Targeted Update

Interventions for cutaneous sporotrichosis

This is a **Targeted update** of the Cochrane Review: Xue S, Gu R, Wu T, Zhang M, Wang X. Oral potassium iodide for the treatment of sporotrichosis. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD006136. DOI: 10.1002/14651858.CD006136.pub2.

Latest search was performed: **23 November, 2016**

Results of the search, list of new references, details of updates to methods, study characteristics, risk of bias assessments and details of data analyses can be found in **Supplementary material**.

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 Sources of Support: Funded by Cochrane as part of a pilot project

What's new

The original Cochrane Review, Oral potassium iodide for the treatment of cutaneous sporotrichosis, which was published in 2009, identified no eligible studies.

The current targeted update widened the scope by searching for all interventions for cutaneous sporotrichosis. The update search was carried out in November 2016.

This targeted update identified four eligible randomised controlled trials (RCTs) with a total of 190 participants. Each RCT studied a different comparison, so combining the results was not possible. Each of the RCTs compared different dosing regimens of the same drug. The quality of the evidence was low or very low.

Key statement

Sporotrichosis is a subacute or chronic fungal infection of the skin, subcutaneous tissue, and surrounding lymphatic vessels. It affects people of all ages and races worldwide although it is most commonly observed in working age adults of between 20 and 50 years. Although potassium iodide, itraconazole, and oral terbinafine are all used in the treatment of sporotrichosis, their effects have not been systematically evaluated.

Four RCTs were included, but all were small and only investigated within-class comparisons of the same drug. The comparisons were as follows: single dose of potassium iodide versus potassium iodide divided into three doses; 200mg/day itraconazole versus a 'pulsed' 400mg/day itraconazole; 100mg/day itraconazole versus 400mg/week itraconazole; and 500mg/day terbinafine versus 1000mg/day terbinafine.

One RCT revealed that more people may be likely to be clinically cured in the long term (more than 6 months) with 1000mg/day oral terbinafine than with 500mg/day oral terbinafine (RR 0.60, 95% CI 0.40 to 0.88, low-quality evidence; 58 participants). Although no clear difference was found between the 2 treatment groups in relation to long-term severe adverse events, due to the very low-quality evidence, we are very uncertain about this result (RR 0.25, 95% CI 0.01 to 4.97, very low-quality evidence; 63 participants). It's worth noting that terbinafine dosage in this trial is higher than that of routine clinical dosages.

For potassium iodide and itraconazole, the results showed no difference between within-class comparisons on medium-term or long-term (where reported) clinical cure and adverse events (where reported); however, as reflected in the aforementioned terbinafine comparison, this was based on low to very low quality. Therefore, these results need to be interpreted with caution.

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Background

Sporotrichosis is a subacute or chronic fungal infection of the skin, subcutaneous tissue, and surrounding lymphatic vessels caused by the *Sporothrix schenckii* complex and other species. Sporotrichosis is divided into four subtypes: lymphocutaneous sporotrichosis, fixed cutaneous sporotrichosis, multifocal or disseminated cutaneous sporotrichosis, and extracutaneous sporotrichosis. The first three types are categorised as cutaneous sporotrichosis. Lesions of cutaneous sporotrichosis usually manifest as nodules; plaques; noduloulcerative, ulcerative, nodulocystic, or warty lesions; and subcutaneous swellings or masses. They often do not cause any symptoms but may cause local itch or pain.

Potassium iodide is an anti-fungal drug listed in the World Health Organization (WHO) essential drug list and generally thought to be the first choice for cutaneous sporotrichosis including fixed and lymphocutaneous types, especially in developing countries. Itraconazole (ITZ) and terbinafine (TBF) are also widely used in clinical medicine for fixed and lymphocutaneous sporotrichosis. Amphotericin B is an optional therapy for multifocal or disseminated cutaneous sporotrichosis. However, the efficacy and safety of these treatments have not been systematically evaluated.

Objectives

To assess the efficacy and safety of all interventions in people with cutaneous sporotrichosis.

Search methods

We conducted the most recent search in November 2016. We searched the Cochrane Skin Group's Specialised Register, the Cochrane Library, CENTRAL, Medline, Embase, Clinicaltrials.gov, International Clinical Trials Registry Platform, and ISRCTN registry. We also handsearched all articles published in the journal 'Mycoses' between 1957 and 2015. The search strategies are available in the **Supplementary material**.

