

Local management of anogenital warts in immunocompetent adults: Systematic review and pooled analysis of randomized-controlled trial data



To the Editor: Although several treatments exist for anogenital warts, no clear treatment hierarchy is mentioned in the latest guidelines.^{1,2} We conducted a pooled analysis of randomized-controlled trials (RCTs) of anogenital wart treatments (provider-administered therapies and patient-administered treatments reported in at least 1 parallel treatment group). Our analysis covered a large number of patients and supplements meta-analyses performed with studies that included only 2 treatment groups.

Our systematic review included RCTs of anogenital wart treatments published up to August 1, 2018, following the methodology described in our systematic review protocol (Prospero no. CRD42015025827).³

In total, 70 RCTs involving 9931 individual patients were included. A high risk of bias was identified in 66 RCTs.⁴

Our main pooled analysis results are summarized in the Table I.^{1,5} The complete clearance rate was higher for provider-administered therapies (92%) than patient-administered treatments (56%), but the recurrence rate was lower for patient-administered treatments (6%) than provider-administered therapies (29%). Surgery was painful in 48% of cases, and CO₂ laser was associated with a recurrence rate of 31%. For electro-surgery, the recurrence rate was high, side effects were low, and the clearance rate was low due to the high

number of patients lost to follow-up in the study by Stone et al;⁵ it would have been 79% with a per-protocol analysis. Trichloroacetic acid was associated with a high clearance rate, a low recurrence rate, and few side effects compared with cryotherapy.³ The latest guidelines¹ include 5-fluorouracil cream but fail to mention potassium hydroxide. Our analysis yielded a high clearance rate and a low recurrence rate for both treatments, suggesting that potassium hydroxide could also be included as first-line treatment in future guidelines; besides, 5-fluorouracil cream caused more low- and medium-grade local side effects than potassium hydroxide. Podophyllotoxin 0.5% solution or cream seemed as effective as cryotherapy or imiquimod but caused more general side effects. Cryotherapy, CO₂ laser, and podophyllotoxin 0.5% solution or cream caused less high-grade local side effects than other treatments. High-grade local side effects were rarely reported for provider-administered therapies with local anesthesia. They seemed equivalent in number between patient-administered treatments and provider-administered therapies but involved different consequences. Recurrent pain or burns after application of patient-administered treatments (eg, imiquimod) can lead to nonadherence, unlike after provider-administered therapies requiring only a single application (eg, CO₂ laser).

Although the risk of bias was high in many of the included studies (unpublished data), our results complement the latest guidelines.¹ Therapies could be selected on the basis of anogenital wart duration

Table I. Pooled-analysis of potential first-line local AGW treatments* for all judgment criteria

Treatment	No. RCTs (total no. ITT patient population)	Clearance	% with type of side effect/outcome quartile†				
			Recurrence	LGL	MGL	HGL	LGG
Patient-administered							
5-Fluorouracil cream	6 (393)	68/Q2	13/Q2	84/Q4	68/Q4	8/Q2	16/Q2
Potassium hydroxide*	2 (54)	63/Q2	6/Q1	17/Q1	50/Q3	NR	17/Q2
Podophyllotoxin 0.5% solution	13 (829)	59/Q2	29/Q3	62/Q3	46/Q3	10/Q2	45/Q4
Podophyllotoxin 0.5% cream	8 (294)	57/Q3	11/Q2	22/Q2	25/Q2	1/Q1	48/Q4
Imiquimod 5%	10 (611)	57/Q3	13/Q2	50/Q3	26/Q2	13/Q3	24/Q3
Polyphenon 15%	3 (477)	54/Q3	7/Q1	60/Q3	8/Q1	7/Q2	11/Q1
Provider-administered without local anesthesia							
Trichloroacetic acid	6 (334)	72/Q2	14/Q2	26/Q2	17/Q2	8/Q2	18/Q2
Cryotherapy	12 (709)	58/Q3	27/Q3	24/Q2	15/Q1	4/Q1	29/Q3
Provider-administered with local anesthesia							
Surgery	2 (48)	92/Q1	20/Q2	NR	42/Q3	NR	48/Q4
CO ₂ laser	6 (329)	88/Q1	31/Q4	57/Q3	43/Q3	0/Q1	10/Q1
Electrosurgery	3 (221)	56‡/Q3	35/Q4	NR	8/Q1	NR	16/Q2

AGW, Anogenital wart; HGL, high-grade local (blisters and ulcerations); ITT, intention-to-treat; LGG, low-grade general (pain requiring analgesics); LGL, low-grade local (stinging, irritation, erythema); MGL, medium-grade local (skin burn, soiling, minor bleeding, erosion, infection); NR, not reported; Q, quartile; RCT, randomized-controlled trial.

*First-line treatments mentioned in current international recommendations.¹ Potassium hydroxide is not included in those guidelines, but our pooled-analysis results indicate that it could be.

†Outcomes are graded best (Q1) to worst (Q4) by quartile.

‡Clearance was 79% after performing a per-protocol analysis of the data provided by Stone et al.⁵

and history of recurrence. Indeed, we found in our pooled analysis that recurrence at 12 months was lower for patient-administered treatments, making these more relevant than provider-administered therapies as a global therapeutic response—although such recurrence is difficult to evaluate because of the methodologic limitations (eg, lost to follow-up, recontamination). Although provider-administered therapies presented the best clearance before 3 months, their reproducibility remains difficult to compare both among RCTs and among treatments (eg, lack of standardization of freezing or surgical procedures). Given the need for local anesthesia, the use of surgery, CO₂ laser, and electrosurgery seem justified when other treatments have failed. Last, knowledge of treatment side effects can assist physicians with adjusting anogenital wart management to the tolerance of the patient.

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Pitfalls and proposed solutions for patient communication about erythropoietic protoporphyria: A survey of parents and adult patients



To the Editor: Erythropoietic protoporphyria (EPP) is a rare inherited defect of heme metabolism resulting in painful photosensitivity.¹ A 1987 survey of 17 EPP

Table I. Demographics and clinical characteristics of EPP patients

Characteristic	Children with EPP, n = 13	Adults with EPP, n = 46
Mean age, y	14.3	49.7
Sex, n (%)		
Male	8 (61.5)	22 (47.8)
Female	5 (38.5)	24 (52.2)
Age at diagnosis, y, mean (range)	6.5 (3-10)	17 (2-57)
Sensitive to indoor lights, n (%)	3 (23.1)	18 (39.1)
Sunlight exposure limit, n		
0-10 min	4	18
10-30 min	4	17
30 min-1 hr	2	8
1-2 hr	2	2
2-3 hr	0	1
≥3 hr	1	0
Words used to describe EPP, %		
Allergy	46	52
Burn	46	50
Internal sunburn	31	28
Photosensitive	54	35
Phototoxic reaction	23	20
Sensitive to the sun	77	83
Other	31	26

Demographics and clinical characteristics were acquired via survey. For EPP patients who were children (<18 years of age), questions were answered by their parents. EPP diagnosis was patient reported or parent reported (for children) and accompanied by the survey participant's description of the method of diagnosis. EPP, Erythropoietic protoporphyria.