Male = 34

Female = 36

Age (mean/SD):

Intervention = 26.03 (SD = 7.83) years

Compare = 25.86 (SD = 7.78) years

Total number randomised: 70

Losses to follow-up: 4 (2 per group)

Interventions	**Intervention (N = 35):** oral prednisolone 20 mg/day for 5 days, 15 mg/day for next 5 days, and 10 mg/day for last 5 days, taken as a single dose after breakfast **Control intervention (N = 35):** placebo tablets similar to prednisolone in colour, size, shape, and taste **Use of concomitant treatment:** the only treatment allowed was a standard pharmaceutical formulation containing calamine lotion with liquid paraffin for topical application. No oral antihistamine or topical steroids were given/allowed to any participant.
Outcomes	**Primary outcome of the trial:** 1. Mean decrease in itch as assessed by participants using a 1-to-10 VAS **Secondary outcomes of the trial:** 1. Reduction in PRSS assessed by the investigator (improvement in PRSS was graded based on the percentage reduction as minimal ≤ 25%, good 26% to 50%, very good 51% to 75%, or excellent ≥ 75%) 2. Adverse effects of treatment 3. Relapse at week 12 Interval of assessment was at week 1, 2, 4, 8, and 12. Digital photographs were taken at presentation and at subsequent follow-up visits. Participants were to be shifted out of the study if there was non-response at 15th day or worsening of lesions or severe intolerance to the administered therapy.
Funding source	Not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 618): "A randomized table provided by a statistician for the generation of the randomization sequence was used for group allocation." Comment: randomisation method considered adequate

Sonthalia 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote (page 618): "A pharmacy-controlled concealment of randomisation was carried out. A clinical coordinator assigned oral prednisolone and placebo to either Group A or Group B and dispensed test medications to participants. The coded containers and the key for group allocation and computer generated random numbers list were secured in a sealed envelope. Hence, the investigators as well as the patients were 'blinded' to the nature of treatment assigned at any point of the trial." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 618): "A pharmacy-controlled concealment of randomisation was carried out. A clinical coordinator assigned oral prednisolone and placebo to either Group A or Group B and dispensed test medications to participants. The coded containers and the key for group allocation and computer generated random numbers list were secured in a sealed envelope. Hence, the investigators as well as the patients were 'blinded' to the nature of treatment assigned at any point of the trial." Comment: investigators and participants were blinded to treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 618): "A pharmacy-controlled concealment of randomisation was carried out. A clinical coordinator assigned oral prednisolone and placebo to either Group A or Group B and dispensed test medications to participants. The coded containers and the key for group allocation and computer generated random numbers list were secured in a sealed envelope. Hence, the investigators as well as the patients were 'blinded' to the nature of treatment assigned at any point of the trial." Quote (page 618): "The dermatologists not involved in randomisation conducted the subsequent clinical assessment." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 2/35 dropouts in each group. Intention-to-treat analysis was applied to some of the outcomes but not all.
Selective reporting (reporting bias)	High risk	The protocol was not available, it was not registered in a prospective clinical trial, and some of the prespecified outcomes were not clearly reported even after several attempts at contacting the authors.
Other bias	Low risk	None found.

Villarama 2002

Methods	This was a randomised, double-blind, placebo-controlled trial (of unknown total duration).
Participants	**Setting:** outpatient dermatology clinic in the Philippines **Inclusion criteria of the trial:** • patients diagnosed with classic PR based on clinical features **Exclusion criteria of the trial:** • atypical presentation of PR • history, signs, and symptoms of other skin disorders like psoriasis, leprosy, pityriasis lichenoides chronica, cutaneous drug eruptions, syphilis, fungal infections, or contact dermatitis

Villarama 2002 *(Continued)*

- use of any systemic medication within 1 week prior to consult
- use of topical corticosteroids at any time during the condition
- history of hypersensitivity to erythromycin
- history of gastrointestinal ulcers or hepatic disease
- pregnant and lactating women
- age below 12 years (due to the unavailability of a placebo for the syrups preparation of erythromycin stearate)

Baseline characteristics:

- groups were comparable with respect to age, sex, duration of disease, lesion count, intensity of itch, history of upper respiratory tract infection, and ASO positivity.

Gender:

Male = 18

Female = 22

Age (mean/SD):

Intervention = 24.65 (SD = 1.2) years

Compare = 27.1 (SD = 1.69) years

Total number randomised: 40

Losses to follow-up: 6 in total, 3 per each group

- 1 participant self-medicated with oral corticosteroid and antihistamine during the first week of treatment.
- 5 participants were lost for follow-up visit after the first week of treatment.

Interventions	**Intervention (N = 20):** oral erythromycin stearate 250 mg 4 times/day for 2 weeks **Control intervention (N = 20):** matching placebo capsules containing flour instead of active ingredient, identical in physical appearance, weight, and external packaging, 4 times/day **Use of concomitant treatment:** no other oral or topical medication was allowed.
Outcomes	**Primary outcome of the trial:** 1. Cure rate, defined as decrease in erythema, size, scaling of lesions, further categorised as: a. complete cure: total disappearance of all existing lesions, complete resolution of erythema and scaling in existing patches with or without residual pigmentation, lack of appearance of new lesions; b. partial: regression in size, scaling, erythema, and number of existing lesions, absence of new lesions; c. no cure: no change in pre-existing lesions or appearance of new lesions **Secondary outcomes of the trial:** 1. Reduction in pruritus score (1-to-10 VAS) 2. Adverse events Interval of assessment was at weeks 2, 4, and 6.
Funding source	Not reported
Notes	-

Villarama 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 5): "A randomisation list using a computer-generated table of random numbers was prepared prior to the start of the trial." Comment: randomisation method considered adequate
Allocation concealment (selection bias)	Low risk	Quote (page 5): "Separate investigators took charge of recording patient assignments, labelling the study drugs and dispensing of test medications." Comment: allocation concealment was likely achieved
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 5): "The clinical evaluator and the patients were blinded to treatment groups. Separate investigators took charge of recording patient assignments, labelling the study drugs and dispensing of test medications." Quote (page 6): "The physical appearance, weight and external packaging of the study drugs were identical." Comment: clinical evaluator and participants were blinded to treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 5): "Laboratory personnel and data analyst were likewise blinded", in addition to above. Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 6/40 dropouts at week 2 (3 per group). Worst-case scenario (no cure) was assumed for dropouts.
Selective reporting (reporting bias)	Low risk	Although the protocol was not available and it was not registered in a prospective clinical trial, all prespecified outcomes were reported.
Other bias	Low risk	None found.

Zhu 1992

Methods	This was a randomised trial (of unknown total duration).
Participants	**Setting:** dermatology department in a university hospital, China **Inclusion criteria of the trial:** • patients with PR **Exclusion criteria of the trial:** no information provided **Baseline characteristics:** • 15 male and 8 female patients • age range was 19 to 45 years, mean age was 27.2 • duration of disease was 7 to 12 days • groups were comparable with respect to age, sex, disease duration, and rash distribution. **Gender:**

Zhu 1992 *(Continued)*

	Male = 15 Female = 8 **Age (mean/SD):** Intervention = unspecified Compare = unspecified **Total number randomised**: 23 **Losses to follow-up:** none
Interventions	**Intervention A (N = 12):** potenline (glycyrrhizin) 80 mL in 500 mL of 10% glucose intravenous solution, once daily, duration unclear; it seems until cure was achieved or up to 10 days (1 treatment cycle) **Intervention B (N = 11):** procaine 300 to 600 mg in 500 mL of 10% glucose intravenous solution, once daily, duration unclear; it seems until cure was achieved or up to 10 days (1 treatment cycle) **Use of concomitant treatment:** participants were not given any other oral or topical drugs
Outcomes	1. Efficacy in terms of resolution of skin lesions and symptoms, categorised as: a. cure: complete resolution of symptoms and skin lesions; b. effective: symptoms improved, with a 70% reduction of skin lesions; c. no effect: symptoms only slightly improved after 10 days of treatment, no improvement of skin lesions or relapsed 2. Time for cure Interval of assessment was not specified; it seems that each participant was followed until cure (complete resolution) was achieved.
Funding source	Unknown
Notes	The study report was originally written in Chinese. Only a translation of the abstract was available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned" Comment: there was no information on how the random sequence was generated
Allocation concealment (selection bias)	Unclear risk	There was no information on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was not blinded, but information was insufficient to permit a judgement as to whether the outcome was likely to be influenced by lack of blinding. Both groups received some form of intravenous therapy.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was not blinded, but information was insufficient to permit a judgement as to whether the outcome was likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts.

Zhu 1992 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

ASO: anti-streptolisyn O
KOH: potassium hydroxide
PR: pityriasis rosea
PRSS: Pityriasis Rosea Severity Score
SD: standard deviation
TPHA: Treponema pallidum hemagglutination assay
UVB: ultraviolet B
VAS: visual analogue scale
VDRL: The Venereal Disease Research Laboratory test

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amatya 2012	The trial was not randomised. Participants were assigned to groups alternatively (correspondence with authors).
Arndt 1983	According to the report "Treatments were given to the right side of the body only; the left side was draped and shielded" (paragraph 3, page 381). There was no randomisation.
Chen 1994	There was no mention of randomisation.
Drago 2006	The trial was neither randomised nor double-blind. Objectivity was achieved by counting the lesions.
Grobe 1984	There was no mention of randomisation.
Gutowski 1950	There was no mention of randomisation.
Kalbarczyk 1957	There was no mention of randomisation.
Karpouzis 2003	There was no mention of randomisation.
Leenutaphong 1995	According to the report "UVB irradiation was given to the right side of the body only; the left side was draped and shielded. Later, 1J of UVA irradiation was given to the left side as a placebo" (paragraph 2, page 997). There was no randomisation.
Merchant 1974	According to the report "Sixty-six patients presented to the Madigan Army Medical Center Dermatology Clinic with pityriasis rosea were treated with ultraviolet light. One-half of their anterior and one-half of their posterior trunk was treated with ultraviolet light. The other half was used as an untreated control". There was no mention of randomisation.
Rasi 2008	There was no mention of randomisation.
Roxas	According to the report, 36 participants were alternatively assigned to study and control groups. This is pseudo-randomisation.
Salin 1957	There was no mention of randomisation.

Study	Reason for exclusion
Sharma 2000	According to the report "Patients were allocated by alternate assignment to either the treatment or the placebo group" (paragraph 2, page 242). This is pseudo-randomisation.
Valkova 2004	According to the report "The irradiation sessions were held in a conventional UV cabin (Waldmann 7001K). Two groups of patients were formed. The first one comprised 24 (23.8%) people. The initial dose of the irradiation was 80% minimal erythema dose (MED). It was increased according to the degree of the preceding erythema. Only the right half of the body was irradiated with UVB. UVA (1 J/cm2) was given as a placebo to the left half of the body. The second group consisted of 77 (76.2%) patients. The UVB irradiation was applied to the whole body. The initial UVB dose was determined according to the phototype". There was no mention of randomisation.
Yamashita 1988	There was no mention of randomisation.

