Supplementary Data

Box S1. Search strings used for literature search

Search string used for systematic reviews:

("Impetigo"[Mesh] OR Impetigo[tiab] OR “School sore”[tiab] OR “School sores”[tiab])

AND

(((search[tiab] OR searched[tiab]) AND (Pubmed[tiab] OR Medline[tiab] OR Cochrane[tiab])) OR “Systematic review”[tiab] OR “meta analysis”[pt] OR meta analysis[tiab] OR meta analysis[Mesh] OR Cochrane Database Syst Rev[ta])

Search string used for prognosis studies:

("Impetigo"[Mesh] OR Impetigo[tiab] OR “School sore”[tiab] OR “School sores”[tiab])

AND

(Prognos*[tiab] OR Cohort[tiab] OR Natural history[tiab])

Table S1. Characteristics of included studies.

	Ruby 1973 (1)	**Zaynoun 1974 (2)**	**Eells 1986 (3)**	**Koning 2002 (4)**	**Koning 2008 (5)**	**Gropper 2014 (6)**	**Rosen 2018 (7)**
Location	USA	Lebanon	Puerto Rico	Netherlands	India, Mexico, Netherlands, Peru	Germany, Romania, South Africa, Ukraine, USA	USA, Russia, South Africa, Germany, Romania, Spain
N	17	12	20	82	71	156	206
Age criteria	"children"	4 months – 65 years*	0 – 18 years	0 -12 years	0 – 44 years*	≥ 2 years	≥2 months*
Age: mean (SD/range) years	NR	NR	3.7 (range 0.17-9)	5.1 (SD 2.7)	8.9 (SD 8.9, 0-44)	17.3 (SD 17.2)	Range 2 months – 80 years
Inclusion criteria	NR	NR (but all were superficial and most were non-bullous)	All "primary skin infections" included, 36/38 were impetigo.	Non-bullous impetigo	Primary bullous and non-bullous impetigo	Bullous and non-bullous impetigo, SIRS ≥8 (exudate ≥1), max extent 100cm^2 or 2% BSA, erythema ≤2cm	Bullous and non-bullous impetigo Total affected area ≤2% BSA (younger than 12 years) or 2-100cm^2 (older than 12 years)

Exclusion criteria	Impetigo in nose/ears/scalp	NR	Recent antibiotic use, other topical or systemic therapy	Immuno-compromise, lesions >5% BSA, subdermal lesions, fever>38.5°C, allergy, hyperthyroidism, recent antibiotic use	SIRS<8, eczema, fever, recent topical therapy use	Other skin disease, systemic antibiotics, axillary fever >37.2°C, bacteraemia, oral/topical/IV antibiotics, topical disinfectants or steroids, immunosuppression, uncontrolled diabetes, pregnancy/lactation, allergy	"Patients with concomitant underlying skin disease, such as preexisting eczematous dermatitis with clinical evidence of secondary infection", bacterial infection that could not be appropriately treated with a topical antibiotic
"Clinical cure" criteria (as defined by trial authors)	Complete epithelialisation, no inflammation	Complete disappearance of lesions	Lesions resolved, nil evidence of infection	Absence of lesions, or dry and without crusts	Lesions absent, or dry without crusts with or without erythema	SIRS 0 for exudates/pus, crusting, warmth, pain; ≤1 for erythema/ inflammation, tissue oedema, itching	SIRS 0 for blistering, exudates and/or pus, crusting, itch and/or pain; SIRS ≤1 for erythema and/or inflammation

"Failure to improve" criteria (as defined by trial authors)	"continuing active and new lesions"	"minimal or no improvement"	"no apparent response to therapy"	NR	NR	"No change in total SIRS score, or total SIRS score increased or decreased ≤10% compared to baseline, and additional antimicrobial therapy of the baseline affected areas was required"	Not fulfilling the criteria for cure. Improvement and failure were both considered clinical failure.
Coding of healed criteria used in this study	*Complete clearance*	*Complete clearance*	*Complete*	*Infection clearance*	*Infection clearance*	*Intermediate*	*Intermediate*
Randomisation	Random numbers list**. Random sequence generation not described	"Coded" treatment "given at random" to patients. Random sequence generation not described	Computer generated sequence; blocks of five	Computer generated sequence; blocks of six; stratified by presence of pre-existing eczema at site of impetigo	2:1 schedule; stratified by age group. Random sequence generation not described	Web generated randomisation; stratified by age. Random sequence generation not described	"Central randomisation via an interactive web response system"; 1:1 schedule; stratified by age group.
Blinding	NR	"Double blind" (not described)	"Double blind" (not described)	Blinding of participants and investigators	Blinding of participants; investigators	Blinding of participants and investigators	"Double-blind" (not described)

					could unbreak blinding in a clinical emergency		
Placebo	Oral suspension (no further details reported)	Topical cream	Topical ointment	Topical cream	Topical ointment	Topical cream	Topical cream
Concurrent treatment	Daily castile soap bath instructed for both treatment and placebo groups	Twice daily hexachlorophene soap 2% wash instructed for both treatment and placebo groups Normal soap use not reported	No other treatment instructions for either treatment or placebo groups; however, participants were excluded if using "another topical" therapy – unclear if this includes soap	Twice daily povidone-iodine shampoo instructed for both treatment and placebo groups Normal soap use not reported	"The use of other topical agents, including antibacterial soaps and lotions, or systemic antibiotics was not allowed during the study" for both groups.	"Only a small number of patients had previously used medications (n=12, mostly antiseptics/ disinfectant) and 113 were administered concomitant medications. This included allowed treatments during screening" – no description of what these allowed treatments were. No mention of soap. No clarification of how the 113 participants were divided among the trial arms.	No other treatment instructions for either treatment or placebo groups. Normal soap use not reported

			and/or disinfectant				
Symptom duration prior to study inclusion	NR	NR	NR	Mean 9.2 days (SD 10.2)	Mean 9.4 days	NR	NR

AGN = acute glomerulonephritis; BSA = body surface area; NR = not reported; SIRS = Skin Infection Rating Scale. *Study comprised mostly children. **In Ruby et al's trial, "when more than one child from a household was entered into the study, all those children received the same treatment" (1), which may have introduced selection bias.

