Genital Warts Treatment

Author/Citation	*Description of Study*	*Population, Sample Size*	*Outcome*	*Summary Points*
Komericki P et al, 2011	Randomized, open label trial of imiquimod 5% cream vs podophyllotoxin 0.5% solution	51 Austrian, immunocompetant, adult, non-pregnant pts were randomized (excluded if warts were judged large enough to warrant removal with surgical excision) 45 pts (7 women, 35 men) completed the intervention. Imiquimod 5% was applied 3x/week until warts cleared or up to 16 weeks, podophyllotoxin 0.5% was applied 2x/day on 3 consecutive days until warts cleared or up to 4 weeks	Complete clearance at the end of treatment period (5 weeks after start of podophyllotoxin and 16 weeks after start of imiquimod) using an intention to treat analysis Side effects, assessed at 2 week intervals throughout therapy	➢ Clearance of baseline warts was statistically identical in the two interventions (72% podophyllotoxin and 75% imiquimod) ➢ No statistically significant difference in side effects, most common local reaction was erythema/inflammation (in 37.8% of all pts)
Zervoudis S et al, 2010	Randomized, evaluator-blinded trial of laser treatment of EGW alone vs laser treatment followed by pidotimod (also known as Polimod, an immune stimulator) plus oral vitamin C	62 Greek women with EGW and perianal warts, excluded if pregnant and if the warts had ever been treated before. All pts treated with CO2 laser vaporization to all of their lesions. Then pts were randomized to no further therapy or to applied pidotimod 2 sachets per day and took oral vitamin C 1000mg per day for 15 days, followed by pidotimod 1 sachet per day and vitamin C 500 mg per day for another 60 days.	Clearance Clinical recurrence at 10 week intervals up to 6 months after laser procedure Adverse events	➢ Complete clearance occurred in 67% of those treated with laser alone, and in 81% of those treated with laser plus pidotimod (not statistically significant) ➢ No recurrences in 6 months of follow-up among those who cleared ➢ One adverse event reported in the laser plus treatment group – nausea on the second day of treatment
Gilson R et al, 2009	Randomized, double-blind trial of weekly cryotherapy plus placebo versus weekly	140 pts aged 18–70, with perianal or EGW totaling at least 1cm2, not treatment in	Complete clearance using intention to treat analysis Recurrence	➢ Complete clearance at 4 and 12 wks was higher in the cryo +

	cryotherapy plus podophyllotoxin 0.15% cream	the last 4 months, investigators had to believe pts could be treated with cryo or podophyllotoxin plus cryo. All pts received weekly cryotherapy for 45s freeze, then the next day started placebo or podophyllotoxin 0.15% cream 2x/day for 3 consecutive days, repeated weekly for up to 4 weeks or until complete clearance. Cryo was repeated weekly for up to 12 weeks or until complete clearance.	Adverse effects	podophyllotoxin group (60% and 60%) than in the cryo alone group (45.7% and 45.7%) but not statistically significant. ➢ No difference in groups by 24 weeks of follow up (68.6% and 64.3%) ➢ More pts discontinued use of the cream in the podophyllotoxin group than the placebo group (18.6% vs 5.7%)
Mi X et al, 2011	Randomized, double blinded, placebo controlled trial of cryotherapy plus placebo and PDT vs cryotherapy plus ALA and PDT	109 pts, aged 18–54 years, immunocompetant, non-pregnant and without internal warts, with perianal or genital warts, were randomized. All pts received cryotherapy, an 8 sec freeze to each wart twice. Immediately following cryotherapy, the pts randomized to cryo + ALA and PDT had their warts treated with 20% ALA solution for 3 hrs. The placebo group received sterile saline soaked gauze for 3 hrs. All pts then had their warts irradiated with a 635nm laser emitting 100J/cm2 for 100mW/cm2. If lesions did not clear, the treatment was repeated in 7 days.	Complete clearance by site of wart Recurrence at 12 weeks Adverse events	Complete clearance after 2 treatments ➢ Overall complete response better in the combination therapy group (70.4% vs 42.4%) ➢ The same (32.4% vs 32.6%) for both treatments for perianal warts ➢ Combination therapy was superior (100% vs 54%) for the urethral meatus ➢ Combination therapy was superior for other external genital warts (94.2% vs 50.5%) ➢ Recurrence rates after 12 wks were less with combination therapy overall (12.5% vs 32.2%) ➢ 100% of the pts in both

				groups had at least mild side effects, including pain, crusting, erosions, but no one withdrew from the study due to side effects.
Liang et al, 2009	Randomized trial of PDT w/ALA or CO2 laser	90 adult, non-pregnant, Chinese pts with distal urethra or GW were randomized to PDT w/ ALA (67pts) or CO2 laser (23 pts). Pts received either 20% ALA solution applied for 3 hrs, followed by PDT with 632 nm at 100J/cm2 at 100mW, or had 2% topical lidocaine applied followed by CO2 laser treatment to all the lesions. Pts were examined one week following therapy, and any pts with residual disease had a repeat treatment, for up to 3 total treatments.	Clearance Recurrence at 12 weeks after last treatment Adverse events	➢ 96% complete clearance after 3 treatments in PDT group ➢ 100% complete clearance after 3 treatments in CO2 laser group ➢ Recurrence rate was significantly lower with the PDT group vs the CO2 group (9.4% vs 17.4%) ➢ Adverse events were all mild, but significantly lower in the PDT group compared to the CO2 group (9% vs 100%)
Yang J et al, 2009	Systematic review with meta-analysis of interferon therapy versus others	12 trials including 1445 pts. 7 trials of local INF vs placebo, 5 of systemic INF vs placebo	Risk of complete response	➢ Complete response more likely with local IFN than placebo (combined RR 2.68, 1.79–4.02 P<0.01) ➢ No statistical differences between systemic INF and placebo for complete response ➢ No differences in risk of relapse between local or systemic INF and placebo