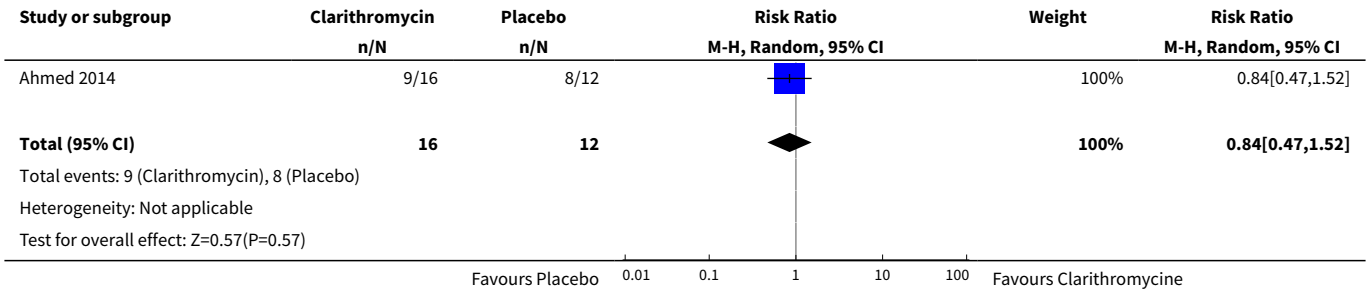
UVA: ultraviolet A
UVB: ultraviolet B

DATA AND ANALYSES

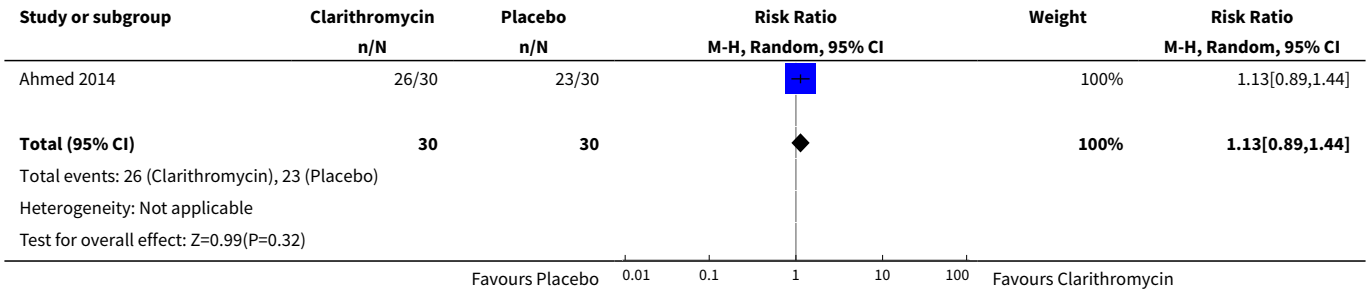
Comparison 1. Clarithromycin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	28	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.47, 1.52]
2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner	1	60	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.89, 1.44]

Analysis 1.1. Comparison 1 Clarithromycin versus placebo, Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.



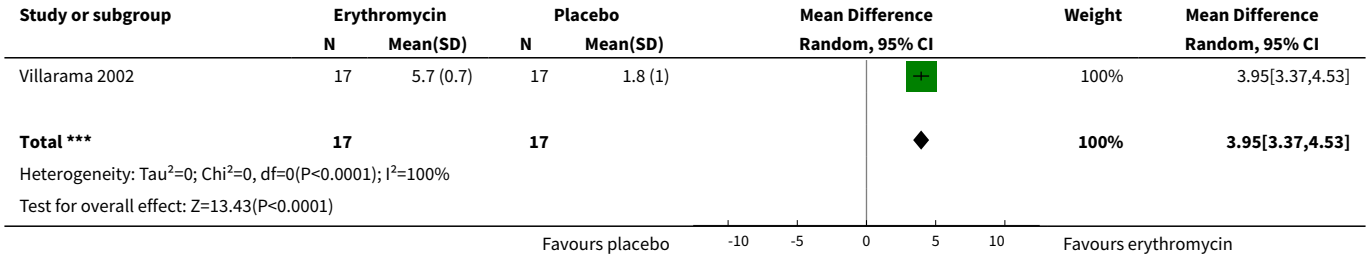
Analysis 1.2. Comparison 1 Clarithromycin versus placebo, Outcome 2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner.



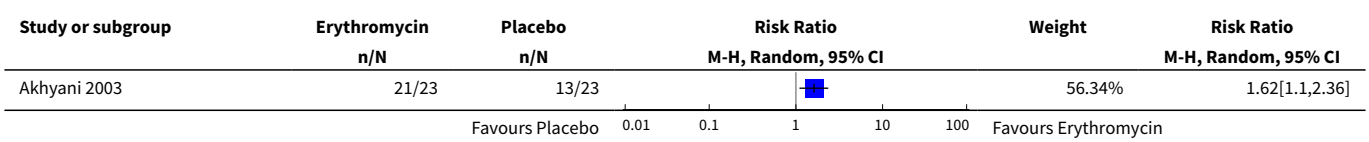
Comparison 2. Erythromycin versus placebo

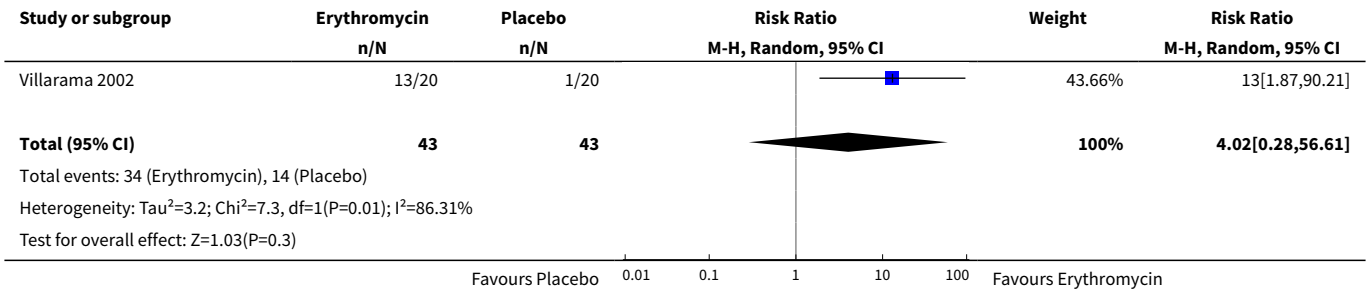
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in itch score within 2 weeks as rated by the participant	1	34	Mean Difference (IV, Random, 95% CI)	3.95 [3.37, 4.53]
2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner	2	86	Risk Ratio (M-H, Random, 95% CI)	4.02 [0.28, 56.61]
3 Minor participant-reported adverse events not requiring withdrawal of the treatment: Gastrointestinal upset	1	34	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.20, 20.04]

Analysis 2.1. Comparison 2 Erythromycin versus placebo, Outcome 1 Reduction in itch score within 2 weeks as rated by the participant.

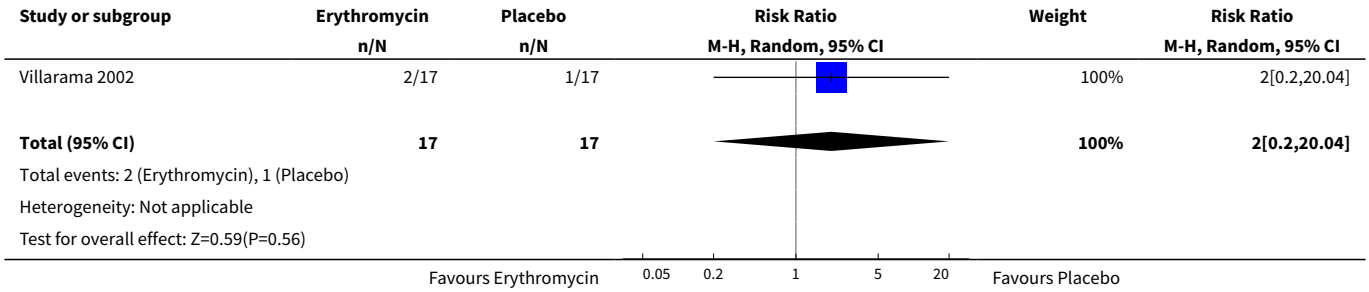


Analysis 2.2. Comparison 2 Erythromycin versus placebo, Outcome 2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner.





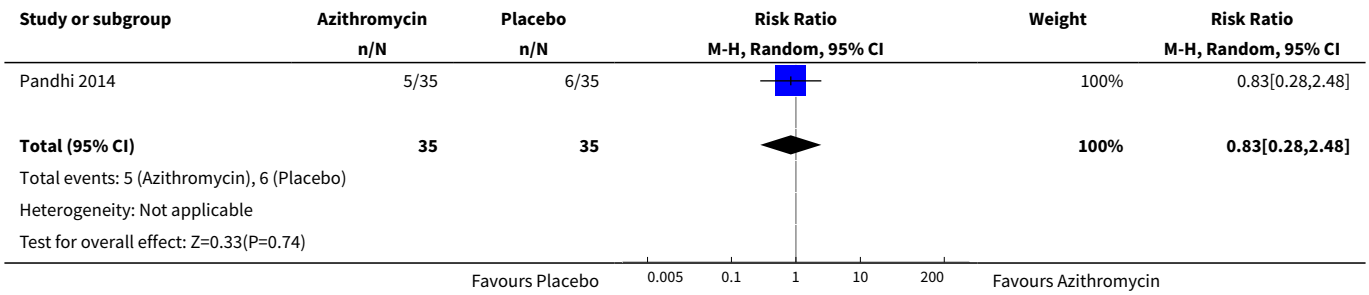
Analysis 2.3. Comparison 2 Erythromycin versus placebo, Outcome 3 Minor participant-reported adverse events not requiring withdrawal of the treatment: Gastrointestinal upset.



