Medical management of Genital Warts

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Outline

Natural history of HPV

Medical options

Different clinical scenarios

Take-home messages

Natural history of HPV infection

- Genital Warts (GW) are a symptom of genital HPV infection
- HPV is transmitted through penetrative sex (less common via non-penetrative)
- HPV prevalence 10-20%; with clinical manifestations in 1%
- 90% of people exposed will not develop GW

Natural history of HPV infection

•Conflicting evidence of condom prevention

•30% of GW will disappear within 4 months of appearence

•90% of HPV infections are cleared up within 2 years (median time to clear up cervical HPV in women 9.4 months)

•GW can recur (3 months after completion of therapy)

•Latency can occur: even years later!

Giulano, Lancet 2011
Winer, Cancer Epidemiol Biomarkers 2011

Natural history of HPV infection

- Individuals with prior HPV can develop GW: through recurrence or new exposure
- 75% of partners of patients with GW will develop them within 8 months

Natural history of HPV infection

Recurrence rates depend on:

general health
smoking

immune status
previous HPV vaccination

specific HPV strains

number of inoculations (contact with an infected individual)
condom use

Medical Treatment

No cure for HPV. The aim of medical treatment is to remove GW

In 30% of cases GW will clear up in 4 months, in 80% the infection will clear up in 24 months

All therapies have high recurrence rates and require long-term or repeat treatment

Treatment depends on:

- Symptoms
- Immunosuppression
- Compliance
- Preferences
- Previous experience
- Cost
- Depending on warts: localization / extension / keratinised / active proliferation
- Others: pregnancy

Medical Treatment

Podophyllotoxin
Sinecatechins
Imiquimod

1st line

Isotretinoin
Trichloroacetic acid
Nitric acid /zinc complex solution
HPV vaccine
Physical destruction: liquid nitrogen, electrocoagulation, photodynamic therapy
Others: 5-FU, interferon intralesional, cidofovir topical

Podophyllotoxin

- Antimitotic drug -> microtubular subunits
- **Podofilox** is safer than podophyllin → high level of mutagens
- 0.15% to 0.5% in cream or solution
- Complete clearance: 43-70%; with a recurrence rate of 13-100%
- Apply BID for 3 consecutive days - 4 weeks. Wash it off at 4 hours
- Burning, itching, pain, inflammation, headache (7%)
- Avoid in pregnancy

Tyring 1998; Greenberg 1991; Kirby 1990; Lacey 2013

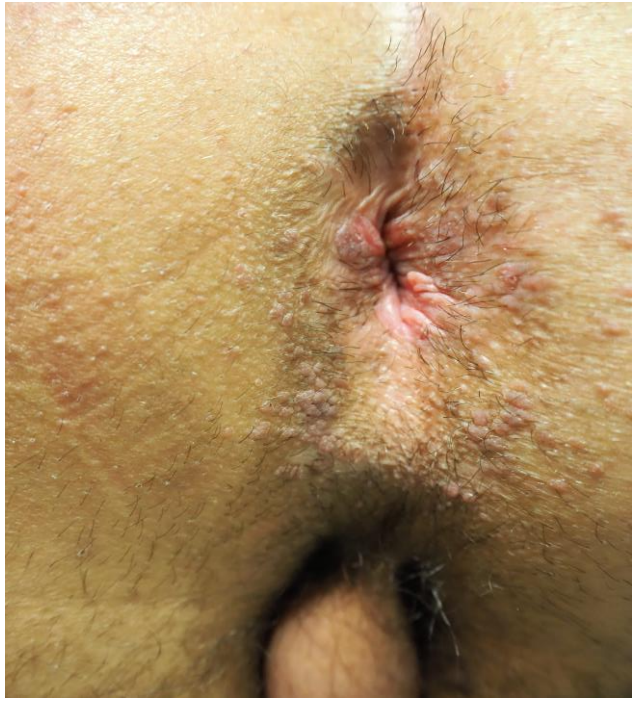
Imiquimod

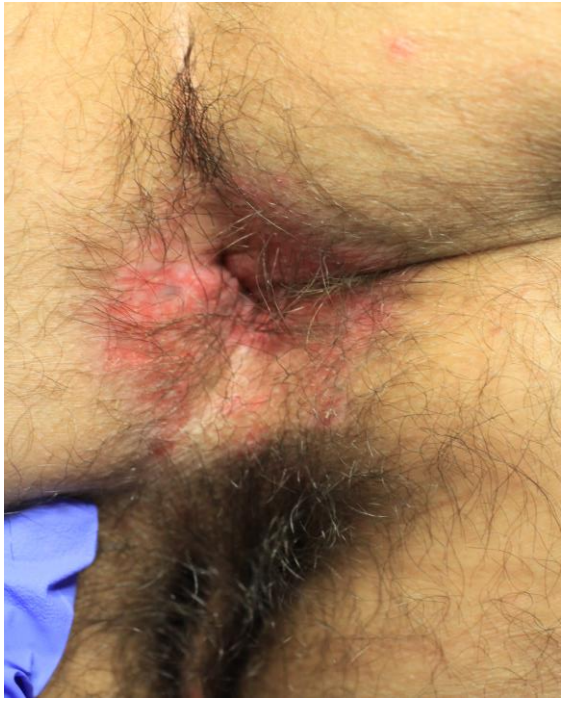
- Agonist Toll-like receptor 7/8
- Immune enhancer → cytotoxic reaction based on T cell-mediated response factors
- **5%** or 3.75% in cream
- 3 times per week x 16 weeks- (5%) vs every day x 8 weeks (3.75%)
- Thin layer and rub it in; leave it on for 6-10h, and wash off afterwards

- Complete clearance: 35-75%; with a recurrence rate of 6-25%
- Less recurrence than podofilox

Grillo-Ardilla, 2014; Lacey 2013; Komericki 2011

Imiquimod





- Secondary effects:

- Local: burning, itching, pain, inflammation, fungal infections, hypopigmentation, vitiligo

- Systemic: myalgia, vertigo, flu-like symptoms, erythema multiforme

- Expensive
- Avoid in pregnancy ?