Selection criteria

Randomised controlled trials (RCTs) of all interventions for sporotrichosis were included. The participants were anyone who had been diagnosed with definite sporotrichosis, based on a positive culture of the fungus. The comparisons were any intervention versus another intervention. The primary outcome was proportion of participants with a clinical cure. The secondary outcomes were proportion with good or excellent improvement, severe adverse events, and changes in quality of life scores. The tertiary outcomes were change in isolation rate of sporotrichosis; change in fungal counts of sporotrichosis; changes in the individual signs of sporotrichosis; duration of remission and prevention of subsequent flares; and minor adverse events (please refer to **Supplementary material** for detailed definition of outcomes, including assessed time points).

Data collection and analysis

We have used the standard methodological procedures expected by Cochrane. Two review authors independently screened references obtained through electronic searches. One review author handsearched references published in the journal 'Mycoses'. For trials meeting the inclusion criteria, two authors independently completed 'Risk of bias' assessments and extracted data for key domains. Risk ratios (RR) were calculated for dichotomous data along with 95% confidence intervals (CIs). Mean differences with 95% CIs were calculated for continuous outcomes.

Main Results

Four RCTs with 190 participants were found that investigated four different treatment comparisons: one looked at splitting potassium iodide into three doses per day compared to a single dose; two compared different itraconazole dosage regimens; and one investigated various doses of oral terbinafine. None of these RCTs were included in the original Cochrane Review. None of the RCTs reported the following outcomes: proportion of participants with clinical cure at short term, proportion with good or excellent improvement, changes in quality of life, change in isolation rate of sporotrichosis, changes in the individual signs of sporotrichosis, and duration of remission and prevention of subsequent flares.

Saturated solution of potassium iodide (SSKI)

One RCT was included which compared SSKI given as one dose (treatment duration: 33.8 ± 7.7 days) versus SSKI given as three doses (treatment duration: 32.2 ± 6.7 days) throughout the day, in children with sporotrichosis. The method of randomisation was not reported, and the participants and personnel were not blinded, hence, introducing high risk of performance and detection bias. Additionally, the study was small (57 children).

There may be no difference between SSKI given as a single dose compared to SSKI divided into 3 doses on medium-term clinical cure (26/26 vs 25/25, RR 1.00, 95% CI 0.93 to 1.08, low-quality evidence, Figure 4). The proportion of participants with clinical cure measured at long-term follow-up was

not reported. Although there was no difference between the trial groups in terms of medium-term severe adverse events (2/28 vs 1/26, RR 1.86, 95% CI 0.18 to 19.29, very low-quality evidence, Figure 5) and minor adverse events (15/28 vs 10/26, RR 1.39, 95% CI 0.77 to 2.53, very low-quality evidence, Figure 6) (Summary of findings table 1), due to the very low-quality evidence, we are uncertain about these results.

Itraconazole (ITZ)

One RCT was included that compared 200mg daily ITZ (treatment duration: 2.8 ± 2.33 months) versus a 'pulsed' ITZ strategy of 400mg daily for one week followed by three weeks of no ITZ treatment (the overall treatment was 2.65 ± 0.81 pulses). Overall, this study had low risk of bias, but included only 50 participants. Results showed that there may be no difference between the groups in the proportion of people with clinical cure either in the medium- (22/24 vs 18/22, RR 1.12, 95% CI 0.89 to 1.41, P = 0.33, low-quality evidence, Figure 7) or long term (23/24 vs 18/22, RR 1.17, 95% CI 0.95 to 1.45, P = 0.15, low-quality evidence, Figure 7). Also, there may be no difference between groups in terms of minor adverse events (4/24 vs 1/22, RR 3.67, 95% CI 0.44 to 30.35, P = 0.23, low-quality evidence, Figure 8); however, the result is highly imprecise as the trial is likely too small to detect a clear difference. No data were reported on severe adverse events (Summary of findings table 2).

One RCT was included that compared 100mg daily ITZ (700mg/week, continuous intervention until cure (range 33 to 75 days)) versus 400mg/week ITZ (continuous intervention till cure (range 20 to 36 days)). Many of the 'Risk of bias' domains were of unclear risk, and the study only included 20 participants. We did not find a difference between the dosing regimens in achieving clinical cure in the medium term (10/10 vs 10/10, RR 1.00, 95% CI 0.83 to 1.20, very low-quality evidence, Figure 9); however, due to the very low-quality evidence, we are uncertain whether this result is true. Other predefined outcomes, including long-term cure and adverse events, were not reported (Summary of findings table 3).