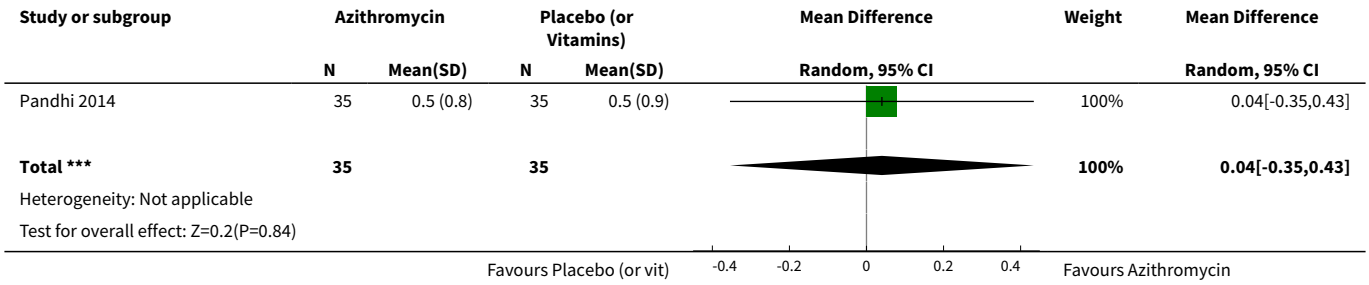
Comparison 3. Azithromycin versus placebo (or vitamins)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	70	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.28, 2.48]
2 Reduction in itch score within 2 weeks as rated by the participant	1	70	Mean Difference (IV, Random, 95% CI)	0.04 [-0.35, 0.43]
3 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner	2	119	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.52, 2.00]
4 Minor participant-reported adverse events not requiring withdrawal of the treatment: Stomach ache	2	119	Risk Ratio (M-H, Random, 95% CI)	5.82 [0.72, 47.10]
5 Minor participant-reported adverse events not requiring withdrawal of the treatment: Diarrhoea	1	49	Risk Ratio (M-H, Random, 95% CI)	4.81 [0.24, 95.25]

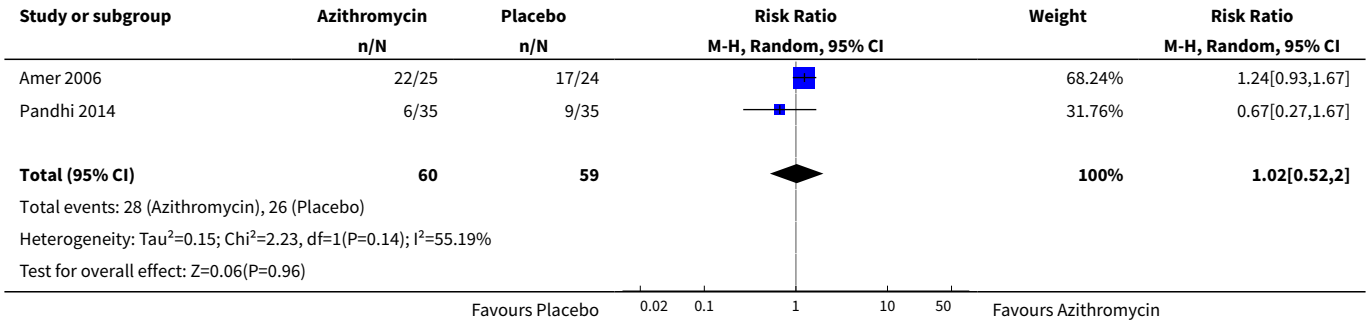
Analysis 3.1. Comparison 3 Azithromycin versus placebo (or vitamins), Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.



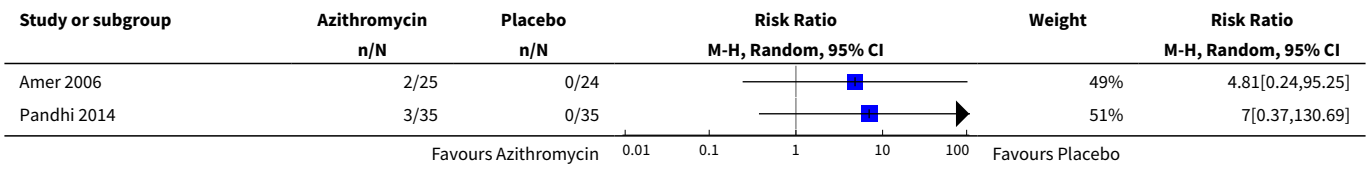
Analysis 3.2. Comparison 3 Azithromycin versus placebo (or vitamins), Outcome 2 Reduction in itch score within 2 weeks as rated by the participant.

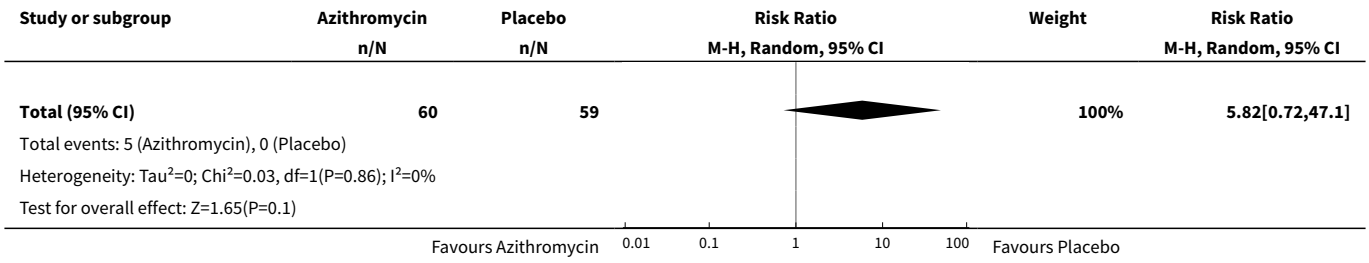


Analysis 3.3. Comparison 3 Azithromycin versus placebo (or vitamins), Outcome 3 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner.

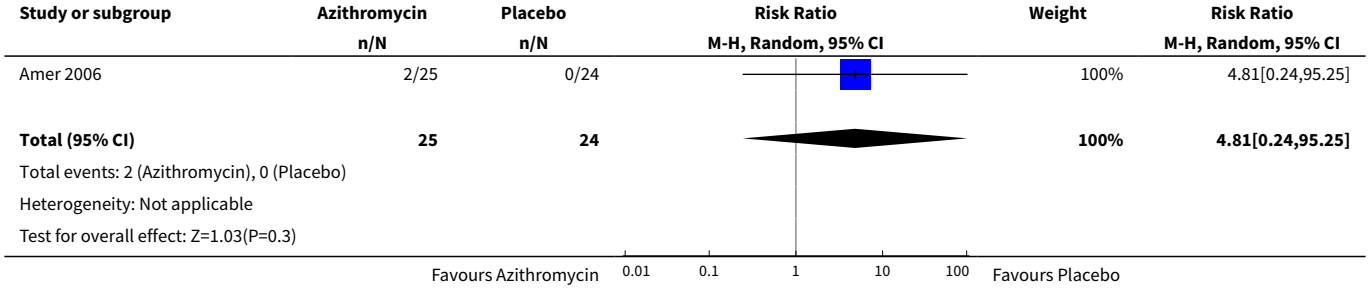


Analysis 3.4. Comparison 3 Azithromycin versus placebo (or vitamins), Outcome 4 Minor participant-reported adverse events not requiring withdrawal of the treatment: Stomach ache.





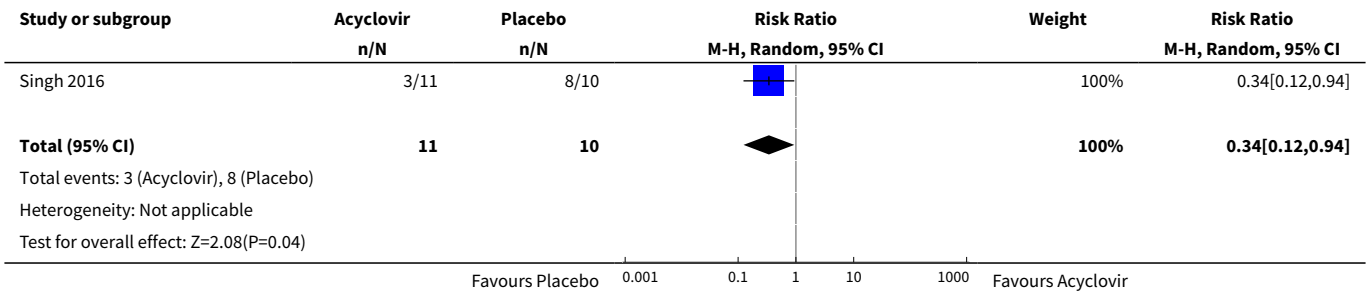
Analysis 3.5. Comparison 3 Azithromycin versus placebo (or vitamins), Outcome 5 Minor participant-reported adverse events not requiring withdrawal of the treatment: Diarrhoea.



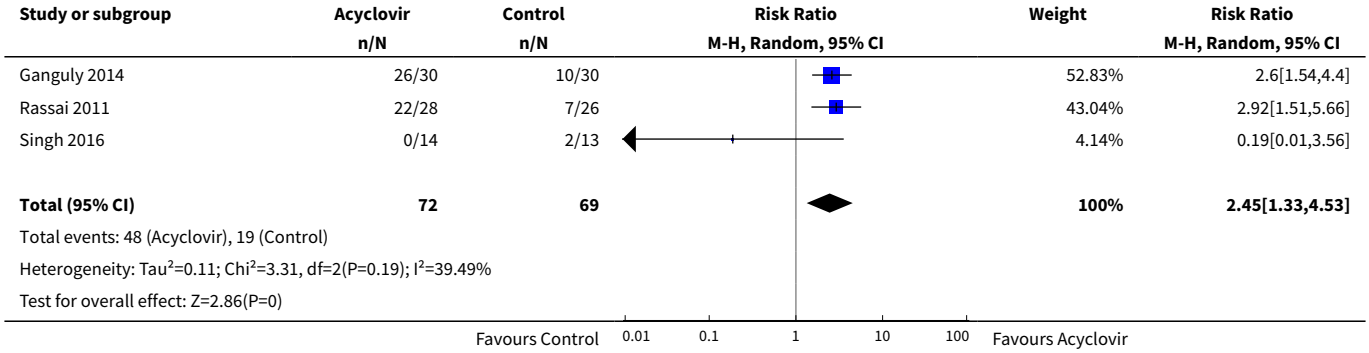
Comparison 4. Acyclovir versus placebo (or vitamins) or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	21	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.12, 0.94]
2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner: Rash by erythema only	3	141	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.33, 4.53]
3 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner: Scaling only	1	54	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.14, 2.01]
4 Minor participant-reported adverse events not requiring withdrawal of the treatment	3	141	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.02]

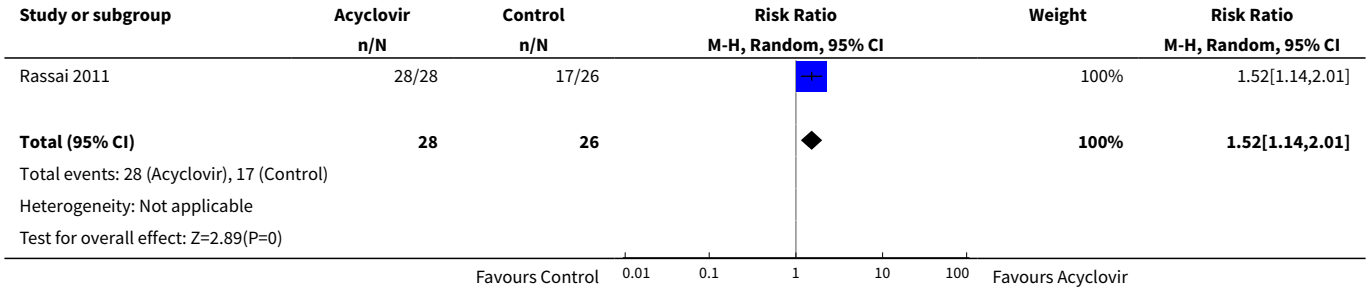
Analysis 4.1. Comparison 4 Acyclovir versus placebo (or vitamins) or no treatment, Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.