Question: Treatment Modalities: 5-FU Efficacy

Author/Citation	*Description of Study*	*Population, Sample Size*	*Outcome*	*Summary Points*
Weisman et al, 1982 (article in German, abstract in English)	Randomized, controlled trial of 0.5% 5-FU and salicylic acid varnish vs "placebo" (salicylic acid varnish without the 5-FU)	59 immunocompetant adults (30 men and 29 women) with GW were randomized. 30 received 0.5% 5-FU and salicylic acid varnish and 29 received salicylic acid varnish without the 5-FU. Within both randomized groups, women were treated 2x/week in the clinic and men self-treated daily at home.	Complete response/cure and median time to cure Partial response "Blood tests" (not further specified in the English abstract) before and after therapy Patch tests to 5-FU after therapy	5-FU + salicylic acid group: ➢ Cured – 18 pts (60%) Median treatment time before cure was 2 wks in men, 3 wks in women ➢ Partial response - 6 pts (20%) ➢ No response – 6 pts (20%) Salicyclic acid varnish alone group: ➢ Cured – 8 pts (28%) Median time to cure was 2.5 weeks for men and 3.5 weeks for women ➢ Partial response – 4 pts (14%) ➢ No response -17 pts (59%) 5-FU + sal acid was superior in producing cure when compared to sal acid alone ($P < 0.01$) Blood tests were the same (and normal) before and after therapy in all patients

				Patch testing after therapy revealed no sensitization
Botacini et al, 1993 (article and abstract available only in Portuguese, some translation done through Google translate)	Randomized, controlled trial of 5% 5-FU cream vs placebo vs podophyllin 2% and 4%	74 immunocompetant women with GW received 5% 5-FU cream, 16 - placebo podophyllin 2% - 5 pts podophyllin 4% - 40 pts	Complete response/cure Partial response	5-FU group: ➢ Cured – 52 pts (70%) ➢ Partial response - 7 pts (10%) ➢ No response – 55 pts (20%) Placebo group: ➢ Cured – 5 pts (31%) ➢ Partial response – 1 pts (6%) ➢ No response - 10 pts (62%) Podophyllin 4% group: ➢ Cured – 3 pts (60%) ➢ Partial response - 1 pts (20%) ➢ No response – 1 pts (20%) Podophyllin 2% group: ➢ Cured – 19 pts (48%) ➢ Partial response – 5 pts (12%) ➢ No response - 16 pts (40%)
Syed et al, 2000	Randomized, controlled-trial of intravaginal 5-FU 1% gel	30 adult immunocompetant women with intravaginal GW received 5-FU 1% gel, 30 received placebo	Cure at 4 weeks after starting treatment Adverse events	5-FU 1% gel group: ➢ Cured – 25 pts (83%) ➢ Adverse events – 2 pts (7%) ➢ Recurrence – 2 pts (7%) Placebo group: ➢ Cured – 4 pts (13%) ➢ Adverse events – 1 pts (3%)

				➢ Recurrence – 1 pts (3%)
Wallin et al, 1977	Randomized, controlled trial of 5% 5-FU cream vs podophyllin 25% gel	42 adult, immunocompetant men with GWs who had not received any treatment in the previous 6 months were randomized to 5% 5-FU cream (20 pts) applied every night for 2 weeks or podophyllin 25% gel applied by a physician once per week, then washed off 4-6 hrs later, for 4 weeks (22 pts).	Cure at 4 weeks Withdrawals Side effects	5-FU group: ➢ Cured at 4 weeks– 10/18 who finished therapy (55%) ➢ •Withdrawals – 2 pts (10%) ➢ Erosions at treatment area reported in 10 (55%, median time to erosions 10 days of treatment) Podophyllin 25% group: ➢ Cured at 4 weeks – 11/19 who finished therapy (58%) ➢ Withdrawals – 3 pts (14%) ➢ Erosions at the glans penis reported in 1 pt (5%) Authors concluded that there were no differences in efficacy between the 2 therapies
Batista C et al, 2010	Cochrane review; meta-analysis (Summary of the above 5 studies plus other studies comparing 5-FU alone to meta-cresol-sulfonic acid, 5-FU + CO2 laser, and 5FU + IFN	Trials of 5-fluorouracil (5-FU) versus placebo or other treatments for safety and efficacy against EGW through August of 2009. 6 trials, including 645 women and 343 men, were found. All pts were aged ≥18 years and non-immunocompromised.		➢ 5FU presented better risk of cure than: placebo (RR 0.39 (0.23–0.67) meta-cresol-sulfonic acid (MCSA) (RR 2.11 (0.83–5.37) or podophyllin 2,4, or 25% (RR 1.26 (0.86–1.82) ➢ 5FU alone had no statistical difference for failure versus 5FU+ CO2 laser (RR 0.69 (0.43–

				1.11) or 5FU +IFN alpha 2A (low dose) (RR 1.02 (0.87–1.119) ➢ 5FU alone had higher risk of failure when compared to 5FU + INF alpha2A (high dose) (RR 10.78 (1.50–77.36) and 5FU + CO2 laser +INF alpha 2A (high dose) (RR 7.97 (2.87–22.13)

Question: Treatment Modalities: Sinecatechins – Efficacy

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Tatti S et al, 2010	Pooled analysis of 2 randomized, controlled, double blind clinical trials of polyphenon E 10% ointment vs vehicle (Pooled analysis of 2 pivotal trials by Stockfleth et al and Tatti et al that were published in 2008 and demonstrated efficacy and safety)	401 pts treated with polyphenon E 10% ointment and 207 pts treated with vehicle in two 16-week phase III studies in adult pts with EGW and perianal warts.	Complete clearance Recurrence Adverse events	➢ OR for complete clearance with polyphenon E 10% ointment vs vehicle was 2.10 (1.485–2.976) in intention to treat analysis (56.3% cleared in treatment group vs 35.4% cleared in the vehicle group) ➢ Gender subgroup analysis showed polyphenon to be more effective in complete clearance for both men and women ➢ Among pts who were clear at 16 wks, there was no difference in recurrence rates 12 weeks later (6.5% vs