Grillo-Ardilla, 2014; Lacey 2013; Komericki 2011

Sinecatechins

- 15% ointment extracted from green tea
- Immunostimulatory, anti-proliferative, anti-tumoral by reducing HPV gene products E6 and E7
- Higher clearance than podofilox and imiquimod, but it takes longer

- 35-55% clearance, recurrence 7%
- It depends on compliance!
- 3 times a day, max 16 weeks

- Burning, itching, pain, inflammation

Tatti 2010; Gross 2007

Efficacy:
Compared to imiquimod 5%: superiority of podophyllotoxin 0.5% solution
Sinecatechins not as good as imiquimod 5%
Imiquimod 5% better than lower concentrations

Recurrence: none were significantly different from placebo

Adverse events (local or mild reactions): higher in podophyllotoxin than imiquimod

Jung JhanJung CJ, Lee WJ, Won CH, Lee MW, Choi JH, Chang SE. Topically applied treatments for external genital warts in nonimmunocompromised patients: a systematic review and network meta-analysis. Br J Dermatol. 2020 Jul;183(1):24-36.

Oral Retinoids: Isotertinoin

- Epithelial differentation and HPV replication

- Adjunct to standard treatments
- Extensive or resistant to initial therapy
- Dosage: 0.5-1 mg/kg/day
- Secondary effects: teratogen, hypetrigliceridemia, hepatoxicity, dryness