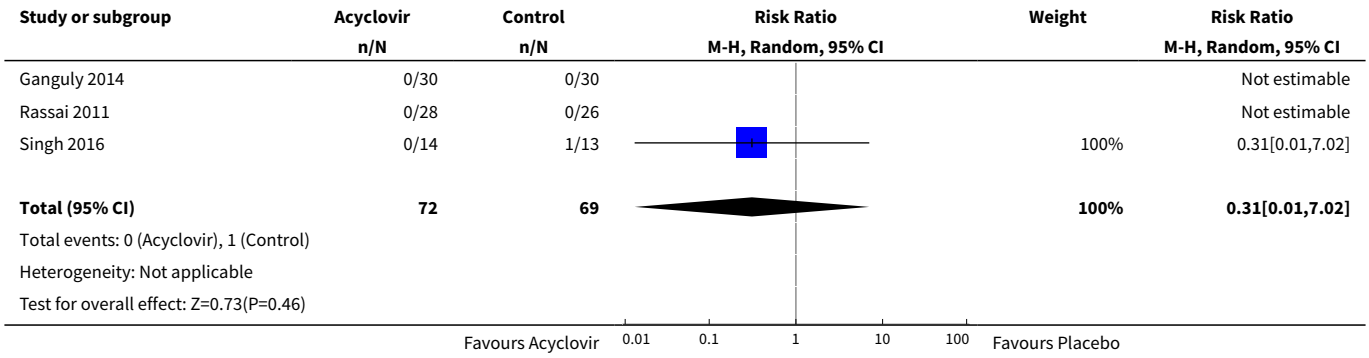
Analysis 4.2. Comparison 4 Acyclovir versus placebo (or vitamins) or no treatment, Outcome 2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner: Rash by erythema only.



Analysis 4.3. Comparison 4 Acyclovir versus placebo (or vitamins) or no treatment, Outcome 3 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner: Scaling only.



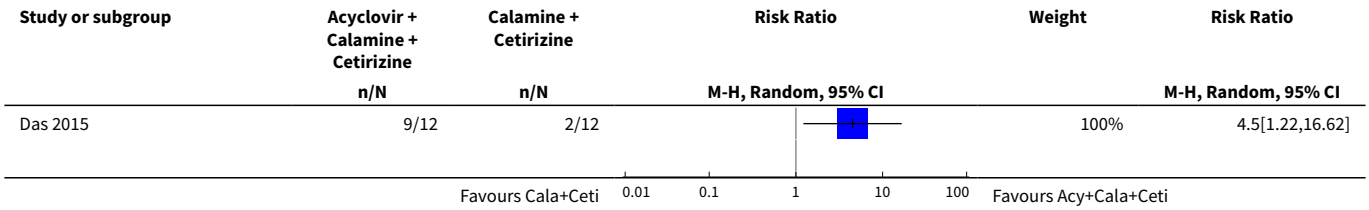
Analysis 4.4. Comparison 4 Acyclovir versus placebo (or vitamins) or no treatment, Outcome 4 Minor participant-reported adverse events not requiring withdrawal of the treatment.

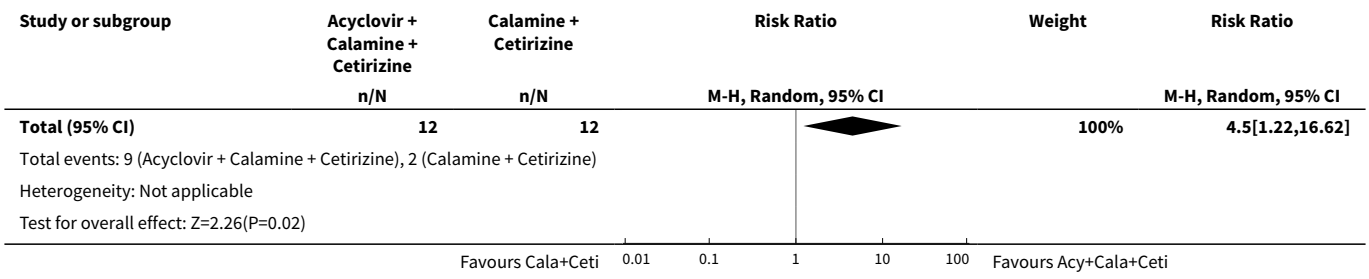


Comparison 5. Acyclovir + calamine + cetirizine versus calamine + cetirizine

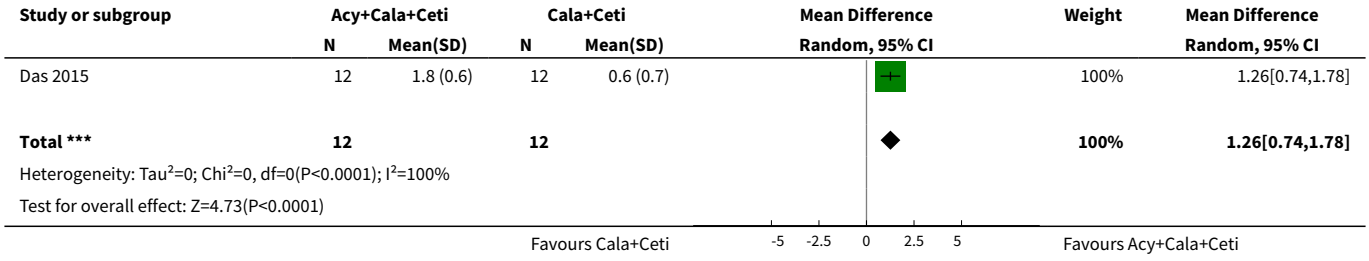
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	24	Risk Ratio (M-H, Random, 95% CI)	4.5 [1.22, 16.62]
2 Reduction in itch score within 2 weeks as rated by the participant	1	24	Mean Difference (IV, Random, 95% CI)	1.26 [0.74, 1.78]
3 Reduction in lesional score within 2 weeks as rated by the participant	1	24	Mean Difference (IV, Random, 95% CI)	3.24 [2.61, 3.87]
4 Minor participant-reported adverse events not requiring withdrawal of the treatment: Headache	1	24	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.40, 122.44]
5 Minor participant-reported adverse events not requiring withdrawal of the treatment: Sleepiness	1	24	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.21, 19.23]
6 Minor participant-reported adverse events not requiring withdrawal of the treatment: Nausea and vomiting	1	24	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.27, 94.34]
7 Minor participant-reported adverse events not requiring withdrawal of the treatment: Dysgeusia	1	24	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 67.06]

Analysis 5.1. Comparison 5 Acyclovir + calamine + cetirizine versus calamine + cetirizine, Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.

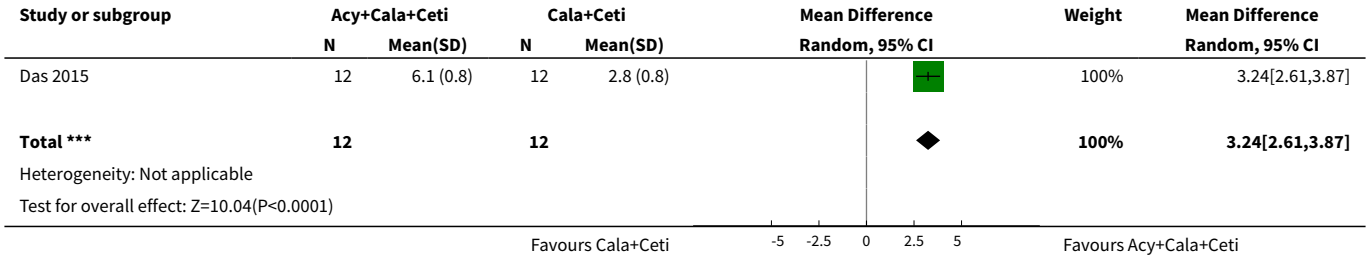




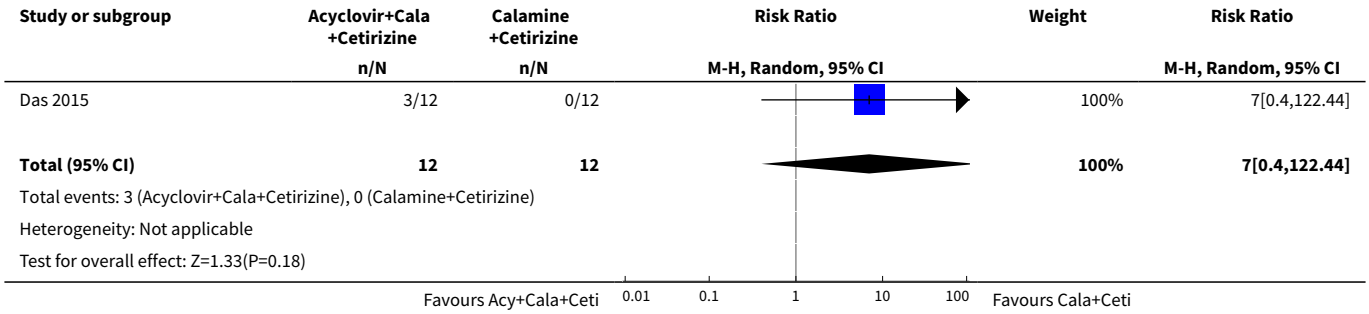
Analysis 5.2. Comparison 5 Acyclovir + calamine + cetirizine versus calamine + cetirizine, Outcome 2 Reduction in itch score within 2 weeks as rated by the participant.



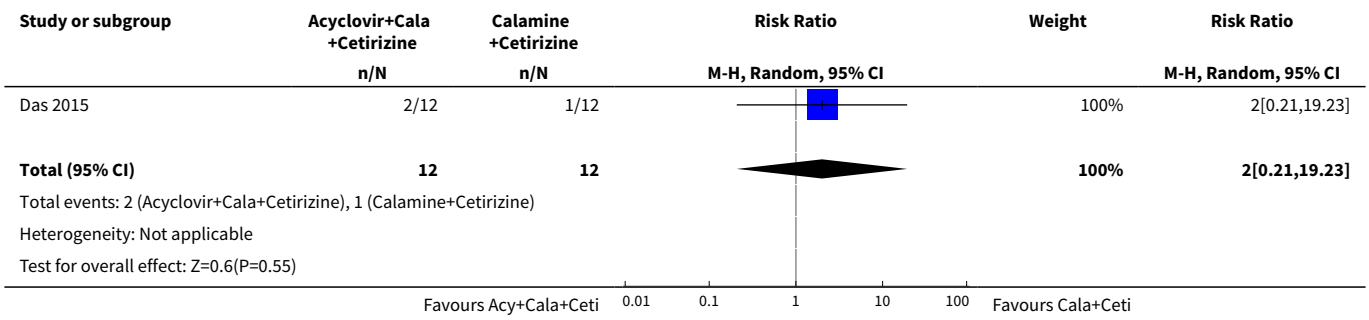
Analysis 5.3. Comparison 5 Acyclovir + calamine + cetirizine versus calamine + cetirizine, Outcome 3 Reduction in lesional score within 2 weeks as rated by the participant.