				5.8%) ➢ Only 1 pt receiving polyphenon had a serious AE related to treatment; pustule vulvovaginitis ➢ 7.0% of the treatment group and 2.4% of the vehicle group reported treatment-related adverse events.
Tzellos T et al, 2010	Meta-analysis of the 3 randomized, placebo-controlled, double blinded studies (Gross et al, Stockfleth et al, and Tatti et al)	2 independent reviewers searched Medline, EMBASE, Med, Web of Science, Cochran data search through Feb 2010, identified 3 randomized placebo-controlled trials of polyphenon E 15% and 10% for treatment of GW. Trial were of high quality and included: 660 men, 587 women	Expressed as risk ratios: -Clearance of baseline warts with 15% ointment and 10% ointment/cream -Clearance of baseline warts and new warts with 15% ointment and 10% ointment/cream Adverse reactions	➢ RR clearance of baseline warts with 15% ointment 1.53 (95% CI 1.29–1.82) ➢ RR clearance of baseline warts and new warts with 15% ointment 1.45 (1.21–1.74) ➢ RR clearance of baseline warts with 10% ointment/cream 1.46 (1.23–1.74) ➢ RR clearance of baseline warts and new warts with 10% ointment/cream 1.42 (1.19–1.70) ➢ Local skin signs and symptoms were mostly mild, no statistical analyses performed

Question: Treatment Modalities: Imiquimod 5% – Efficacy

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Greensill A et al, 2012	Case series	50 British adolescent pts (aged 13–17 yrs) treated with	Clearance Recurrence	➢ 45 pts completed, 5 pts could not tolerate

		imiquimod, 40 girls, 10 boys, 3 diabetics, 5 pts were Rxd with TCA or cryo at the same time.	Adverse events	(?maybe due to erythema/irritation? Not clear) ➢ Of 45 who completed therapy, 66% full clearance in <2 months, and 86% full clearance in <6 months ➢ 3 recurrences of 45 – at 9, 18, and 36 months after Rx completed
Masuko T et al, 2011	Case report	28 month old Japanese girl with perianal warts, treated with imiquimod 5% cream, 3 x/week overnight until complete clearance.	Clearance Recurrence Adverse events	➢ Response at 2 weeks, complete clearance at 7 weeks ➢ No recurrence 4 weeks after complete clearance ➢ "Inflammatory response" was the only adverse event noted
Brandt H et al, 2010	Case series	4 Brazilian children (aged 1–2 years) with perianal and GWs. One previously treated with podophyllin. All treated with imiquimod 3x/week. Treatment continued for a total of 6 weeks in all cases.	Clearance Recurrence Adverse events	➢ 2 cases resolved completely after 3 weeks of treatment ➢ 2 cases resolved completely after 4 weeks of treatment ➢ 1 case had moderate erythema on treated skin; no other AEs ➢ No recurrences 6 months after treatment stopped

Question: Treatment Modalities: Imiquimod 5% – Safety, adverse events

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Kumar B et al, 2011	Case series	22 immunocompetant Indian men with GW applied imiquimod 5% cream 2x/day	Complete resolution Adverse events	➢ Complete resolution in 54% (time frame not defined)

		for 3 days per week up to 24 weeks.		➢ 27.3% had local adverse reactions, most after 2 wks of treatment ➢ 1 pt had severe irritation at 7 weeks, then developed vitiligo of the treated area that lasted for 7 months ➢ 45.5% of pts reported belching and epigastric discomfort at some point during therapy ➢ 36.6% of pts reported fever, myalgias, fatigue or headache at some point during therapy ➢ 1 pt developed erythema multiforme of the palms and oral mucosa 2 wks after starting imiquimod (no HSV testing done, pt had h/o oral HSV)
Anadkat M et al, 2011	Case report	43 yo American man with HIV, Burkitt's lymphoma in remission, treated for 5 penile genital warts with monthly cryotherapy and 3x/week imiquimod 5% cream.	Clearance Adverse events	➢ Mild improvement in warts ➢ Mild irritation at the site of application ➢ After 3 months of imiquimod Rx, had a PET scan for routine surveillance of his lymphoma which showed inguinal adenopathy and uptake, repeat scan four months later had increased adenopathy, so he had a biopsy that revealed reactive

				changes. Imiquimod was then stopped, cryotherapy every 4 weeks continued, and 2 months after the imiquimod was stopped the PET was repeated and the adenopathy had resolved.
O'Mahony C et al, 2010	Case series	One pt, 37 yo uncircumcised man with lesions on penis genital warts vs lichen sclerosis, bx more c/w GW, treated with imiquimod 5% (application schedule not reported) after 3 wks, lesions appeared more like lichen sclerosis and bx was c/w lichen sclerosis. One pt, 21 yo uncircumcised man with lesions on the penis c/w GW vs lichen planus, no biopsy done, after 7 wks of imiquimod had typical lichen planus lesions that evolved into more reticulated/erosive lesions. Both pts skin conditions resolved with stopping imiquimod and circumcision.		➢ Possible association of lichen sclerosis after 3 wks of imiquimod therapy to the penis in 1 pt ➢ Possible association of lichen planus after 7 wks of imiquimod therapy to the penis on 1 pt
Conde J et al, 2010	Case report	55 yo woman who used imiquimod 5% cream to a section of her anterior scalp for 9 weeks for treatment of a basal cell carcinoma, then developed an area of hair loss at the site of treatment and	Adverse event	➢ Self-resolving telogen effluvium possibly related to 9 weeks of daily imiquimod scalp treatment for basal cell carcinoma