- Clearance rate 56% at 3 months; relapse 12%

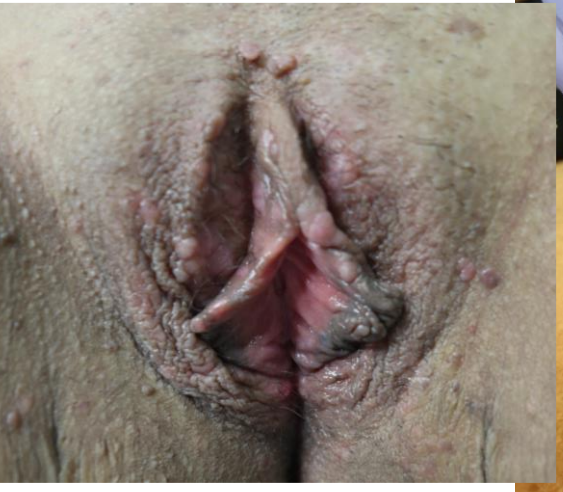
Oren-Shabtai et al. Dermatology, 2020

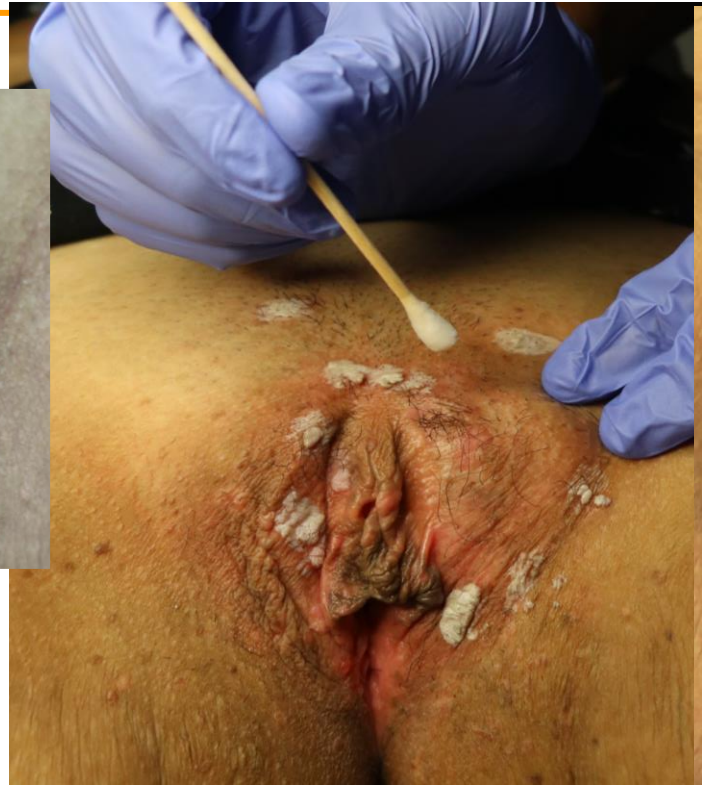
Trichloracetic acid

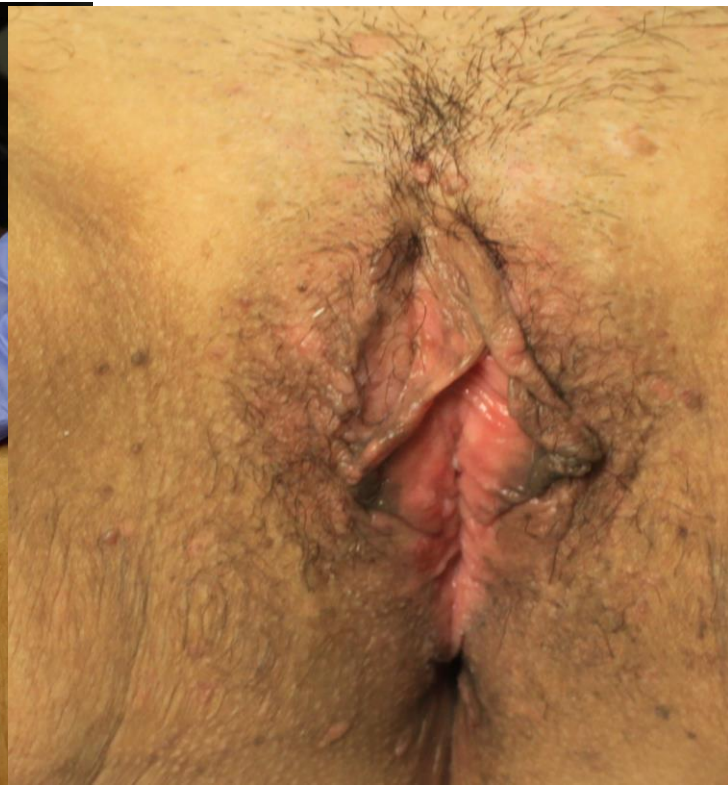
- 85%, provider applied
- Every two weeks for up 6 treatments
- Caustic agent
- Small warts
- Avoid vagina, cervix and meatus
- < cryosurgery (86% vs 70% Clearance)
- Skin erosion / ulcer / scarring

Abdullah AN, et al. Treatment of external genital warts comparing cryotherapy (liquid nitrogen) and trichloroacetic acid. Sex Transm Dis. 1993 Nov-Dec;20(6):344-5.

Trichloracetic acid







Female, 27 years-old
Renal Transplant, CIN 3, multiple surgical excisions, laser.
Unresponsive to imiquimod and podophylotoxin

Multiple GW → TCA 85% with improvement

Other medical treatments

- **5-fluorouracil 5%**
- **Interferon il.** Response rate 36-63% as monotherapy
- **Complex nitric acid /zinc** : difficult to treat warts. Acts by desiccation. Well tolerated.
- **Cidofovir 1-3% gel**: 3 - 5 days a week (every other week) maximum 6 cicles, or intralesionally
- **Cantharidin**

HPV Vaccination

- Gardasil 9 ®