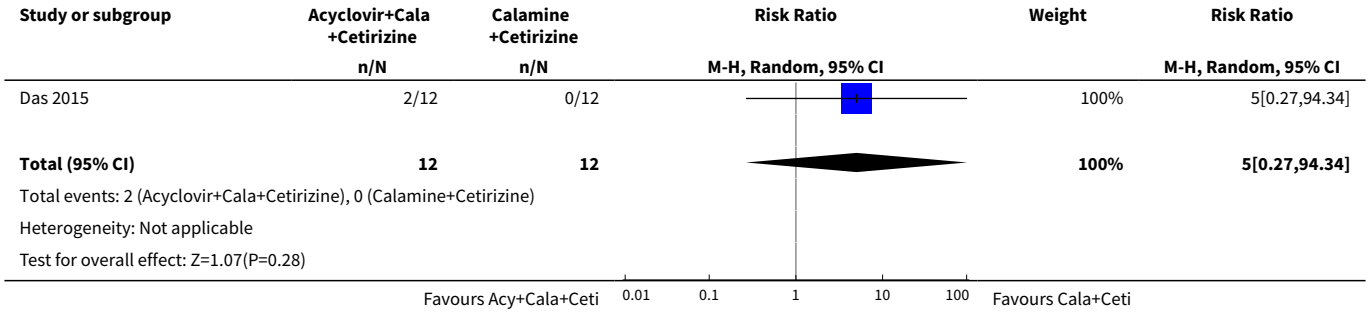
Analysis 5.4. Comparison 5 Acyclovir + calamine + cetirizine versus calamine + cetirizine, Outcome 4 Minor participant-reported adverse events not requiring withdrawal of the treatment: Headache.



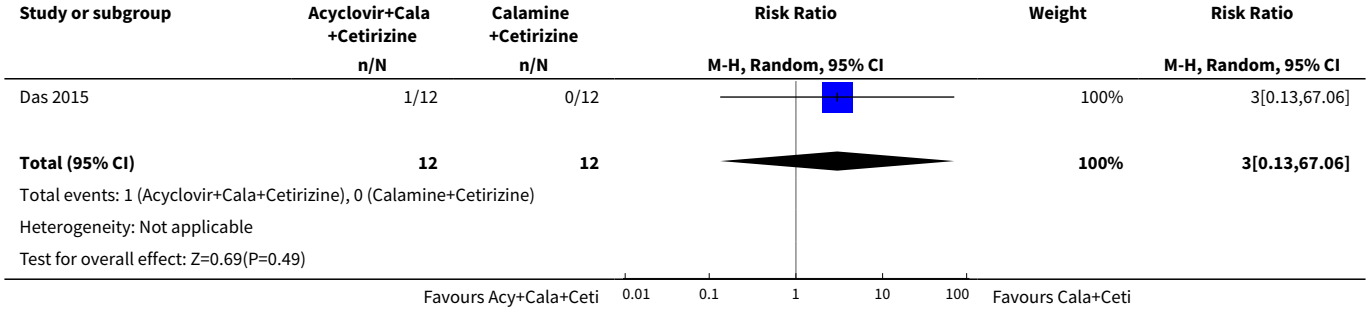
Analysis 5.5. Comparison 5 Acyclovir + calamine + cetirizine versus calamine + cetirizine, Outcome 5 Minor participant-reported adverse events not requiring withdrawal of the treatment: Sleepiness.



Analysis 5.6. Comparison 5 Acyclovir + calamine + cetirizine versus calamine + cetirizine, Outcome 6 Minor participant-reported adverse events not requiring withdrawal of the treatment: Nausea and vomiting.



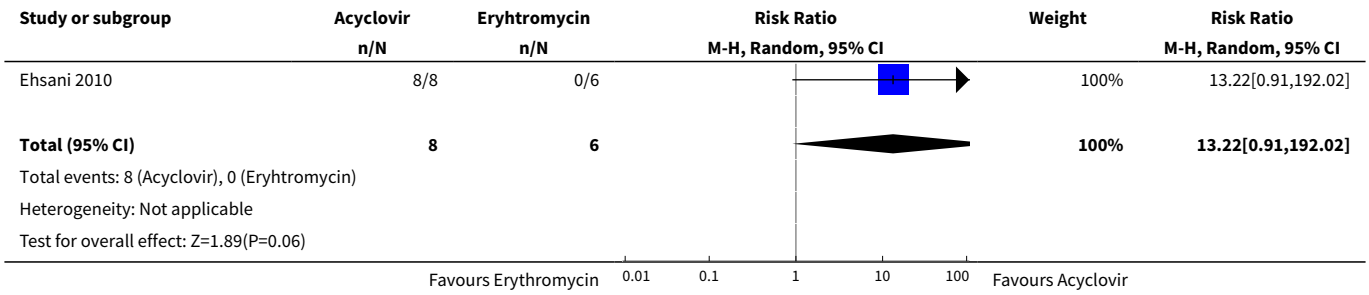
Analysis 5.7. Comparison 5 Acyclovir + calamine + cetirizine versus calamine + cetirizine, Outcome 7 Minor participant-reported adverse events not requiring withdrawal of the treatment: Dysgeusia.



Comparison 6. Acyclovir versus erythromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	14	Risk Ratio (M-H, Random, 95% CI)	13.22 [0.91, 192.02]

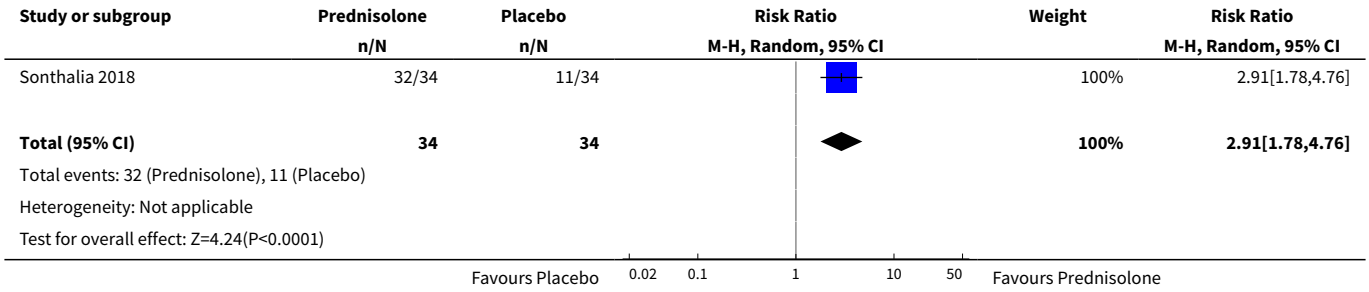
Analysis 6.1. Comparison 6 Acyclovir versus erythromycin, Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.



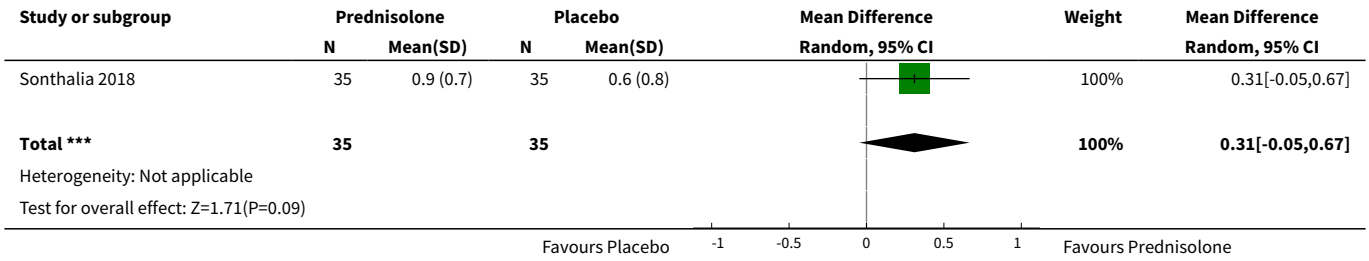
Comparison 7. Prednisolone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	68	Risk Ratio (M-H, Random, 95% CI)	2.91 [1.78, 4.76]
2 Reduction in itch score within 2 weeks as rated by the participant	1	70	Mean Difference (IV, Random, 95% CI)	0.31 [-0.05, 0.67]
3 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner	1	70	Risk Ratio (M-H, Random, 95% CI)	1.62 [1.23, 2.13]
4 Minor participant-reported adverse events not requiring withdrawal of the treatment: Mild gastric hyperacidity	1	70	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.25, 100.53]
5 Minor participant-reported adverse events not requiring withdrawal of the treatment: Anxiety and palpitations	1	70	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 71.22]
6 Minor participant-reported adverse events not requiring withdrawal of the treatment: Belching	1	70	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.91]
7 Minor participant-reported adverse events not requiring withdrawal of the treatment: Stye	1	70	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.91]
8 The proportion of participants with relapse at 12 weeks	1	70	Risk Ratio (M-H, Random, 95% CI)	6.0 [0.76, 47.29]

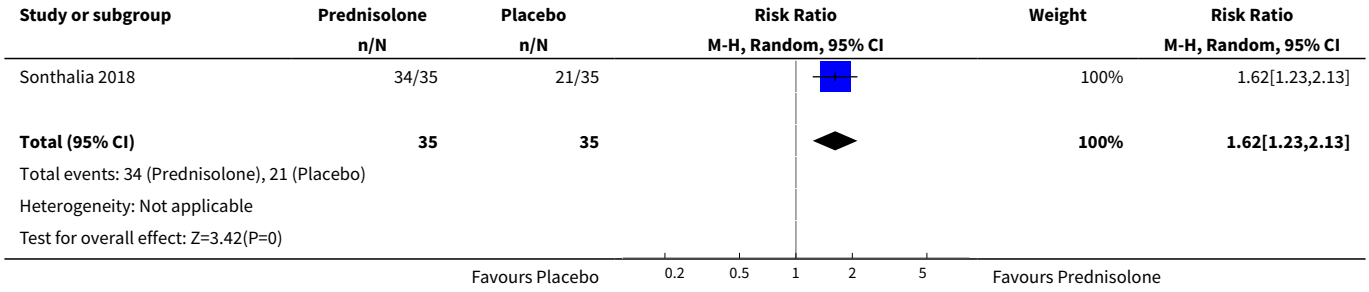
Analysis 7.1. Comparison 7 Prednisolone versus placebo, Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.



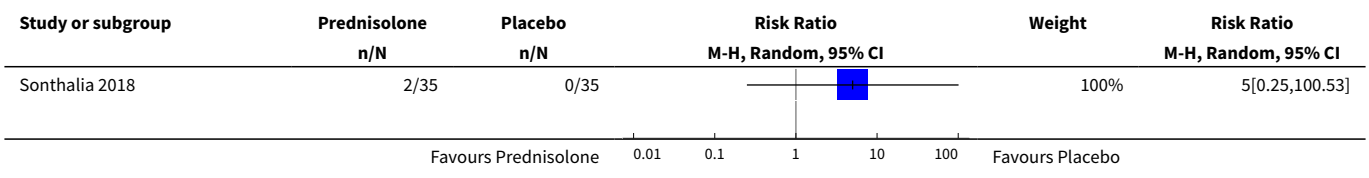
Analysis 7.2. Comparison 7 Prednisolone versus placebo, Outcome 2 Reduction in itch score within 2 weeks as rated by the participant.