		the vertex 6 weeks after stopping imiquimod. Biopsies demonstrated telogen effluvium, which progressed for three months, and then began to reverse itself and her hair growth was normal 5 months after stopping imiquimod therapy.		
Dominques E et al, 2012	Case report	44 yo man with h/o lichen planus, last outbreak 15 yrs ago, with lesions on the lower lip actinic chelitis vs lichen planus, treated with imiquimod 5% cream x 4 applications, then developed worsening of lesions on lip and typical LP on extremities	Adverse event	➢ Possible reactivation of lichen planus with brief imiquimod treatment on the lip
Mosher J, Lio P, 2012	Case report	2 yr old healthy girl treated with daily imiquimod over lower abdomen for molluscum, developed dermatitis and fevers by 2 wks of treatment. Treatment continued, therapy for presumed cellulitis was started, but fevers continued and pt had a febrile tonic-clonic seizure about 3 wks into imiquimod therapy. Fevers stopped and dermatitis began to resolve one day after imiquimod therapy was stopped	Adverse event	➢ Possible fevers and dermatitis associated with daily imiquimod use in a 2 yr old child
Patel U et al, 2012	Case report	74 yo man with no personal or family history of psoriasis started imiquimod 5% cream		➢ Possible association of new onset, widespread psoriasis away from the

		to his scalp daily for actinic keratosis. Within a few weeks he developed widespread, typical lesions of psoriasis and nail involvement of psoriasis, confirmed by 2 biopsies. These responded to stopping imiquimod, and topical and UV therapies for psoriasis over several months.		site of application of daily imiquimod for actinic keratosis.

Question: Treatment Modalities: Imiquimod 3.75% – Efficacy

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Baker D et al, 2011	Combined results of 2 randomized, double-blinded placebo-controlled trials	534 American women > aged 12 years with genital and anal warts >1 cm2, randomized to placebo, or daily treatment with imiquimod 2.5% or 3.75% cream until clearance of up to 8 weeks.	Clearance Recurrence Adverse events	➢ Complete clearance at the end of 8 weeks: 14.2% - placebo, 28.3%-imiquimod 2.5% and 36.6% imiquimod 3.75% ➢ Safety related discontinuation rates were 0.9%-placebo, 1.4%-imiquimod 2.5%, 2.3%-imiquimod 3.75%

Question: Treatment Modalities: Imiquimod 3.75% – Safety, adverse events

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Wu J et al, 2012	Pharmacokinetic study	18 adults with GW applied up to 1 packet of imiquimod 3.75% cream daily for 3 weeks. Blood was obtained before dose 1, 7, 14, and 21.	Blood levels of imiquimod Adverse events	➢ Steady state was achieved at day 7. ➢ Low blood levels of imiquimod were found. ➢ 16.7% reported adverse events.

				➢ No patients discontinued due to adverse events ➢ 1 interrupted Rx due to an ulcer at Rx site

Question: Treatment Modalities: Photodynamic Therapy—Efficacy

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Wang H et al, 2012	Case series	56 Chinese patients with cervical and EGW treated with ALA 10% gel for 4 hrs, then 635 nm laser at 100 J cm2. Treatment repeated at 2 wk intervals for as long as lesions remained visible.	Complete clearance rate at 1–4 sessions HPV DNA clearance rate Recurrence Adverse events	➢ Complete clearance at 1–4 sessions was 98.2%, HPV clearance rate was 83.9% ➢ 10 cases had complete clearance of cervical lesions and HPV DNA clearance after 1 treatment ➢ Recurrence was 3.6% at 6–24 months ➢ AEs were "minimal"
Yuan-gang L et al, 2012	Case series	40 Chinese pts with 5-25 perianal warts (24 men, 16 women), all underwent curettage to remove visible lesions down to the dermis, then 2 days after curettage, had PDT: 10% 5-ALA cream applied under an occlusive bandage for 3 hrs, warts all treated for 10 min with 635 nm laser at 177 mW/cm2. PDT repeated at 1 and 3 wks.	Clearance at 1 and 3 months following completion of 3 sessions of PDT Recurrence Adverse events	➢ Clearance at 1 month - 100% and no recurrence ➢ At 3 months – 6 cases relapsed, recurrence of 15% ➢ Patient satisfaction was 100% at 1 month and 95% at 3 months ➢ No adverse events
Chen M et al, 2011	Case series	48 HIV negative Chinese women with cervical warts, aged 20–34 years, 9 pts had been treated before with	Clearance after 1, 2 and 3 PDT sessions Recurrence Adverse events	➢ 62.5% cleared after 1 PDT session ➢ An additional 25% cleared after 2 PDT

		electrofulgration and has recurrences, 39 were primary presentations. All had 20% 5 ALA gel on a gauze pad applied to the lesions on the cervix and a 5mm border of normal cervix, for 3 hours. Then all Rxd with 635 nm 100J/cm2 at 100mW. PDT was repeated at week 1 and 2 if lesions were still present at that evaluation.		sessions ➢ An additional 8.3% cleared after 3 PDT sessions ➢ Complete clearance at 1 weeks after 3 PDT sessions was 95.8% ➢ No difference in clearance rates between primary presentations and pts who had been treated with electrofulgration before ➢ Recurrence rate at 12 months after completion of therapy was 4.4%. ➢ Pts who had total lesion size of <1cm required statistically significantly fewer sessions than those who had lesions >1 cm. ➢ No cervical scarring was observed in any pts ➢ Erythema and edema of the cervix 1 week after a treatment session was observed in 25% of pts ➢ Mild burning or irritation during treatment was reported by 12.5% ➢ 5 pts reported menstrual disorders that resolved 2–3 months following the last treatment.
Giomi B et al, 2011	Case series	15 Italian adult pts (10 men, 5 women) with external GW. All GW had previously been	Clearance Changes in immunohistochemical profile	➢ 60% (9/15) pts had complete clearance after 5 treatments