Oral terbinafine (TBF)

One RCT was included that compared 500mg/day oral TBF (treatment duration: 17.7 ± 5.8 weeks) versus 1000mg/day oral TBF (treatment duration: 13.9 ± 6.7 weeks). While random sequence generation was unclear, there was also a high drop-out rate concerning clinical cure resulting in high risk of attrition bias. Although 1000mg/day oral TBF was favoured in terms of attaining medium-term clinical cure (15/27 vs 25/31, RR 0.69, 95% CI 0.47 to 1.01, very low-quality evidence, Figure 10), the very low quality of this evidence means we are uncertain of the truth of this effect. 1000mg/day oral TBF may be favoured in terms of achieving long-term clinical cure (14/27 vs 27/31, RR 0.60, 95% CI 0.4 to 0.88, low-quality evidence, Figure 10).

Although statistical results did not to demonstrate clear difference between the groups in terms of severe adverse event rate in the long term (0/28 vs 2/35, RR 0.25, 95% CI 0.01 to 4.97, very low-quality evidence, Figure 11) or minor adverse events (10/28 vs 17/35, RR 0.74, 95% CI 0.40 to 1.34, very low-quality evidence, Figure 13) (Summary of findings table 4), due to very low-quality evidence, we are uncertain of the effect.

Implications and conclusions

Although potassium iodide, itraconazole and terbinafine are used in clinical medicine for the treatment of sporotrichosis, there is limited RCT evidence on their effectiveness and safety for sporotrichosis (Table 1 to Table 4). This review included four RCTs, and each compared within-class comparisons of the same drug; none compared the drugs against each other. These RCTs reported limited outcomes, and most showed no clear difference between treatment groups, except one RCT that demonstrated that more people may be clinically cured in the long term (more than 6 months) with 1000mg/day oral terbinafine than with 500mg/day oral terbinafine. Although there was no difference in adverse events, we are uncertain if this is true because of the very low-quality evidence base. It's worth noting that terbinafine dosage in this trial is higher than that of routine clinical dosages. No data were reported for the proportion with good or excellent improvement and quality of life scores. Also, for itraconazole 100mg/day (700mg/week) versus itraconazole 400mg/week, the outcome of adverse events was not measured.

The overall quality of evidence was low or very low due to high risk of bias in included studies and imprecision of the results. Most included studies may be too small to detect a clear difference, and in the absence of any placebo-controlled studies, it is unclear how many cases would resolve spontaneously over time. Therefore, current findings need to be applied with caution, and are insufficient to conclude any best treatment for sporotrichosis. More clinical trials on this topic with larger sample size and good follow-up are needed. More data should be reported on proportions of symptom improvement and quality of life.

Summary of findings table 1: potassium iodide as a single dose versus potassium iodide divided into three doses for sporotrichosis

***Patients and setting*: children with a culture confirmed diagnosis of cutaneous sporotrichosis (mean age: 7.5 years, mean length of illness: 13.3 months). Study set in Peru.**
***Comparison:* daily total dosage of saturated solution of potassium iodide (SSKI) divided into 3 doses given at different times versus daily SSKI given as a single dose.**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) No. of participants & studies	**Quality of the evidence (GRADE)**
		Control: SSKI divided into 3 doses	Intervention: SSKI as a single dose		
Proportion of participants with clinical cure - medium term (4 weeks to 6 months)	There may be no difference between the two groups in terms of achieving medium-term clinical cure.	1000 per 1000	1000 per 1000	RR 1 (0.93 to 1.08) Based on data from 51 participants in one study.	□□□□ LOW[1,2]
		No difference per 1000 participants.			
Proportion of participants with clinical cure - long term (more than 6 months)	The included study did not report this outcome.				
Proportion of participants with good or excellent improvement	The included study did not report this outcome.				
Severe adverse events – medium term (4 weeks to 6 months)	Although no clear difference was found between the 2 treatment groups in terms of their effect on severe adverse events in the medium term, we are uncertain about this result, because the quality of the evidence for this outcome and comparison was very low.	39 per 1000	72 per 1000	RR 1.86 (0.18 to 19.29) Based on data from 54 participants in one study.	□□□□ VERY LOW[1,3]
		Difference 33 more per 1000 participants (95% CI: 32 fewer to 713 more per 1000 participants)			
Changes in quality of life score	The included study did not report this outcome.				
Change in isolation rate of sporotrichosis from baseline to assessed follow-up time	The included study did not report this outcome.				
Change in fungal counts of sporotrichosis from baseline to assessed follow-up time	The included study did not report this outcome.				
Changes in the individual signs of sporotrichosis as assessed by a physician from baseline to assessed follow-up time	The included study did not report this outcome.				
Duration of remission and prevention of subsequent flares	The included study did not report this outcome.				
Minor adverse events	Although no clear difference was	385 per 1000	535 per 1000	RR 1.39 (0.77 to 2.53)	□□□□

	found between the 2 treatment groups in terms of their effect on minor adverse events, we are uncertain about this result, because the quality of the evidence for this outcome and comparison was very low.	Difference 177 more per 1000 participants (95% CI: 82 fewer to 548 more per 1000 participants)	Based on data from 54 participants in one study.	VERY LOW[1,3]

CI=confidence interval; MD=Mean difference; RR=Risk ratio. [1]Downgraded one level for serious risk of bias: high risk of performance and detection bias. [2]Downgraded one level for serious imprecision: less than desired optimal information size. [3]Downgraded two levels for very serious imprecision: small sample size and wide confidence intervals.