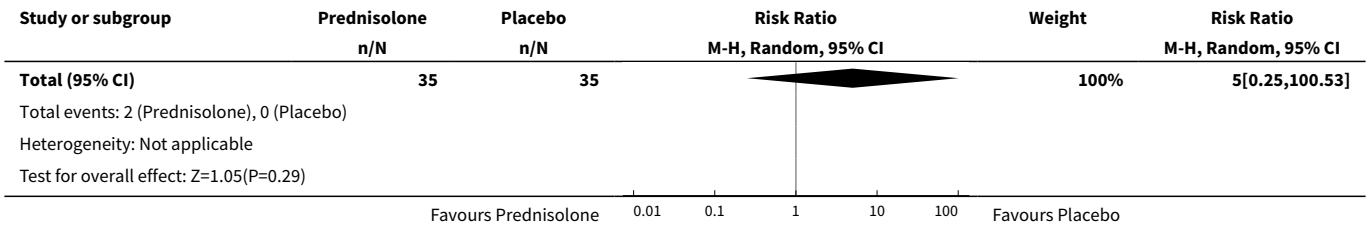


Analysis 7.3. Comparison 7 Prednisolone versus placebo, Outcome 3 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner.

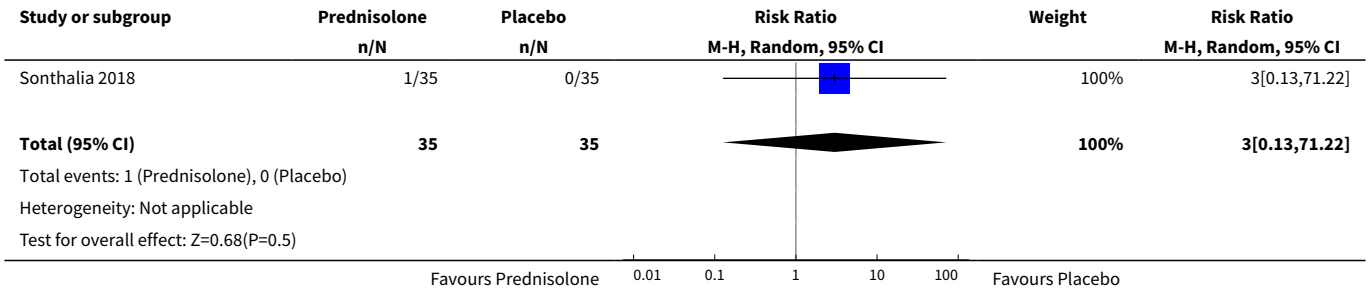


Analysis 7.4. Comparison 7 Prednisolone versus placebo, Outcome 4 Minor participant-reported adverse events not requiring withdrawal of the treatment: Mild gastric hyperacidity.

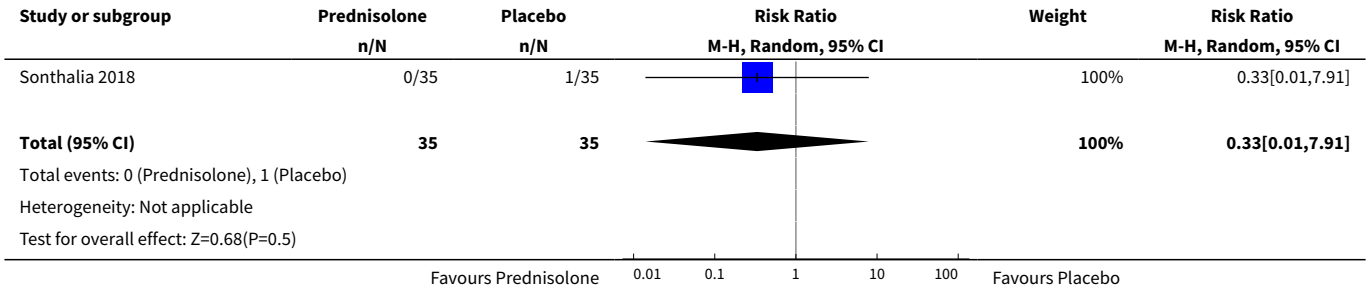




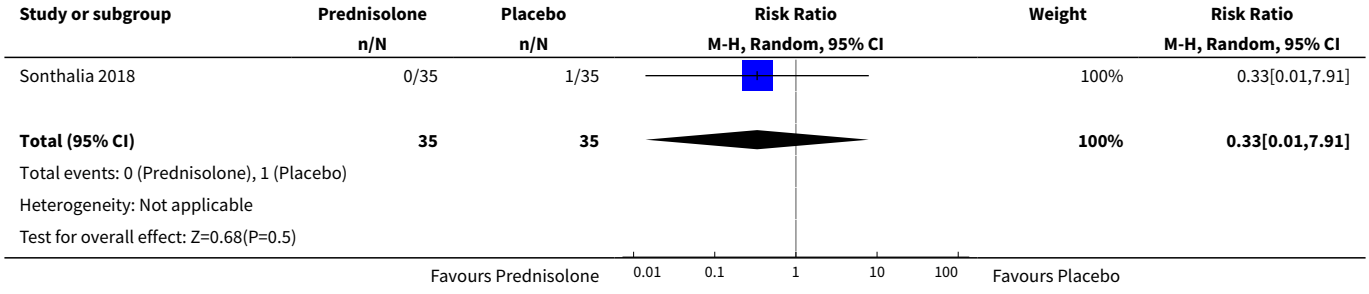
Analysis 7.5. Comparison 7 Prednisolone versus placebo, Outcome 5 Minor participant-reported adverse events not requiring withdrawal of the treatment: Anxiety and palpitations.



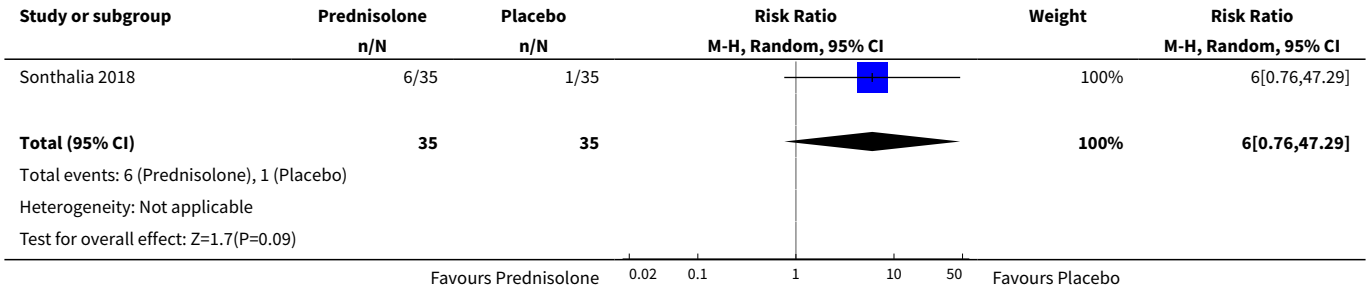
Analysis 7.6. Comparison 7 Prednisolone versus placebo, Outcome 6 Minor participant-reported adverse events not requiring withdrawal of the treatment: Belching.



Analysis 7.7. Comparison 7 Prednisolone versus placebo, Outcome 7 Minor participant-reported adverse events not requiring withdrawal of the treatment: Stye.



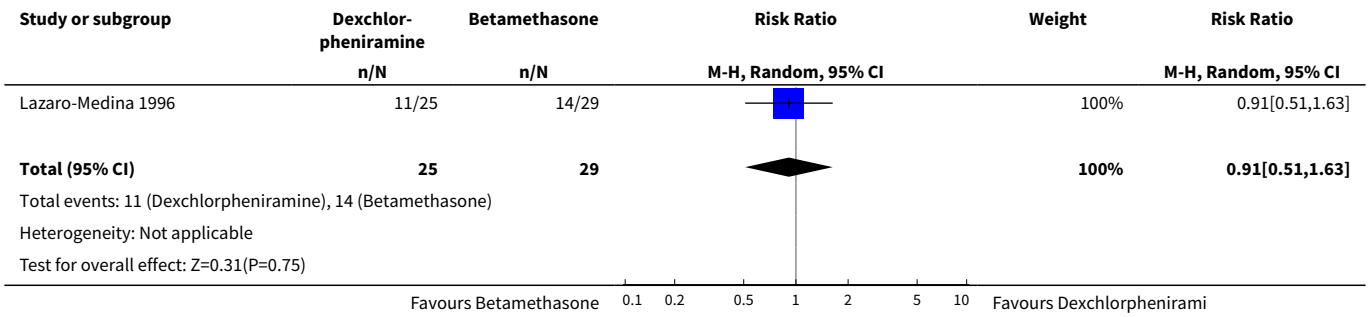
Analysis 7.8. Comparison 7 Prednisolone versus placebo, Outcome 8 The proportion of participants with relapse at 12 weeks.



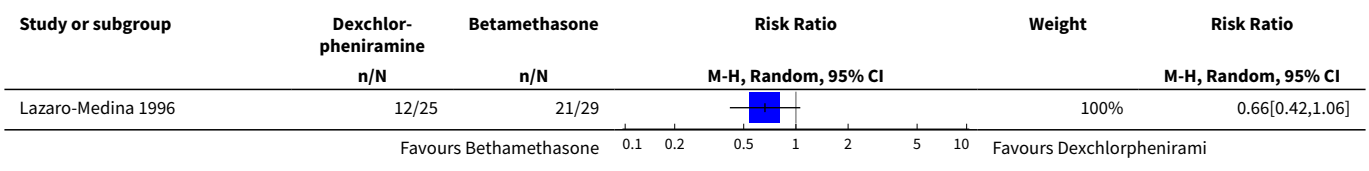
Comparison 8. Dexchlorpheniramine versus betamethasone

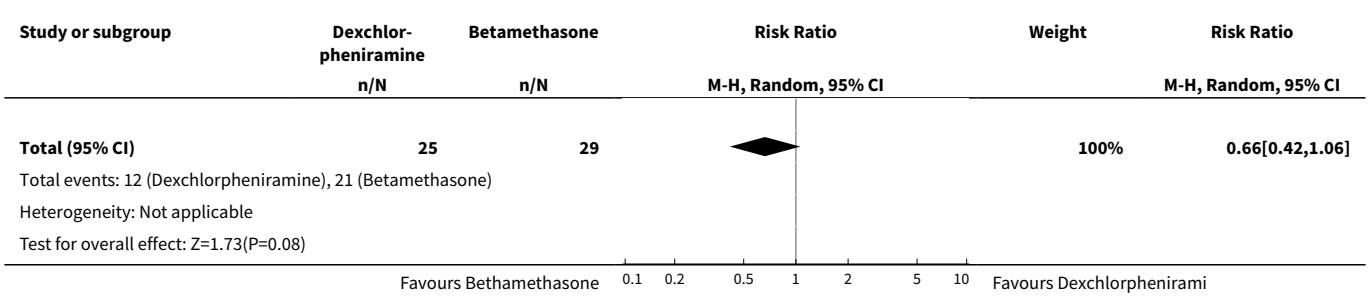
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	54	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.51, 1.63]
2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner	1	54	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.42, 1.06]

Analysis 8.1. Comparison 8 Dexchlorpheniramine versus betamethasone, Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.