		treated topically, but a wash-out period of at least 3 months took place before the study. All were treated with 16.6 % gel ALA under occlusion for 3 hrs, then with 635nm laser at 110 J/cm2 for 2 min. Evaluated at 48 hrs after treatment; at that time, biopsies were also taken. Treatment was repeated every 10 days while lesions were still visible, up to 5 treatments.	of cells on biopsy	➢ CD4+ lymphocytes and Langerhans cells increased in the superficial dermis over the course of treatment ➢ Mild burning, transient erythema and erosions were noted (no information about how many pts experienced these)
Gattai R et al, 2010	Randomized trial of PDT alone vs PDT followed by laser CO2 vaporization for endoanal warts	22 Italian pts with endoanal warts randomized, 21 completed study. All pts had ALA 16% gel applied to their lesions using anoscopy, after 3 hrs, irradiated with 635nm laser for total dose of 200J/cm2. 10 pts then were treated with laser CO2 vaporization 60 min after PDT. If lesions did not resolve, PDT only pts had repeat PDT treatment at week 2, 4, and 6.	Clearance Recurrence at 12 months Pain medication requirements	➢ 91% (10/11) pts completely cleared with PDT alone (required a mean of 1.36 treatments) ➢ 90% (9/10) pts completely cleared with PDT and CO2 laser (required a mean of 1 treatment) ➢ 0/10 pts in PDT group had a recurrence at 12 months ➢ 2/10 pts in the PDT and CO2 group had a recurrence at 12 months ➢ 1/11 pts in PDT group required post-op paracetamol ➢ 7/10 pts in the PDT and CO2 group required post-op paracetamol
Nucci V et al, 2010	Case series	15 Italian pts aged 16–38 years (7 men, 7 women) with	Clearance Recurrence	➢ 9 pts had complete clearance after 1 session

		anogenital warts, some on the urethral mucosa, some treated previously, were all treated with 16% 5 ALA gel under occlusion for 3 hrs, then 630nm laser at 120 mJ/cm2 for a total dose of 150 J/cm2. Additional treatments were performed every 15 days if needed.	Adverse events	➢ 4 additional pts had complete clearance after 2 sessions ➢ These 13 pts had no recurrences in 12 months ➢ Minor burning during the procedure was the only adverse event reported
Chen M et al, 2010	Case report	9 year old Chinese girl with vulvar warts, treated with 20% ALA for 3 hrs, followed by 630nm wavelength He-Ne laser. Treatment was repeated in one week.	Clearance Recurrence Adverse events	➢ Lesions were completely cleared one week after therapy ➢ No recurrence or scarring 6 months after 2 treatments ➢ Slight vulvar pain and edema for one day following therapy
Inada N et al, 2011	Case series	40 Brazilian women aged 16–65 years with various grades of EGW were treated with 20% ALA for 6 hrs, followed by 640nm laser for a total dose of 200 J/cm2.		➢ 90% of pts cleared completely after 3 sessions ➢ Pts reported burning or stinging pain during the procedure
Sun et al, 2012	Case series	86 adult Chinese pts with urethral condyloma (1-40mm from the urethral meatus) Rxd with 19.09% ALA for 3hrs, followed by Rx with 635nm laser with a fluence of 100J/cm2 for 20 min. Treatment repeated weekly for 3 wks.	Response 1 week after 3 treatments were completed and 1 week after 6 treatments were completed Recurrence 3 months after all treatments were completed Adverse events	➢ 88.4% pts cleared after 3 treatments ➢ All pts cleared after 6 treatments ➢ 3 months after treatment completion, 16.3% of pts (all men) had a relapse ➢ 57% of pts reported an adverse event, all were transient and tolerable

Question: Treatment Modalities: Podophyllin/podophyllum resin – Efficacy

Author/Citation	***Study Design***	***Population, Sample Size***	***Outcome***	***Summary Points***
Lassus A, 1984	Randomized, open-label trial of podophyllotoxin 0.5% solution vs podophyllin 20%	100 men with penile GW were randomized to 0.5% podophyllotoxin solution applied at home, 2x/day for 3 consecutive days per week, (48pts) or podophyllin 20% ethanolic solution was applied once per week in the clinic (52 pts). Patients were evaluated once per week, and if they cleared treatment was stopped. Pts were treated for up to 4 weeks.	Complete cure after 1 treatment and 4 treatments Recurrence at 3 months post starting treatment	Podophyllotoxin group: ➢ Cure after 1 treatment 45 (94%) ➢ Cure after 4 treatments 48 (100%) ➢ Relapse 11 (23%) Podophyllin group: ➢ Cure after 1 treatment 15 (29%) ➢ Cure after 4 treatments 37 (71%) ➢ Relapse 14 (38%) No statistical tests were performed to evaluate the differences between these cure rates. "Local adverse reactions were fewer and milder in the podophyllotoxin group"
Edwards A, et al, 1988	Randomized, open-label trial of podophyllotoxin 0.5% vs podophyllin 20%	65 men with penile EGW were randomized to podophyllotoxin 0.5% 2x/day for 3 consecutive days each week or podophyllin 20% applied by a doctor in a clinic once per week. Patients were evaluated once per week, and treatment was stopped if they cleared. Treatment was continued for a maximum of 6 weeks.	Complete cure Relapse 3 months after treatment started Side effects CBC, liver function tests, chemistry panels were taken at baseline, resolution, or 3 and 6 weeks if no resolution	Podophyllotoxin group: ➢ Lost to f/u 10 pt ➢ Cure after 6 weeks 28/32 (88%) ➢ Relapse 5 (18%) ➢ Side effects "mild, transient" 21/32 (65%) pt Podophyllin group: ➢ Lost to f/u 4 pts ➢ Cure after 6 weeks 12/19 (63%) ➢ Relapse 4 (33%)