- Preventative, not therapeutic

- Reduction in GW after vaccination:

  67% in females/ 48% in males aged 15-19

  54% in females / 32% in males aged 20-24

  (Drolet at al. Lancet 2019)

  64% overall in Australia; a reduction of 98% in Australian-born women < 21 (Khawar et al, The Lancet Regional Health 2021)

HPV Vaccination

- Vaccination at young ages (11-12 years)
- MSM, people living with HIV, immunocompromised should be vaccinatd before 26

- Therapeutic effect?
- Women with CIN vaccinated: ↓ subsequent HPV related disease and high grade
- MSM with high grade AIN: ↓recurrences
- GW: 3 studies, meta-analysis → **no reduction in recurrence rates**

Kang, Gynecol Oncol 2013; Garland Int J Cancer 2016; Swedish Clin Inf Dis 2012; Husein-El Ahmed Int J STD 2020

Physical treatments

- Simple surgical excision / Cryosurgery / ECG / Laser Vaporization

  Isolated lesions
  Large (> 1 cm) or exophytic
  Hyperkeratotic
  Adjuvant to medical treatments

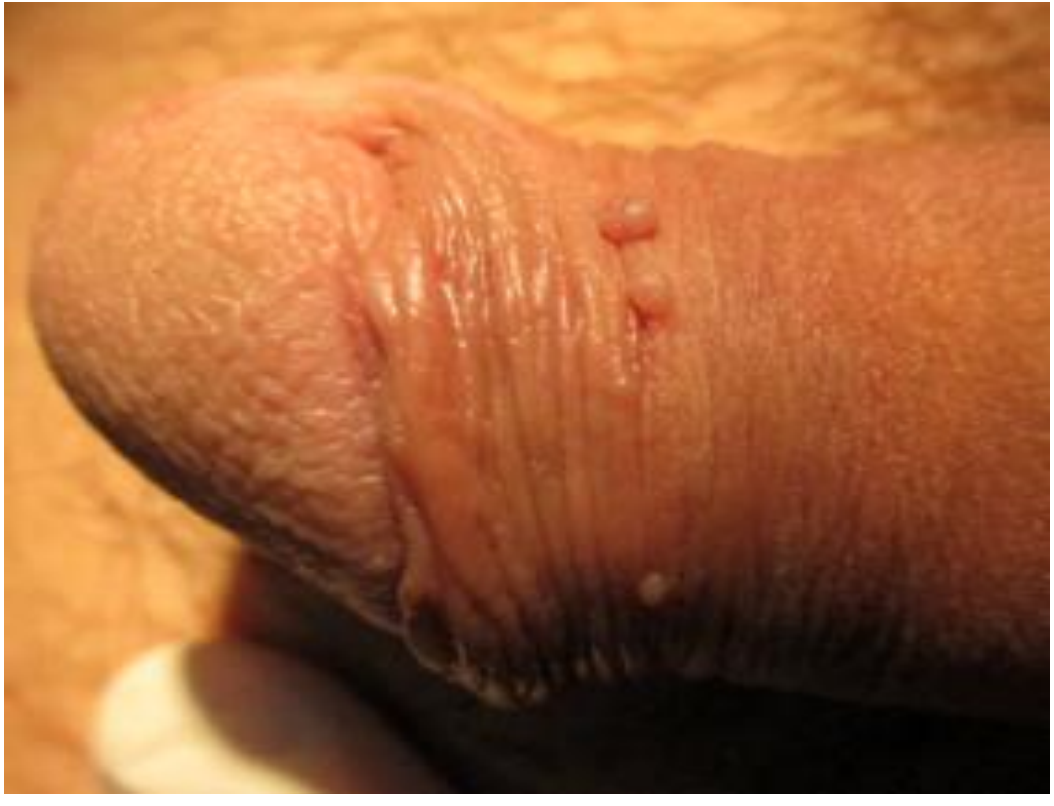
- Photodynamic therapy

  Off-label
  Topical ALA (or intralesionally) + light exposure → destroys the warts by oxidative injury