Summary of findings table 2: Itraconazole 200mg/day versus 'Pulsed' itraconazole 400mg/d for sporotrichosis

***Patients and setting*: Patients with cutaneous sporotrichosis (median age: 52yrs, median length of illness: 4 weeks). Study was set in China**

Comparison: Daily ITZ (200mg/day) versus 'Pulsed' ITZ (400 mg/day for 1 week followed by no itraconazole treatment for 3 weeks)

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) No. of participants & studies	**Quality of the evidence (GRADE)**
		Control: 'Pulsed' ITZ (400mg/day for 1 week followed by no itraconazole for 3 weeks)	Intervention: Daily ITZ (200mg/day)		
Proportion of participants with clinical cure - medium term (4 weeks to 6 months)	There may be no difference between the groups in the proportion of people achieving clinical cure in the medium term.	818 per 1000	916 per 1000	RR 1.12 (0.89 to 1.41) Based on data from 46 participants in 1 study.	□□□□ LOW[1]
		Difference 98 more per 1000 participants (95% CI: 90 fewer to 335 more per 1000 participants)			
Proportion of participants with clinical cure - long term (more than 6 months)	There may be no difference between the groups in the proportion of people achieving clinical cure in the long term.	818 per 1000	957 per 1000	RR 1.17 (0.95 to 1.45) Based on data from 46 participants in 1 study.	□□□□ LOW[1]
		Difference 139 more per 1000 participants (95% CI: 41 fewer to 368 more per 1000 participants)			
Proportion of participants with good or excellent improvement	The included study did not report this outcome.				
Severe adverse effects	The included study did not report this outcome.				
Changes in quality of life scores	The included study did not report this outcome.				
Change in isolation rate of sporotrichosis from baseline to assessed follow-up time	The included study did not report this outcome.				
Change in fungal counts of sporotrichosis from baseline to assessed follow-up time	The included study did not report this outcome.				
Changes in the individual signs of sporotrichosis as assessed by a physician from baseline to assessed follow-up time	The included study did not report this outcome.				
Duration of remission and	The included study did not report this outcome.				

prevention of subsequent flares					
Minor adverse events	There may be no difference in minor adverse events using daily ITZ compared to 'pulsed' ITZ.	45 per 1000	167 per 1000	RR 3.67 (0.44 to 30.35) Based on data from 46 participants in 1 study.	□□□□ LOW[1]
		Difference 122 more per 1000 participants (95% CI: 25 fewer to 1000 more per 1000 participants)			

CI=confidence interval; MD=Mean difference; RR=Risk ratio.[1]Downgraded by 2 levels for very serious imprecision: small sample size and wide confidence interval.

Summary of findings table 3: itraconazole 100mg/day (700mg/week) versus itraconazole 400mg/week for sporotrichosis

***Patients and setting*: people with sporotrichosis defined as a *Sporothrix schenckii* complex positive fungal culture (median age: not given [range 9 – 72 years], median length of illness: not given [range: 1 month – 2.5 years]. Study set in China.**
***Comparison:* ITZ (Sporanox) 100mg/day (700mg/week) versus ITZ (Sporanox) 400mg/week (200mg twice per week)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) No. of participants & studies	**Quality of the evidence (GRADE)**
		Control: ITZ 400mg/week	Intervention: ITZ 700mg/week		
Proportion of participants with clinical cure – medium term (4 weeks – 6 months)	Although no clear difference was found between the 2 treatment groups in terms of their effect on medium-term clinical cure, we are uncertain about this result, because the quality of the evidence for this outcome and comparison was very low.	1000 per 1000	1000 per 1000	RR 1 (0.83 to 1.2) Based on data from 20 participants in 1 study.	□□□□ VERY LOW[1,2]
		No difference per 1000 participants.			
Proportion of participants with clinical cure – long term (more than 6 months)	The included study did not report this outcome.				
Proportion of participants with good or excellent improvement	The included study did not report this outcome.				
Severe adverse effects	The included study did not report this outcome.				
Changes in quality of life score	The included study did not report this outcome.				
Change in isolation rate of sporotrichosis from baseline to assessed follow-up time	The included study did not report this outcome.				
Change in fungal counts of sporotrichosis from baseline to assessed follow-up time	The included study did not report this outcome.				
Changes in the individual signs of sporotrichosis as assessed by a physician from baseline to assessed follow-up time	The included study did not report this outcome.				