				➢ Side effects "mild, transient" 15/19 (77%) pt No biochemical abnormalities observed in pts at any time
Kinghorn GR et al, 1993	Randomized, open-label trial of podophyllotoxin 0.5% lotion vs podophyllin 25% solution	205 adult pts were randomized to treatment with either self-applied podophyllotoxin 0.5% lotion 2x/day on 3 consecutive days of the week, or physician-applied podophyllin 25% solution 2x/week. Pts were evaluated once per week and treatment was stopped if they were clear. Treatment was continued for up to 5 weeks	Complete cure at 1 week and at 5 weeks Cure of particular wart sites at 5 weeks	Podophyllotoxin group: ➢ Cure after 5 weeks 86% of men, 72% of women ➢ 81% of 180 treated warts Podophyllin group: ➢ Cure after 5weeks 78% of men and 62% of women ➢ 61% of 95 treated sites Comparison of cure rates at 5 weeks $P = 0.08$ in men, 0.14 in women Comparison of treated sites $P < 0.01$) Side effects mild in both groups
Lacey CJN, 2003	Open label randomised controlled trial and economic evaluation of podophyllotoxin sol 0.5%, podophyllotoxin cream 0.15% and podophyllin (podophyllotoxin was self-applied twice a day for 3 consecutive days + 4 days off therapy, and 25% podophyllin in tincture of benzoin was applied 2x a	358 immunocompetant men and women with genital warts.	Treatment arm—no difference in baseline characteristics Podophyllotoxin sol and podophyllotoxin cream with increased odds for remission compared to podophyllin (3.0 and 2.5 times more likely to produce cure). P Sol statistically sign c/w podophyllin but not with p cr in all analysis	➢ Podophyllotoxin 2.5 to 3x more likely to produce a cure compared to podophyllin ➢ Podophyllin: 17% side effects (not significantly different from podophyllotoxin) ➢ No systemic side effects from podophyllin. ➢ Also covered cost effectiveness, and podophyllotoxin was

	week in clinic) All tx for 4 weeks		Side effects were 33% for p sol, 24% for cream and 17% for podophyllin. Ulceration 10-18%, no statistically sign difference in tx side effects	more cost-effective than podophyllin.

Question: Treatment Modalities: Podophyllin/podophyllum resin – Safety

Author/Citation	***Study Design***	***Population, Sample Size***	***Outcome***	***Summary Points***
Ward JW et al, 1954	Case report	18 yo woman, 17 wks pregnant, large (8cm x 7cm) condyloma over her perineum, including vulva and perianal area. Treated with "light sedation," had "multiple biopsies" of the lesion taken, and then the lesion was covered with "light" 25% podophyllin. The area was not washed off until the pt developed neurologic findings, 30 hours after the procedure.	30 hours after the procedure the patient became lethargic, then unresponsive and was diagnosed with toxic encephalopathy. She rapidly developed adynamic ileus and renal failure and died on the 7th day after the procedure. Autopsy revealed "congestion of all organs."	The authors conclude that in order to prevent systemic toxicity: ➢ Podophyllin should be applied only to intact skin ➢ Podophyllin should be washed off within 1 hour
Shirren et al, 1966	Case report	25 yo man with perianal warts, treated with podophyllin solution	Developed vomiting, agitation, coma, recovery took 3 weeks	• Written in German, no abstract, information is from other reviews
Chamberlain MJ et al, 1972	Case report	18 yo previously health woman in 34th week of her first, healthy pregnancy had vaginal bleeding and on exam was found to have "florid vulvar warts" which were "friable." She was put under general anesthesia and treated	She had peripheral motor and sensory neuropathies as she awoke from anesthesia, and arousal from anesthesia took longer than usual. Two days post-operatively, she developed abdominal pain, uterine firmness, and the fetal	• The authors conclude that the fetal loss and neuropathy was due to podophyllum toxicity. • The authors do not include information on how long the podophyllum was left on

		with 25% podophyllum, a total volume of 7.5ml.	heart rate could no longer be heard. She then developed nausea, vomiting, progressive neuropathy including diplopia. 12 days post-op the baby was stillborn, with no abnormalities except placental infarcts. The patient's neuropathy slowly improved, but she was not walking on her own until 3 months post-op. Many months later, the patient did fully recover and went on to conceive again and deliver a healthy baby.	the skin • In this case, the podophyllum was applied to skin described as "friable" and possibly over a large area.
Montaldi DH et al, 1974	Case report	20 yo woman with massive vulvar condylomata was treated with partial excision, followed by immediate application of podophyllin resin in the operating room.	Although she initially awoke from surgery, she developed obtundation within 20 hours of the surgery. Vomiting, coma, flaccid paralysis, pancreatitis, recovered in 25 days	• Authors concluded this was due to podophyllin toxicity.
Slater GE et al, 1978	Case report	16 yo girl treated as an outpatient for "massive, friable" vulval condyloma. She was instructed to wash the treated area off in 3-4 hours.	7 hours after being treated in clinic she returned to clinic with abdominal pain, nausea, vomiting, diarrhea and was noted to be lethargic. She was treated for dyspepsia and sent home. The following morning she was unarousable, admitted to the hospital with fever, tachycardia, decreased reflexes, and it was discovered that the podophyllin had not been completely washed off.	• Authors conclude this patients toxic encephalopathy and permanent peripheral neuropathy was due to podophyllin toxicity. • Podophyllin was used over a large, friable area and was not washed off in the recommended time. • Podophyllin toxicity was not recognized initially.