- Single wart (or small multiple low number)
- Multiple warts
- Refractory disease
- Genital warts in oral mucosae
- Urethral condyloma
- Genital warts in pregnancy
- Genital warts in children

Single Wart (or small multiple low number)

Criotherapy or electrocoagulation with anesthesia



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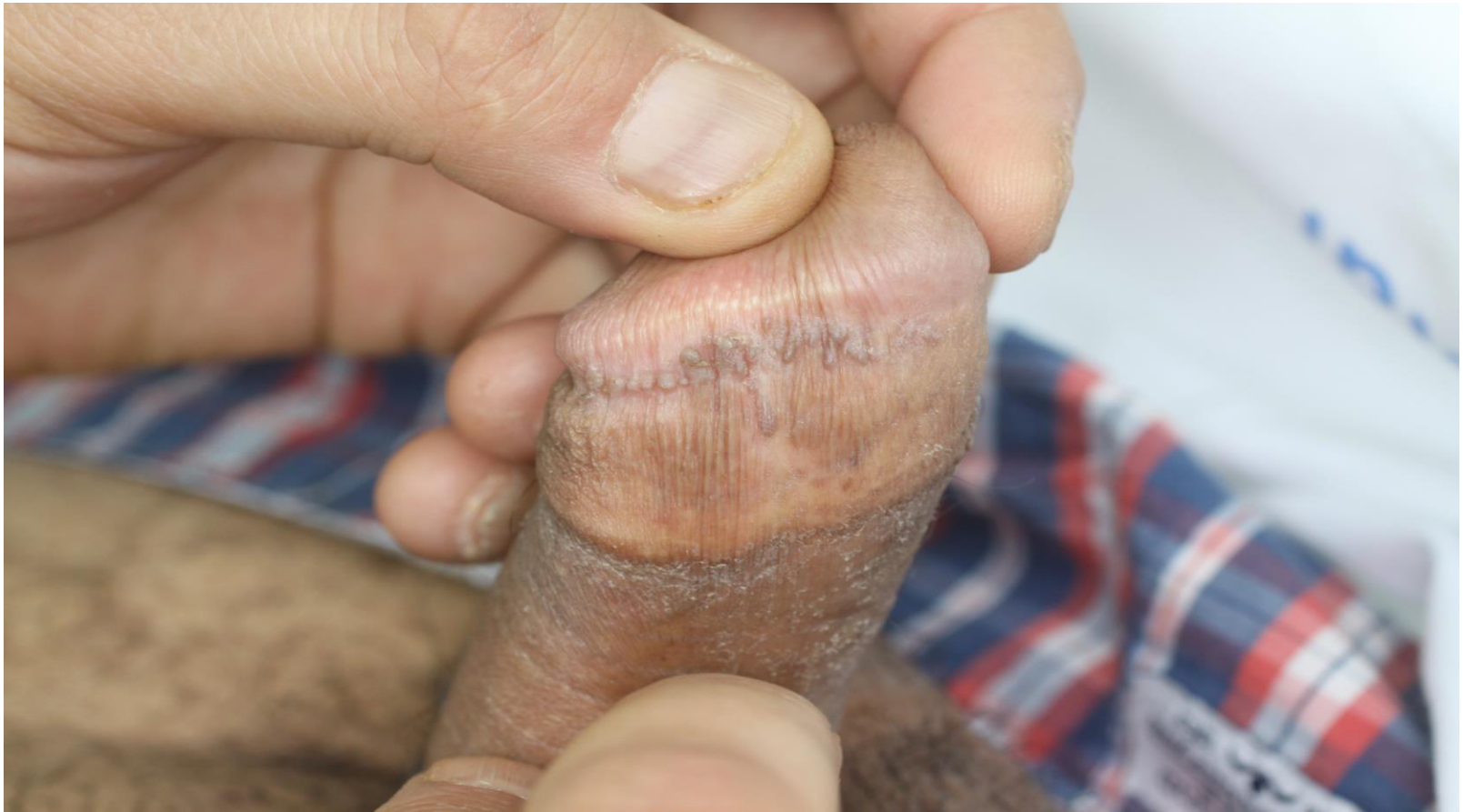