Duration of remission and prevention of subsequent flares	The included study did not report this outcome.
Minor adverse effects	The included study did not report this outcome.

CI=confidence interval; MD=Mean difference; RR=Risk ratio.[1]Downgraded by 1 level for serious risk of bias.[2]Downgraded by 2 levels for very serious imprecision: small sample size and wide confidence interval.

Summary of findings table 4: oral terbinafine 500mg/day versus oral terbinafine 1000mg/day for sporotrichosis

***Patients and setting*: Patients with *Sporothrix schenckii* complex cutaneous or lymphocutaneous infection (mean age: 38.5 years, mean length of illness: not stated). Multinational study in 3 centres; Brazil, Colombia and USA.**
***Comparison:* Oral TBF 500mg once daily versus oral TBF 1000mg daily (500mg twice per day)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) No. of participants & studies	**Quality of the evidence (GRADE)**
		Control: Oral TBF 1000mg	Intervention: Oral TBF 500mg		
Proportion of participants with clinical cure – medium term (4 weeks to 6 months)	Although 1000mg/day oral TBF was favoured in terms of medium-term clinical cure, we are uncertain about this result because the quality of the evidence for this outcome and comparison was very low.	806 per 1000	556 per 1000 Difference 250 fewer per 1000 participants (95% CI: 427 fewer to 9 more per 1000 participants)	RR 0.69 (0.47 to 1.01) Based on data from 58 participants in one study.	□□□□ VERY LOW[1,4]
Proportion of participants with clinical cure – long term (more than 6 months)	1000mg/day oral TBF may be favoured in terms of achieving long-term clinical cure.	871 per 1000	523 per 1000 Difference 348 fewer per 1000 participants (95% CI: 523 to 105 fewer per 1000 participants)	RR 0.6 (0.4 to 0.88) Based on data from 58 participants in one study.	□□□□ LOW[1,3]
Proportion of patients with good or excellent improvement	The included study did not report this outcome.				
Severe adverse events – long term (more than 6 months)	Although no clear difference was found between the 2 treatment groups, we are uncertain about this result, because the quality of the evidence for this outcome and comparison was very low.	57 per 1000	14 per 1000 Difference 43 fewer per 1000 participants (95% CI: 56 fewer to 227 more per 1000 participants)	RR 0.25 (0.01 to 4.97) Based on data from 63 participants in one study.	□□□□ VERY LOW[2,4]
Changes in quality of life score	The included study did not report this outcome.				
Change in isolation rate of sporotrichosis from baseline to assessed follow-up time	The included study did not report this outcome.				
Change in fungal counts of sporotrichosis from baseline to	Although 1000mg/day oral TBF was favoured in terms of reducing	Average reduction in lesion size: 10.75	MD reduction 4.01 cm^2 higher (0.03	Based on data from 58 participants in one study	□□□□ VERY LOW[1,3]

assessed follow-up time: reduction in size (cm^2)	lesion size, imprecision means we are not confident in this result, and we are uncertain about the effect of the treatments on this outcome because the quality of the evidence for this outcome and comparison was very low.	cm^2	cm^2 lower to 8.05 cm^2 higher) compared to the control group		
		-	-		
Changes in the individual signs of sporotrichosis as assessed by a physician from baseline to assessed follow-up time	The included study did not report this outcome.				
Duration of remission and prevention of subsequent flares	The included study did not report this outcome.				
Minor adverse events	Although no clear difference was found between the 2 treatment groups, we are uncertain about this result, because the quality of the evidence for this outcome and comparison was very low.	486 per 1000	359 per 1000	RR 0.74 (0.4 to 1.34) Based on data from 63 participants in one study.	□□□□ VERY LOW[2,4]
		Difference 127 fewer per 1000 participants (95% CI: 292 fewer to 165 more per 1000 participants)			

CI=confidence interval; MD=Mean difference; RR=Risk ratio.[1]Downgraded one level for serious risk of bias: high risk of attrition bias. [2]Downgraded one level for serious risk of bias: unclear risk of allocation and allocation concealment.[3]Downgraded one level for serious imprecision: less than desired optimal information size.[4]Downgraded two levels for very serious imprecision: small sample size and wide confidence intervals.