			The patient had a complicated hospital course with EEG abnormalities, intubation and ventilator support, detoxification therapy with gastric charcoal lavage and venovenous shunt placement, but ultimately recovered and was discharged on day 8. She had long term peripheral neuropathies that did not resolve.	
Stoehr et al, 1978	Case report	15 yo girl with "large" vulvar condyloma was treated as an inpatient with 20% podophyllin. The lesion had been biopsied at some point during the week prior to the treatment.	The length of time the podophyllin was on the skin is not reported, but the patient developed dizziness, nausea, vomiting, and abdominal pain "a short time" after the podophyllin was applied. Despite that, the patient was treated with podophyllin twice during the following day. She then developed fever, obtundation, elevated liver enzymes, ileus, and over the next several days developed bone marrow failure with clinically significant decreases in all cell lineages. With supportive therapy she recovered fully over 3 weeks.	• Authors conclude this was due to podophyllin toxicity • Podophyllin was applied to a large, friable area • Toxicity seemed to develop very acutely (unclear how long the podophyllin was left on) and was not recognized, so pt was treated 2 more times in one day.
Karol MD et al, 1980	Case report	24 yo woman received in-clinic topical application of podophyllum resin for EGW, once a week for 5 weeks, from the 25th to 29th week of	The baby was born without complications, full-term with a simian crease on the left palm, bilateral preauricular skin tags, and a cardiac	• The authors conclude that the congenital abnormalities were due to podophyllum systemic absorption.

		pregnancy. Each time the podophyllum was left on for 4 hours, and then washed off. During pregnancy, the patient's only other medications were chloroquine and primaquine due to exposure to malaria.	murmur that resolved.	• There is no information about how extensive an area was treated with podophyllum.
Filley CM et al, 1982	Case report	22 yo woman with vulvar, cervical and vaginal condyloma applied in the office. Pt had had 2 previous treatments, and podophyllin was washed off in 1 hour and she tolerated those treatments. On the 3rd treatment, it is unclear if she washed off the podophyllin or not.	On the same day as treatment, she developed lethargy, and by day 3 after treatment she developed psychosis, then toxic encephalopathy, ileus, pancytopenia and peripheral neuropathy. She slowly recovered with supportive care, but 10 months after the treatment still had peripheral neuropathy.	• Authors conclude this was due to podophyllin toxicity • Unclear how large the treated area was, or if the lesions were friable, also unclear how long podophyllin was in contact with skin.
Conard et al, 1990	Case report	17 yo previously healthy woman with multiple vaginal and cervical condyloma, and particularly large lesion (3cm x 6cm), treated with epidural anesthesia, followed by CO2 laser fulgration to the vulva. Then immediately following the laser treatment the patient was treated with 17.5% podophyllin to the "remaining condylomata"	Two hours after the procedure the patient had normal motor and sensory function of her lower extremities and was awake and alert. Thirteen hours post-op the pt developed fever, tachypnea, tachycardia, and 16 hours post-op the patient became obtunded. She developed worsening fever, non-cardiogenic pulmonary edema, and abnormalities of red blood cells that were consistent with a toxic event. Blood cultures and lumbar puncture were normal. She eventually developed renal	• The authors conclude that in this case, podophyllin toxicity was likely not recognized immediately due to the patient having received epidural morphine and her neurologic symptoms initially being thought to be due to morphine overdose or sepsis. • In this case, podophyllin was possibly used on broken skin, and was not washed off in the recommended amount of time

			failure, coma, and died 26 hours post-op. The podophyllin was washed off sometime between 16 and 26 hours post-operatively.	

Question: Treatment Modalities: Podophyllin (podophyllum) – Reviews

Author/Citation	***Study Design***	***Population, Sample Size***	***Outcome***	***Summary Points***
Lacey CJN et al, 2012	European Guidelines for the management of anogenital warts – based on a systemic review of randomized controlled trials		Recommended therapies: patient applied: podophyllotoxin, imiquimod, sinecatechins provider administered: cryotherapy, TCA, electrocautery, scissor excision	➢ Recommend against using podophyllin, cite that 10% contains mutagenic compounds quercetin and kaempherol, and severe systemic toxicity after topical use has been described.
Gormley RH and Kovarik CL, 2012	CME article outlining approach to genital wart treatment in the immunocompromised host, aimed at dermatologists			➢ Recommended against using podophyllin, (level IIB evidence) citing low efficacy compared to other therapies, possibility of serious side effects
Fraser PA et al, 1993	Review article with one set of authors arguing for a motion to eliminate podophyllin as a treatment for EGW used in Dublin's venereal disease clinics, and another author arguing to continue use of podophyllin.		*Authors arguing AGAINST the use of podophyllin argued:* - Podophyllin formulations are unstable, not standardized, while podophyllotoxin is standardized - Systemic toxicity resulting in death, fetal loss, and neurotoxicity has been reported from use (usually mis-use) of podophyllin, and not with podophyllotoxin - Podophyllotoxin has clearance rates and recurrence rates that are at least the same as podophyllin, and in many studies better	➢ The arguments that podophyllin is less standardized, possibly less effective, potentially more dangerous, and more expensive than podophyllotoxin were not countered, and were even specifically conceded in the paper.