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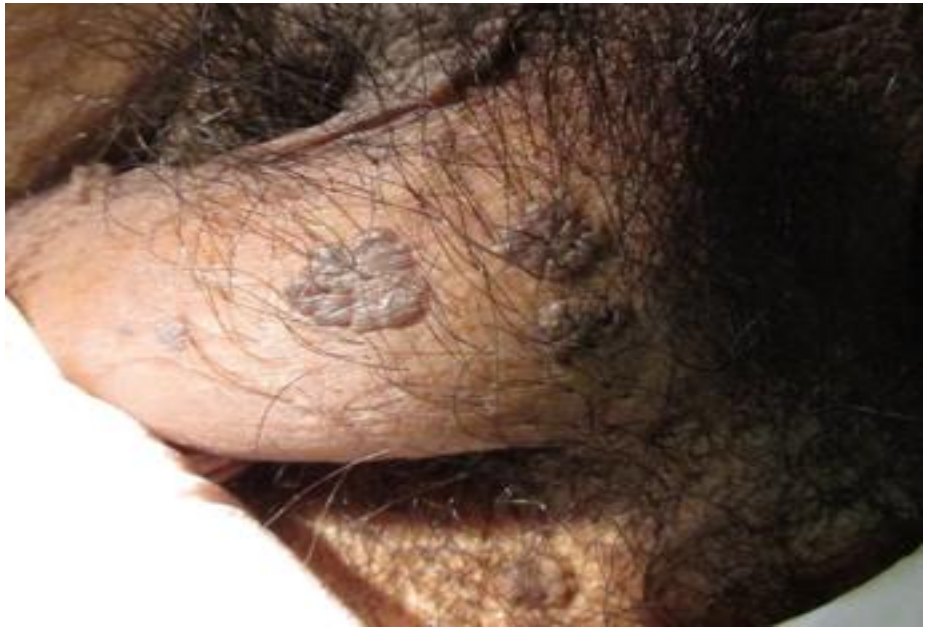
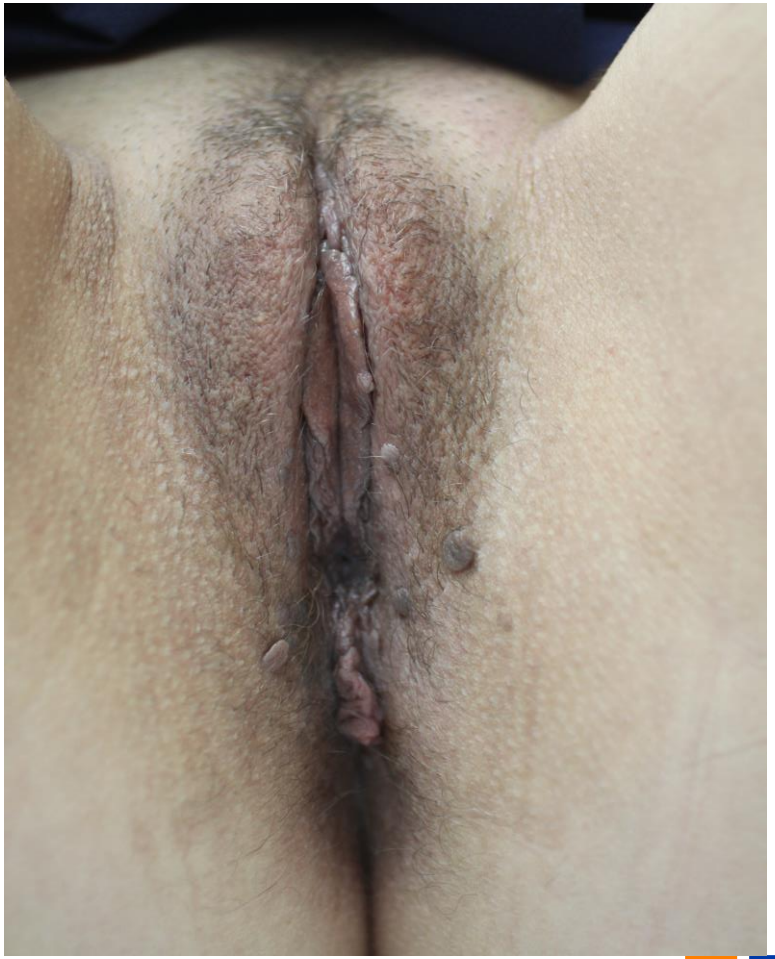




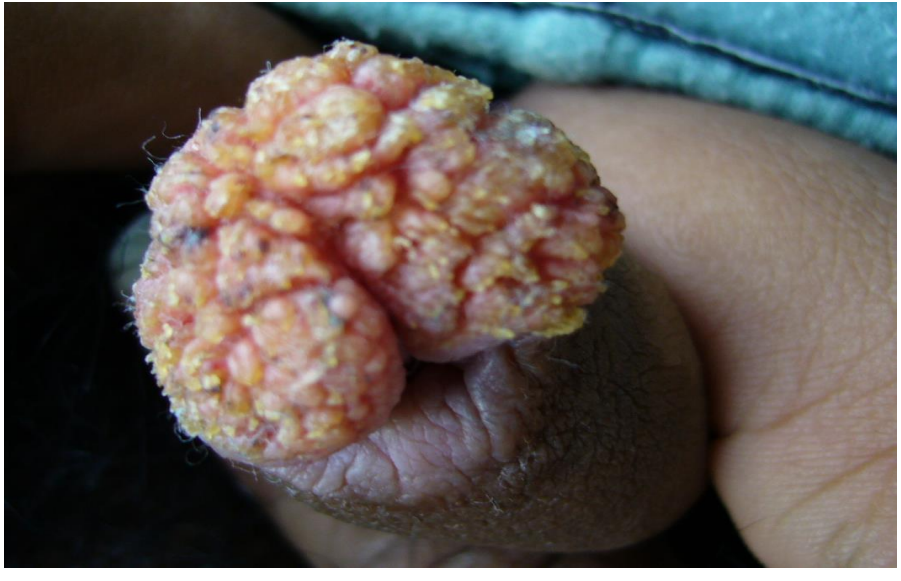
Hyperkeratotic / Hyperpigmented → long-lasting lesions
tend to not respond to medical treatment

Multiple Warts or Extensive Disease

Surgical Excision

Plus

Topical agents for the remaining disease



Combinations: patient-applied and clinician-administered often used but efficacy and safety data are limited