Table S2. Outcome data from included studies.

	Ruby 1973 (1)	Zaynoun 1974 (2)	Eells 1986 (3)	Koning 2002 (4)	Koning 2008 (5)	Gropper 2014 (6)	Rosen 2018 (7)
% of participants with clinical cure							
Day 5	0%	-	-	-	-	-	-
Day 6	-	-	-	-	-	-	78/206 (38%)
Day 7	-	6/12 (50%)	-	10/80 (13%)	37/71 (52%)	115/156 (74%)	
Day 8	-	-	8/19 (42%)	-	-	-	-
Day 10	8%	-	-	-	-	-	-
Day 14	-	-	-	46/77 (60%)	28/71 (39%)	-	-
Day 28	-	-	-	69/78 (88%)	-	-	-
% of participants with clinical improvement							
Day 5	-	-	-	-	-	-	-
Day 6	-	-	-	-	-	-	161/206 (78%)
Day 7	-	3/12 (25%)	-	37/80 (46%)	-	-	-
Day 8	-	-	8/19 (42%)	-	-	-	-

Day 10	-	-	-	-	-	-	-
Day 14	-	-	-	20/77 (26%)	-	-	-
Day 28	-	-	-	7/78 (9%)	-	-	-
% of participants with failure to improve							
Day 5	100%	-	-	-	-	-	-
Day 6	-	-	-	-	-	-	41/206 (20%)[a]
Day 7	-	3/12 (25%)	-	33/80 (41%)	-	36/156 (23%)	-
Day 8	-	-	3/19 (16%)	-	-	-	-
Day 10	92%	-	-	-	-	-	-
Day 14	-	-	-	11/77 (14%)	-	-	-
Day 28	-	-	-	2/78 (3%)	-	-	-
% participants who left placebo group and commenced antibiotics	Not reported	Not reported	0%	7/82 (9%)	27/71 (38%)	3/156 (2%)	Unclear; 13 discontinued the study due to worsening or lack of response but not clear if they then

							received antibiotics.
Follow-up duration (day 1 = commenced placebo)	10 days Final follow up was 10 days after initial clinic visit. Unclear when placebo treatment began	7 days “Results after 1 week of treatment”; “evaluation of improvement had to be limited to the first week of therapy”	8 days Initial visit was considered “pretreatment”; final follow-up was “seven to nine days after starting therapy” (up to 12 days was acceptable)”	28 days Patients started treatment “usually the same day” as initial visit. Follow up was 7 days “after the start of treatment”	14 days Treatment went for day 1-5, “end of therapy” was at “day 7” and “end of follow-up” was at “14 days”	7 days Placebo treatment started on day 1 (same day as initial visit)	6-7 days Treatment given for 5 days and day 6-7 was “end of therapy”. Does not specify what day 1 is, but the “first application” appears to have been done at the initial visit. Assessment at 10-13 days mentioned, but results not reported.

Adverse effects in placebo group	Reports only on acute glomerulo-nephritis: experienced by no participants	Not reported	Nil adverse events, nil abnormal laboratory events	Pain (6/82, 7.3%) Redness (2/82, 2.4%) Burning from placebo cream (1/82, 1.2%) Itch (2/82, 2.4%) Irritation due to shampoo & cream (1/82, 1.2%) Other (3/82, 3.7%)	Itch (1/71, 1.4%) Paraesthesia (1/71, 1.4%)	Nil adverse events, nil abnormal laboratory tests	7/205 (3.4%) experienced at least 1 adverse effect (nil serious)
Adverse effects in treatment group(s)	Reports only on acute glomerulonephritis: nil	Not reported	Nil adverse events, nil abnormal laboratory events			Nasopharyngitis (4/156, 2.6%)	

a: secondary endpoint of 'clinical failure' was participants who did not meet the definition of 'clinical success' which was a broader measure and defined as: "a total absence of the treated lesions [lesion extension score, 0] or the treated lesions became dry without crusts compared with baseline [SIRS score of 0 for exudate and crusting]), or improvement (defined as decrease in the size of the affected area, number of lesions, or both), such that no further antimicrobial therapy was necessary." This study's data for the primary endpoint of clinical failure was not extracted as their definition of 'failure' also included participants who clinically improved.

References

1. Ruby RJ, Nelson JD. The influence of hexachlorophene scrubs on the response to placebo or penicillin therapy in impetigo. Pediatrics. 1973;52(6):854-9.
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4. Koning S, van Suijlekom-Smit LW, Nouwen JL, Verduin CM, Bernsen RM, Oranje AP, et al. Fusidic acid cream in the treatment of impetigo in general practice: double blind randomised placebo controlled trial. BMJ. 2002;324(7331):203-6.
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6. Gropper S, Albareda N, Chelius K, Kruger D, Mitha I, Vahed Y, et al. Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. Future Microbiol. 2014;9(9):1013-23.
7. Rosen T, Albareda N, Rosenberg N, Alonso FG, Roth S, Zsolt I, et al. Efficacy and Safety of Ozenoxacin Cream for Treatment of Adult and Pediatric Patients With Impetigo: A Randomized Clinical Trial. JAMA Dermatol. 2018;154(7):806-13.