			than podophyllin -Podophyllotoxin therapy is less expensive than in-office podophyllin therapy *Author arguing FOR the use of podophyllin argued:* -When podophyllin is used correctly in the office there are low risks of systemic toxicity -Home therapy of any type is often unsuccessful because patients are bad at identifying new or small lesions -The Dublin Venereal Disease society wants people to come into clinic for treatment both because it is economically good for the clinic, and because it confers more opportunities for counseling and screening	➢ However, the motion to eliminate podophyllin from the treatment guidelines was sturck down, with a vote of 129 voting for, and 136 voting against.
Petersen CS, Weismann K, 1995	Using high-pressure liquid chromatography, the amounts of 2 mutagenic flavonoids, quercetin and kaempherol found in podophyllin 20% resin were estimated.	Basic science study, used 3 batches of podophyllin 20%		➢ Quercetin and kaempherol made up 2.5-3.8 and 6.0-6.4% of the dry substance of podophyllin 20%, and podophyllotoxin made up 12.7-13.8% of the dry substance of podophyllin.
Longstaff E, 2001	Review of the literature on podophyllin safety-opinion and data	Review of the studies including animal studies, case reports, reproductive toxicity for podophyllin and podophyllotoxin safety	Podophyllotoxin clearly safe, case reports of 2 deaths with topical application of podophyllin (these were related to open wounds allowing entry of the drug systemically, and large areas that were treated). Teratogenicity and reproductive studies are limited, some data on lack of stability of the drug podophyllin	• Summary of data about podophyllin: information on lack of stability of product, questionable safety with regard to teratogenicity studies, some cases of systemic toxicity with topical application, low

				efficacy
Von Krogh G, 2001	Review of safety of podophyllin office therapy—opinion and data	Same as above	Issues covered included: long term efficacy rates not confirmed, severe local and systemic toxicity, mutagenic properties, and quality control problems.	• Similar issues covered

Question: Treatment Modalities: Other treatments – Efficacy

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Jardine et al, 2012	Randomized controlled trial of HPV6 L1	Healthy adults with GW presenting to STD clinics in Australia (144) and China (236), Pts had GW treated with destructive modalities, then were randomized to receive placebo or 1ug, 5ug, or 25 ug of HPV6 L1, 2 doses, 4 weeks apart.	Primary endpoint – recurrent GW 2 months after destructive treatment	➢ Patients were analyzed by site ➢ 2 higher doses of HPV6 L1 were associated with less disease recurrence at 6 months (no statistical test for significant performed) at the Australia site, no differences seen at the China sites. ➢ No serious adverse events were reported in any group.
Friedman M et al 2009	Case series of new immunomodulators tellurate AS101	74 adult Israeli pts (48 women 26 men) with EGW treated with the topical immunomodulator tellurate AS101, 15%. All pts applied the cream 2x/day for up to 16 weeks		➢ Complete clearing was seen in 76% of pts ➢ At 6 months after treatment, 4% of pts had recurrence ➢ Most common adverse events were itching, soreness, and erythema
Sethuraman G et al, 2009	Case series of Rx with PDL	5 children with perianal and perianal warts (reported as	Complete clearance	➢ 5/5 had complete clearance after an

		part of a case series of 61 children with all types of warts) were treated with pulsed-dye laser (PDL).		average of 2.2 treatments, avg of 7.1 J/cm2 with avg 56 pulses per treatment ➢ No comments on how these particular pts tolerated therapy

Question: Treatment Modalities: Special Populations: Pregnant Women

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Yang et al, 2012	Case series	5 pregnant (2 or 3 trimester) Chinese women aged 25–32 years, with vulvar, perianal warts each Rx with ALA and PDT up to 4 treatments, 1-2 weeks apart.	Clearance, recurrence, AE, pregnancy outcome	• All women had completed clearance after up to 4 Rx • No recurrences with 6–25 months of f/u • No serious adverse events • All delivered healthy babies
Ciavattini et al, 2012	Case series	4 pregnant Italian women (2 or 3 trimester) 5% imiquimod applied once per day, 3/days per week x 4 weeks.	Clearance at 4 weeks of therapy, AE, pregnancy outcomes	• Outcome at 4 weeks of therapy: 2 had completed clearance, 2 had partial clearance • 3 of 4 women had erythema as an adverse event • 3 women delivered by C-section due to non-reassuring FHR at full term • 1 woman developed eclampsia and had C-section at 34 weeks

				• All infants healthy
Eassa B et al, 2011	Case series	40 Egyptian pregnant women, aged 20–35 yrs with EGW were treated with weekly intradermal injections of purified protein derivative (PPD)	Complete, partial, minimal responses Adverse events	• Overall improvement was 85% and was related to reactivity to tuberculin • 47.5% had complete clearance • 37.5% had a partial response • 7.5% had a minimal response • 7.5% had no response • "Minimal" side effects

Question: Treatment Modalities: Special Populations: Immunocompromised

Author/Citation	***Description of Study***	***Population, Sample Size***	***Outcome***	***Summary Points***
Trakatelli M et al, 2010	Review of the safety and efficacy of imiquimod 5% cream in organ transplant patients	Review of other studies – describes a total of 14 reports (case series and randomized trials) of more than 100 organ transplant pts treated with imiquimod for various skin diseases (including Ulrich et al below)	Graft rejection Signs of systemic toxicity (e.g. clinically increased serum creatinine in renal Tx pts)	• No graft rejection has been reported to date in a pt being treated with imiquimod • No clinically significant changes in lab work or other signs of systemic toxicity
Saiag P et al, 2009	Case series	50 HIV adults in Belgium and France, on ART with CD4+ counts ≥200 cells/mm3 and plasma viral RNA <104 copies 4 weeks prior to therapy, with EGW. Imiquimod 5% cream was applied to all warts 3x/wk for up to 16 wks	Complete clearance at 16 wks LR and HR HPV DNA in lesions	• Complete clearance observed in 32% of pts at 16 wks • At enrollment, 90% of lesions had HPV DNA, became undetectable after 16 wks of treatment in 40% of those studied • No changes in CD4 count or viral load seen during the study

				• Erythema (seen in 22%) and ulceration (seen in 12%) were the most common local reactions
Ulrich C et al, 2005	Randomized, placebo-controlled trial of imiquimod for actinic keratosis to establish safety in solid organ transplant pts	43 pts with kidney, heart, or liver Tx applied 2 sachets of imiquimod 5% cream or vehicle to an area of 100cm2 3x/wk for 16 wks (regardless of lesions clearing)	Laboratory abnormalities Graft failure Requirements of increased immunosuppression	• No graft rejection in either arm • No significant changes or trends in laboratory analyses