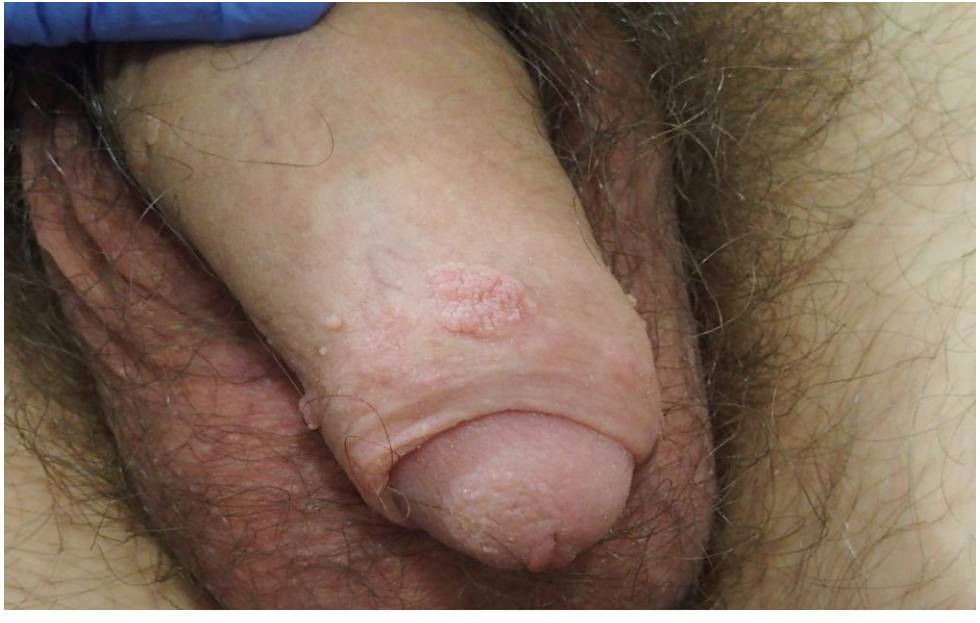
On, et al; 2014
Gilson et al, 2009

Multiple Warts or Extensive Disease

Criotherapy

Plus

Topical agents for the remaining disease



Combinations: patient-applied and clinician-administered often used but efficacy and safety data are limited

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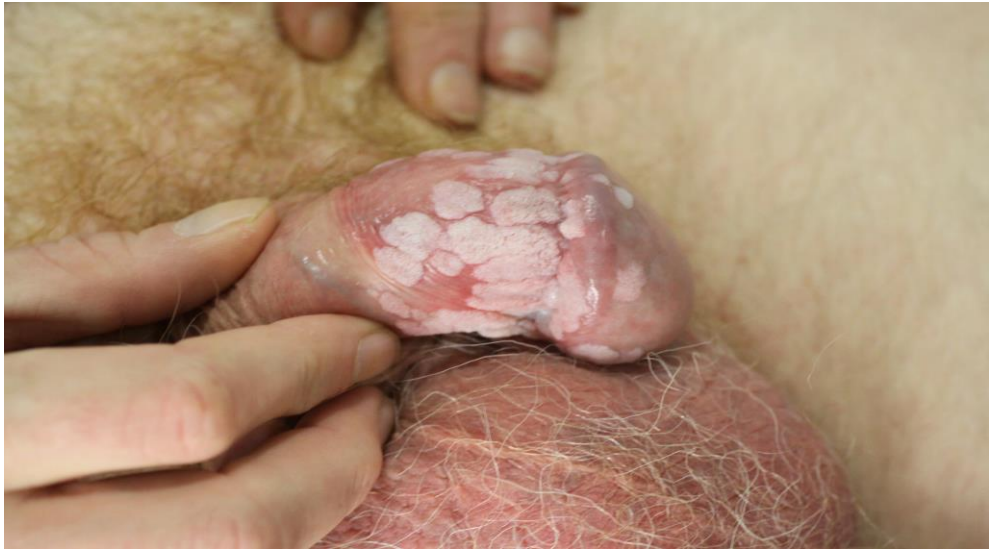
Multiple Warts or Extensive Disease

Topical agents

Plus

Surgical Excision or Laser



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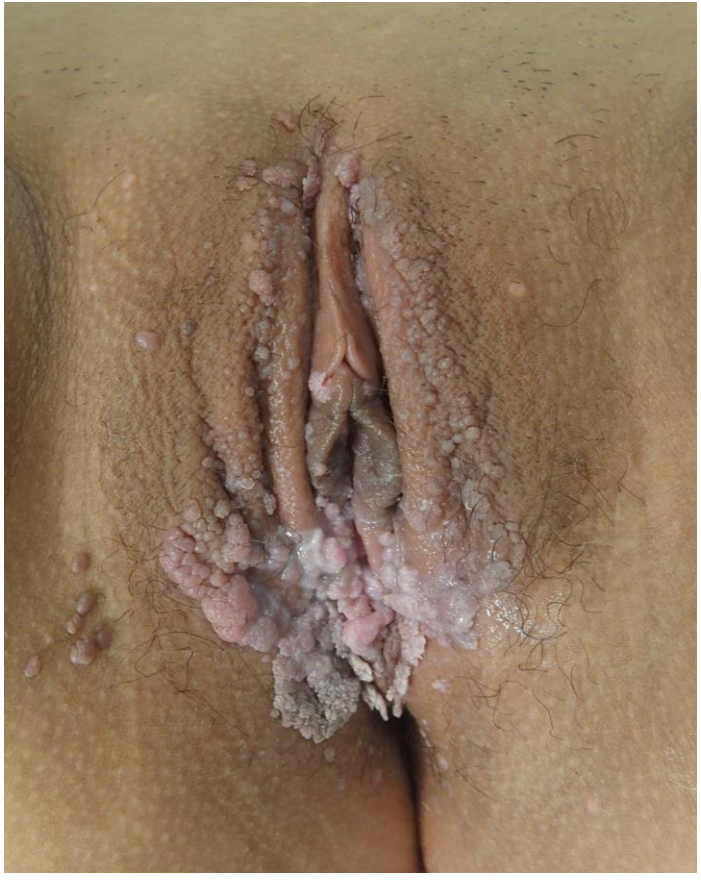
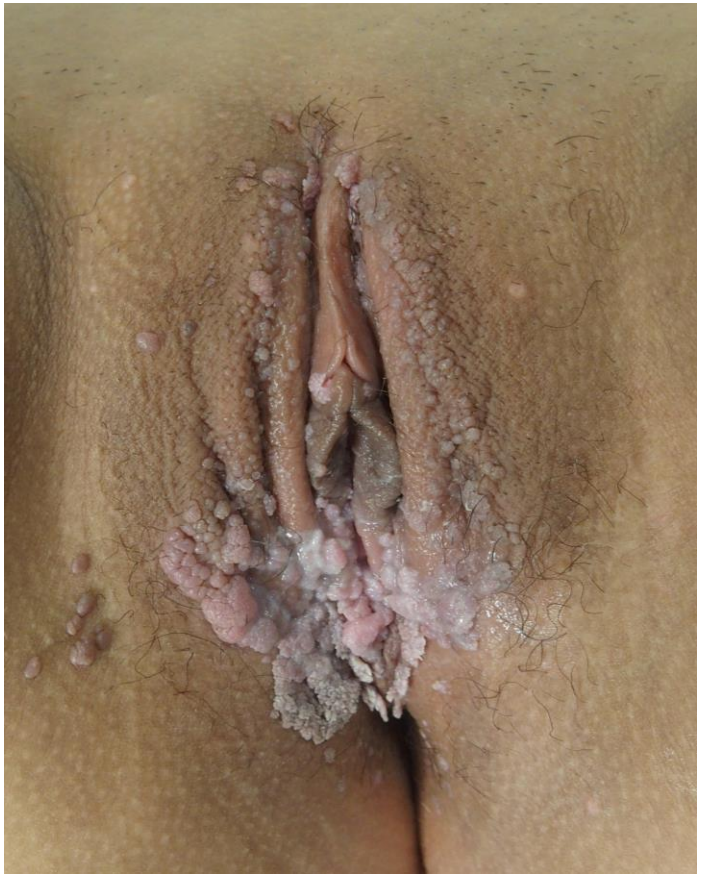
Refractory Disease