Analysis 8.2. Comparison 8 Dexchlorpheniramine versus betamethasone, Outcome 2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner.

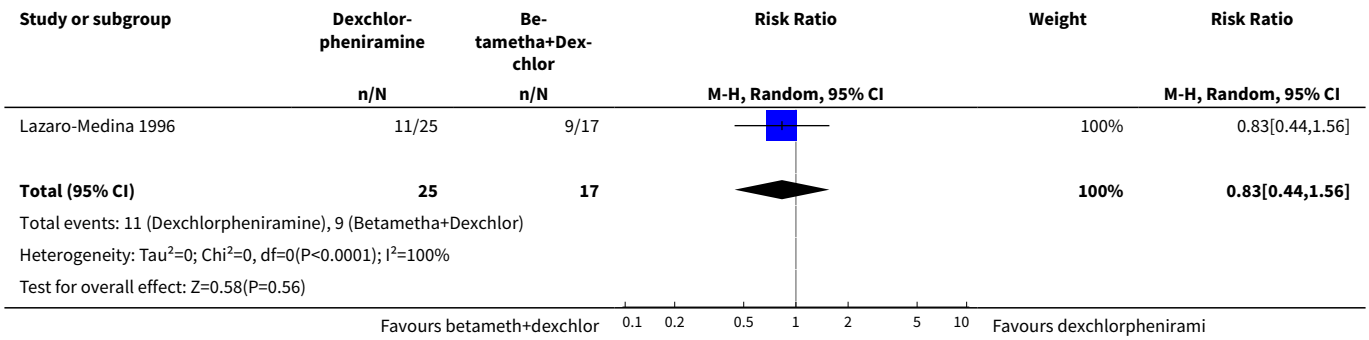




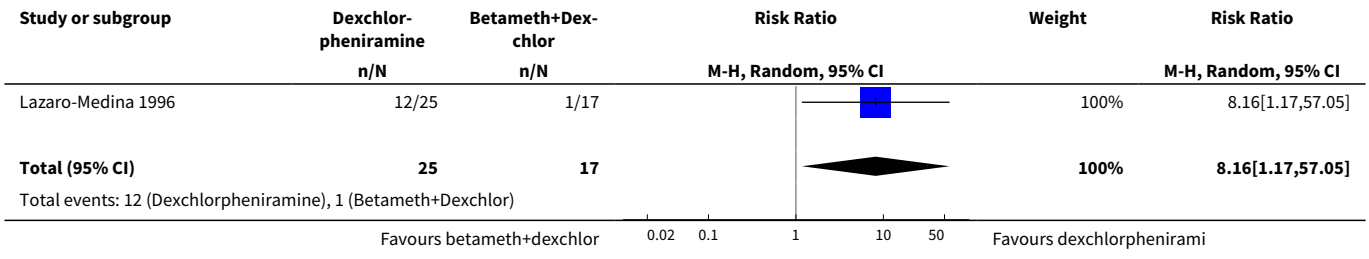
Comparison 9. Dexchlorpheniramine versus dexchlorpheniramine + betamethasone

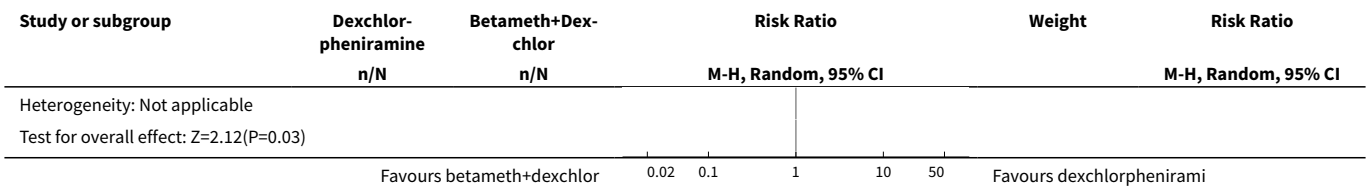
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	42	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.44, 1.56]
2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner	1	42	Risk Ratio (M-H, Random, 95% CI)	8.16 [1.17, 57.05]

Analysis 9.1. Comparison 9 Dexchlorpheniramine versus dexchlorpheniramine + betamethasone, Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.



Analysis 9.2. Comparison 9 Dexchlorpheniramine versus dexchlorpheniramine + betamethasone, Outcome 2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner.

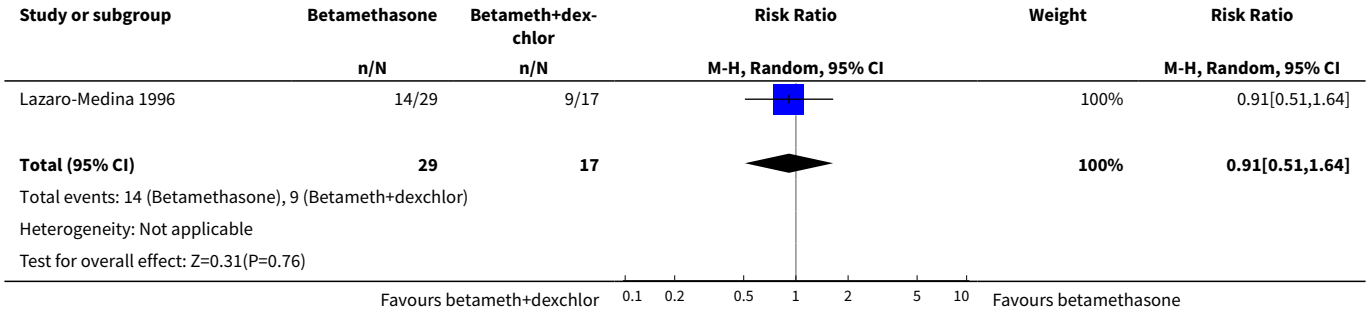




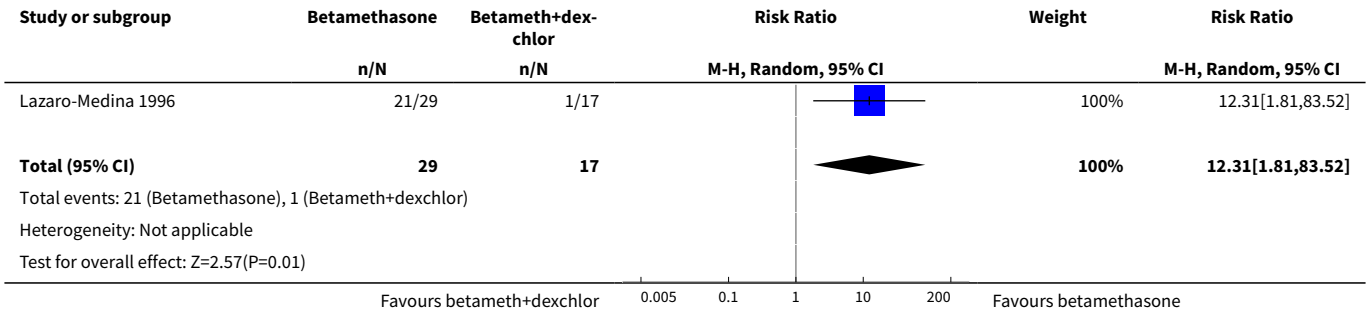
Comparison 10. Betamethasone versus dexchlorpheniramine + betamethasone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant	1	46	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.51, 1.64]
2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner	1	46	Risk Ratio (M-H, Random, 95% CI)	12.31 [1.81, 83.52]

Analysis 10.1. Comparison 10 Betamethasone versus dexchlorpheniramine + betamethasone, Outcome 1 The proportion of participants with resolution of itch within 2 weeks as rated by the participant.



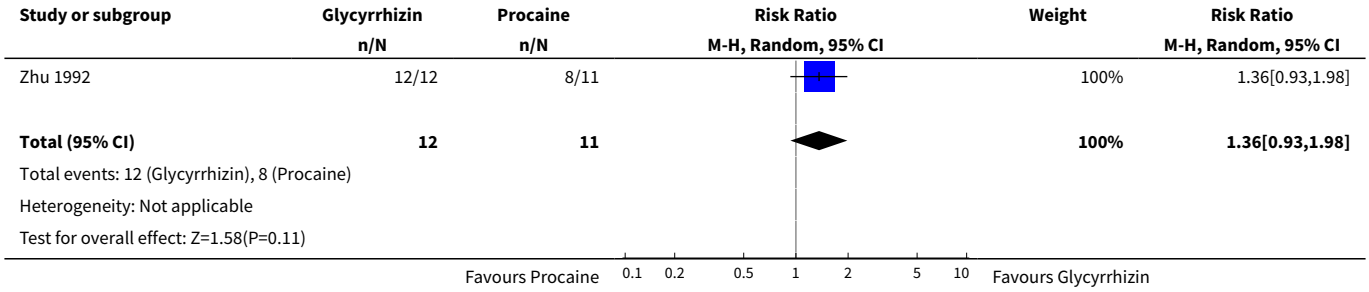
Analysis 10.2. Comparison 10 Betamethasone versus dexchlorpheniramine + betamethasone, Outcome 2 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner.



Comparison 11. Glycyrrhizin versus procaine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner	1	23	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.93, 1.98]

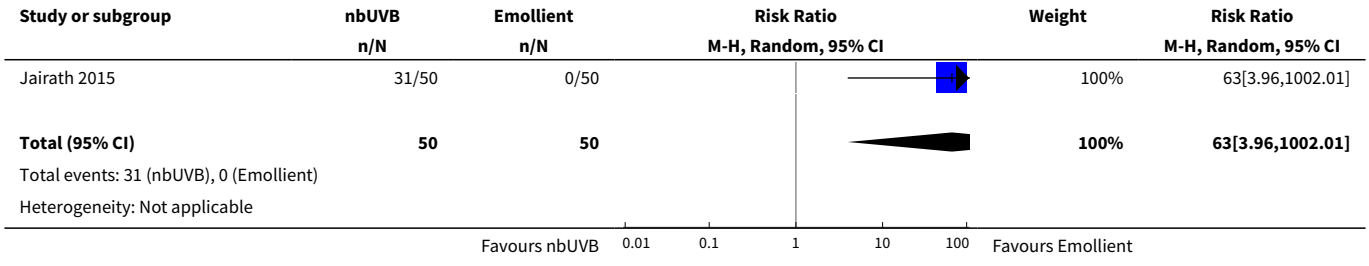
Analysis 11.1. Comparison 11 Glycyrrhizin versus procaine, Outcome 1 The proportion of participants with good or excellent rash improvement within 2 weeks as rated by a medical practitioner.