- GW for 3 years
- Immunosupressed with azatioprine for systemic lupus
- Combinations:
  Physical therapy (Criotherapy + LaserCO2)
  with imiquimod / sinecathetins / podophylotoxin

Refractory Disease



Transplants
HIV
Immunosuppressed patients

Multiple and persistent HPV (oncogenic)
High risk for AIN, CIN, penile or vulvar cancer

Poor treatment response
High recurrence rates
No spontaneous resolution

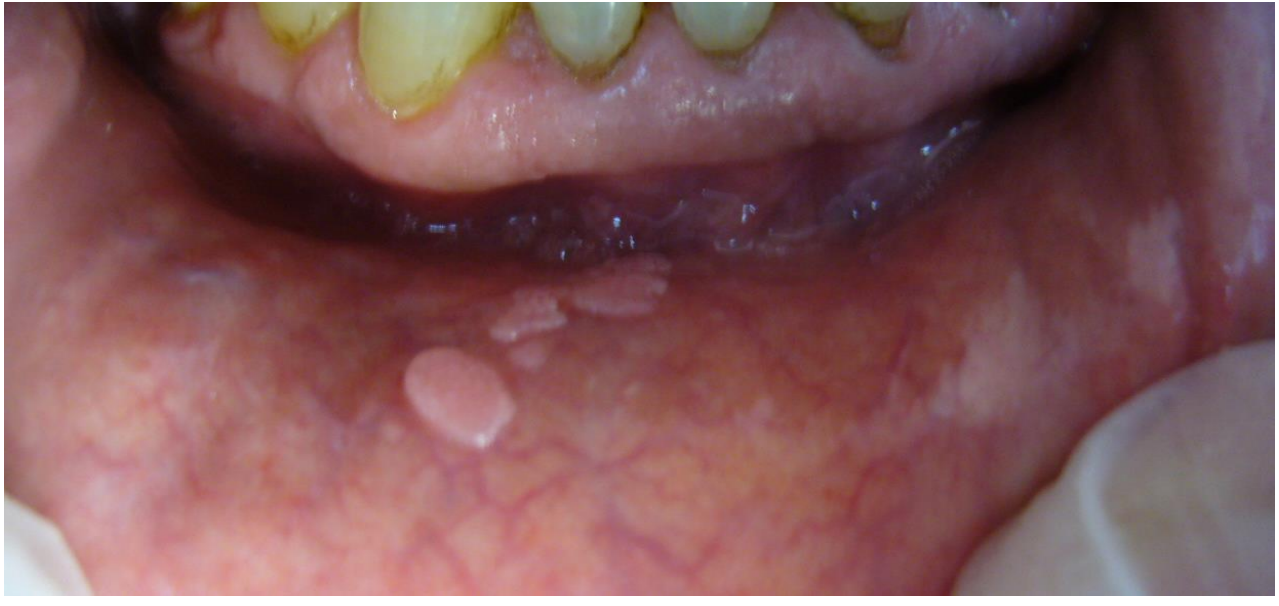
COMBINATION AND ROTATION OF TREATMENTS

SCREENING NEOPLASIA

Genital Warts in Oral Mucosae

Physical methods

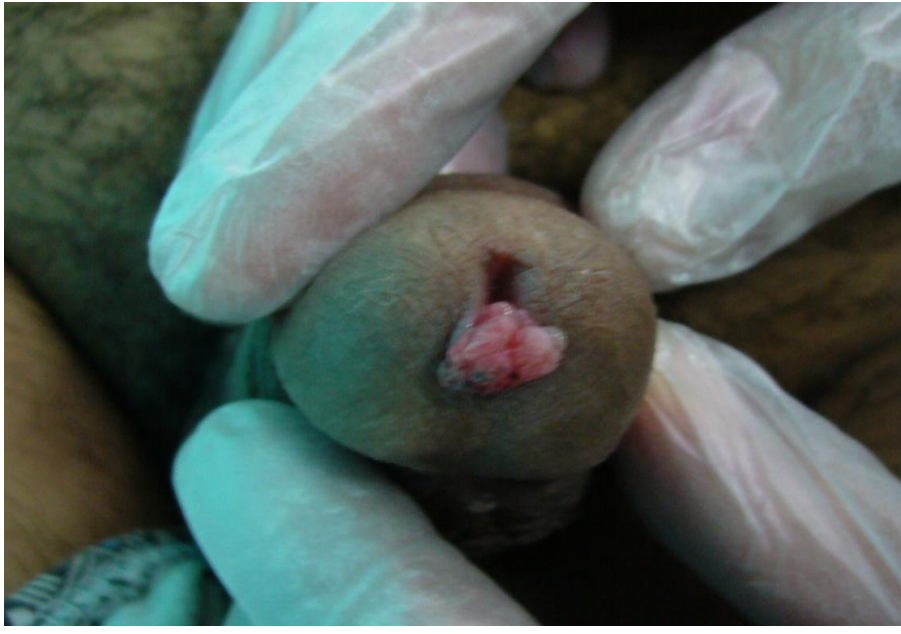
Imiquimod



Urethral condyloma

- Accounts for 10-28% of patients with GW
- Isolated or accompanying external GW
- Distal urethra or the meatus, but cases with extensive urethral or bladder involvement
- Urinary symptoms
- Treatment risk to strictures / fistulae / pain intercourse / erectil dysfunction

- Treatment: observation if asymptomatic / Criotherapy / Imiquimod



Genital Warts in Pregnancy

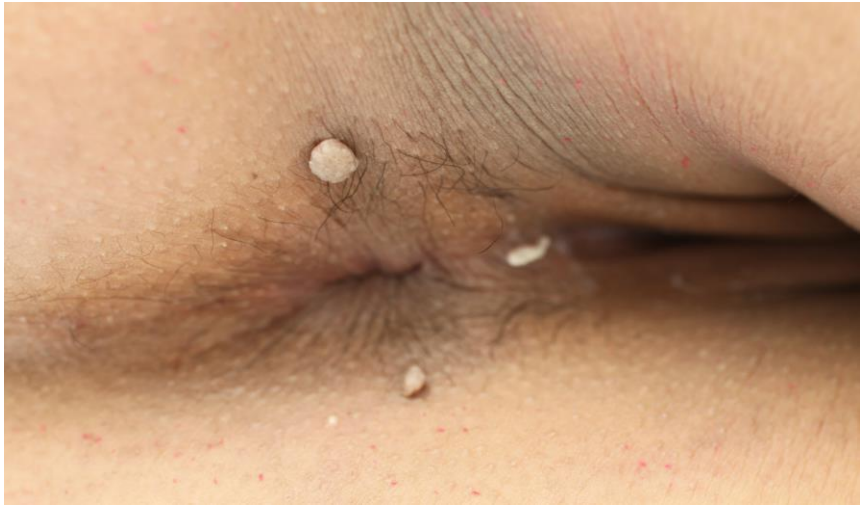
- Lesions tend to grow rapidly

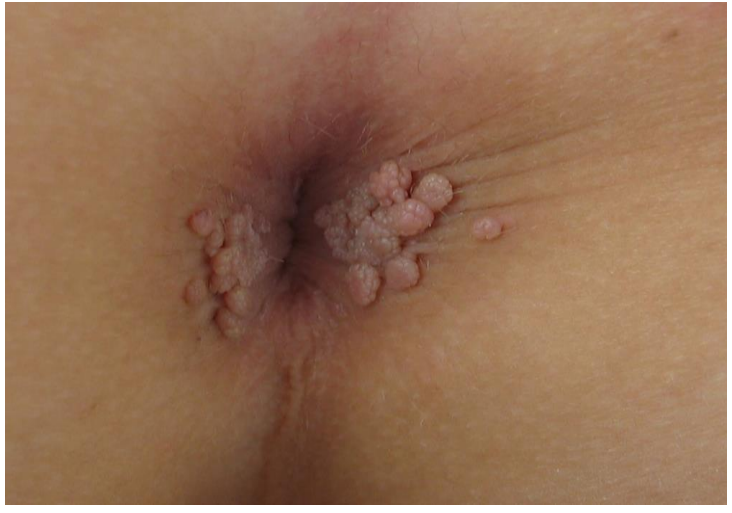
- Risk of JORRP: 1 case per 144 births in pregnant women with GW
- Treat to reduce viral load

- Laser therapy / Criotherapy as 1st choice

- NOT TO USE: 5FU, podophylotoxin, sinecathetins
- Imiquimod ?
  - No teratogenic or toxic effects
  - “Use if clearly needed “
  - Widely used in Japan (Suzuki et al, Japan J Infec Dis 2016)

Genital warts in children





- Treat if symptomatic. Spontaneous resolution; 70% in the 1st year; 90% in two years
- Criotherapy, surgery, electrocoagulation
- Topical imiquimod - out of indication
- Remember to rule out sexual abuse: > 4 years old

Take-home messages

1. Provide patients with a comprehensive explanation of natural history of HPV.
2. Treatment is focused on removing GW and recurrences seem not to be influenced
3. 1st line medical treatment: podophylotoxin / imiquimod / sinecatethins- with similar rate of clearance and recurrence
4. Combinations often used:
    - For big lesions
    - To treat recurrences
    - In refractory disease

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GUIDELINES

2019 IUSTI-Europe guideline for the management of anogenital warts

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Human Papillomavirus and Genital Warts: A Review of the Evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines

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