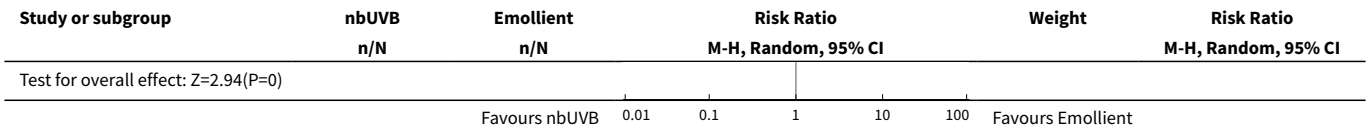


Comparison 12. Ultraviolet phototherapy versus emollient

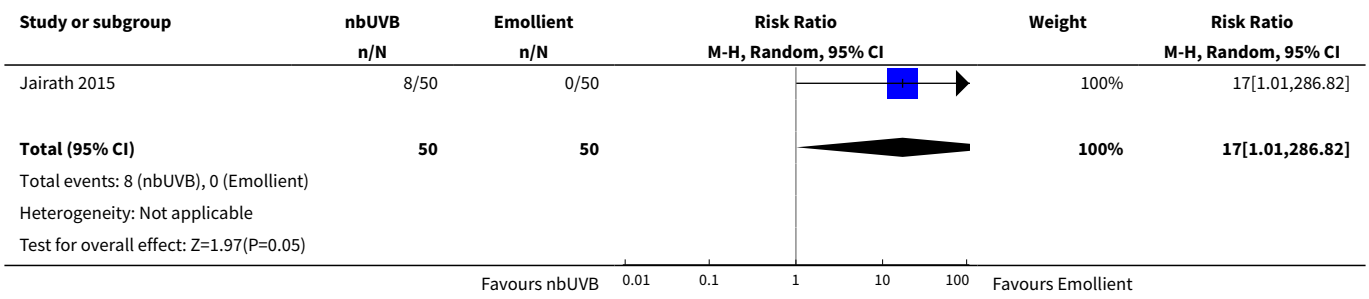
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Minor participant-reported adverse events not requiring withdrawal of the treatment: Hyperpigmentation	1	100	Risk Ratio (M-H, Random, 95% CI)	63.00 [3.96, 1002.01]
2 Minor participant-reported adverse events not requiring withdrawal of the treatment: Hypopigmentation	1	100	Risk Ratio (M-H, Random, 95% CI)	17.0 [1.01, 286.82]
3 Minor participant-reported adverse events not requiring withdrawal of the treatment: Burning sensation	1	100	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.37, 132.10]

Analysis 12.1. Comparison 12 Ultraviolet phototherapy versus emollient, Outcome 1 Minor participant-reported adverse events not requiring withdrawal of the treatment: Hyperpigmentation.

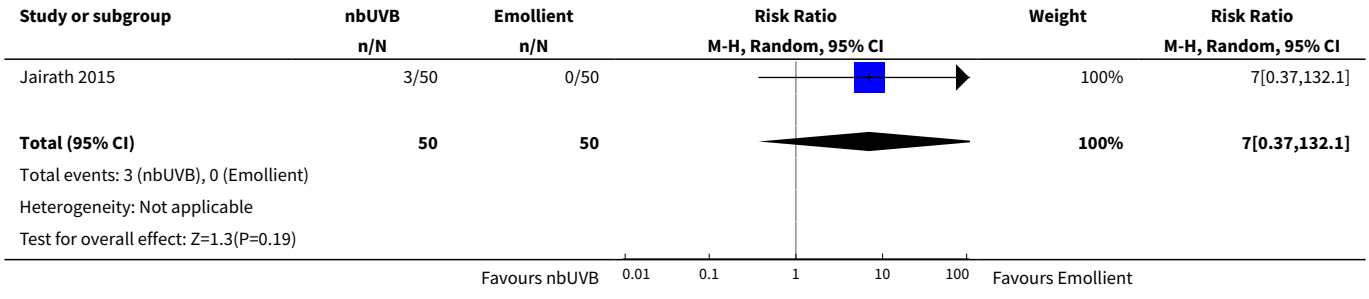




Analysis 12.2. Comparison 12 Ultraviolet phototherapy versus emollient, Outcome 2 Minor participant-reported adverse events not requiring withdrawal of the treatment: Hypopigmentation.



Analysis 12.3. Comparison 12 Ultraviolet phototherapy versus emollient, Outcome 3 Minor participant-reported adverse events not requiring withdrawal of the treatment: Burning sensation.



APPENDICES

Appendix 1. Cochrane Skin Group Specialised Register/CRS search strategy

(pityriasis and (rosea or Gibert or Vidal or circinata or marginata or maculata))

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 pit?riasis and (rosea or Gibert or Vidal or circinata or marginata or maculata)
#2 MeSH descriptor: [Pityriasis Rosea] this term only
#3 #1 or #2

Appendix 3. MEDLINE (Ovid) search strategy

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.

6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. Pityriasis Rosea/
12. pit?riasis rosea.mp.
13. (pit?riasis and Gibert).mp.
14. (pit?riasis and Vidal).mp.
15. pit?riasis circinata et marginata.mp.
16. pit?riasis maculata et circinata.mp.
17. (pit?riasis and circinata).mp.
18. (pit?riasis and marginata).mp.
19. (pit?riasis and maculata).mp.
20. or/11-19
21. 10 and 20

[Lines 1-10: Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 4. Embase (Ovid) search strategy

1. pityriasis rosea/
2. pit?riasis rosea.mp.
3. (pit?riasis and Gibert).mp.
4. (pit?riasis and Vidal).mp.
5. pit?riasis circinata et marginata.mp.
6. pit?riasis maculata et circinata.mp.
7. (pit?riasis and circinata).mp.
8. (pit?riasis and marginata).mp.
9. (pit?riasis and maculata).mp.
10. or/1-9
11. crossover procedure.sh.
12. double-blind procedure.sh.
13. single-blind procedure.sh.
14. (crossover$ or cross over$).tw.
15. placebo$.tw.
16. (doubl$ adj blind$).tw.
17. allocat$.tw.
18. trial.ti.
19. randomised controlled trial.sh.
20. random$.tw.
21. or/11-20
22. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
23. human/ or normal human/
24. 22 and 23
25. 22 not 24
26. 21 not 25
27. 10 and 26

Appendix 5. LILACS search strategy

(pityriasis OR pitiriasis) AND (rosada OR rosea OR gibert OR vidal OR circinata OR marginata OR maculata)

In LILACS we searched using the Controlled clinical trials topic-specific query filter.

Appendix 6. Search strategy for trials registers

Pityriasis rosea
Pityriasis Vidal
Pityriasis Gibert
Pityriasis circinata
Pityriasis marginata

Appendix 7. Search strategy for adverse effects (PubMed)

(Drug hypersensitivity [mh] OR Drug toxicity [mh] OR Product surveillance, postmarketing [mh] OR safety [mh] OR adverse effects [Subheading] OR chemically induced [Subheading] OR Adverse [tw] OR side effect* [tw] OR toxicity [tw] OR chemically-induced [tw] OR safety [tw]) AND (Pityriasis rosea [mh] OR Pityriasis rosea [tw] OR Pityriasis marginata [tw])

WHAT'S NEW

Date	Event	Description
28 October 2019	New citation required and conclusions have changed	Studies assessing several new interventions, such as azithromycin, clarithromycin, acyclovir, prednisolone, and UVB phototherapy, have been included. The authors have changed.
28 October 2019	New search has been performed	This update included 11 new studies with 613 additional participants. We incorporated new MECIR standards into this update of the review. We used GRADE methodology to assess evidence quality and draw conclusions about our certainty in the review findings.

HISTORY

Protocol first published: Issue 1, 2005
Review first published: Issue 2, 2007

Date	Event	Description
1 October 2015	New search has been performed	Converted to new review format
2 August 2007	New search has been performed	Minor update
21 February 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JCR and SP are joint first authors as they contributed equally to this review.
JCR was the contact person with the editorial base and co-ordinated contributions from the co-authors.
JCR and SP wrote the final draft of the review.
SP wrote the clinical sections of the Background.
JCR, CJG, SP, and ICK screened papers against eligibility criteria.
JCR, CJG, SP, and ICK obtained data on ongoing and unpublished studies.
JCR and SP contacted the study authors and sought additional information regarding trials.
JCR, CJG, SP, LR, and ICK appraised the quality of papers.
JCR, CJG, SP, and ICK extracted data for the review.
JCR, CJG, SP, ICK, and LR entered data into Review Manager 5.
CJG, LR, JCR, SP, and ICK analysed and interpreted the data.
CJG, JCR, SP, LR, and ICK worked on the Methods sections.
JCR and SP responded to the clinical comments of the referees. JCR, CJG, and SP responded to the methodology and statistics comments of the referees.
MLSR was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes were relevant to consumers.
JCR is the guarantor of the update.

Disclaimer

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DECLARATIONS OF INTEREST

Jose Contreras-Ruiz: none known.
Sandra Peternel: none known.
Carlos Jiménez Gutiérrez: none known.
Ivana Culav-Koscak: none known.
Ludovic Reveiz: none known. Ludovic Reveiz has contributed to this review in a personal capacity and during his spare time. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the organization where he works.
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol, intravenous Chinese medicine was not included, but since it was described in the first version of this review, we added it to Types of interventions.

The original protocol did not mention time points, but in the previous version of this review, the authors state in the 'Timing of outcome assessment' section, "We chose 2 weeks as people without any active treatment usually have spontaneous recovery in between 2 and 12 weeks". Since this concept has not changed, we decided to use the same timing of outcome.

We modified outcomes in line with current Cochrane advice to have only two primary outcomes: one harm, and one benefit. The primary outcomes in this review are the proportion of participants with good or excellent rash improvement within two weeks, as rated by the participant, and serious adverse events, that is serious enough to require withdrawal of the treatment. The latter was considered a secondary outcome in the protocol, and the proportion of participants with resolution of itch, as rated by the participant, previously a primary outcome, became a secondary outcome.

In the original protocol, the participant-rated global assessments of rash and itch improvement were the primary outcome measures when available. If information for these outcomes was not available, the medical practitioner global rating would be used. If information for both measures was available, both would be taken into account. No attempt would be made to combine these measures, as they are often not well correlated. Since itch improvement at week 2 became a secondary outcome, and in line with current Cochrane guidelines, this was no longer necessary or desirable.

The Methods have been updated since the protocol was published to align with the new Cochrane standards (e.g. the 'Risk of bias' tool has been updated) (Higgins 2011).

For this update, we did not search BIOSIS Previews, as the team no longer had access to this database. In our search for additional unpublished literature, we did not contact the pharmaceutical industry for this update, but we included additional trials registers, as listed in the Methods sections.

The protocol stated that the results would be expressed in odds ratios and as number needed to treat where appropriate, for a range of plausible control event rates; in this new review, the results are presented as risk ratios and 95% confidence intervals for dichotomous outcomes whenever this was possible.

In this update we added to the Methods how we handled continuous outcome data with missing standard deviations from change in baseline mean values. We used the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* where a correlation coefficient is used to calculate the missing standard deviations, using a coefficient of 0.7. We also ran sensitivity analyses using the values of 0.5 and 0.8.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Infective Agents [therapeutic use]; Erythromycin [therapeutic use]; Glycyrrhizic Acid [therapeutic use]; Histamine H1 Antagonists [therapeutic use]; Pityriasis Rosea [drug therapy] [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male