Warts and Molluscum

Inaugural Dermatology Innovation Symposium

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No Commercial Disclosures
I will be discussing off label medicines in children

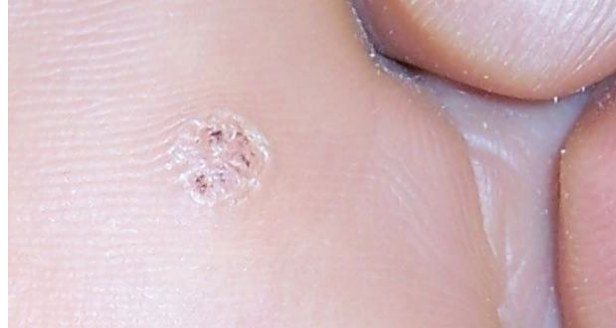
Learning Objectives:

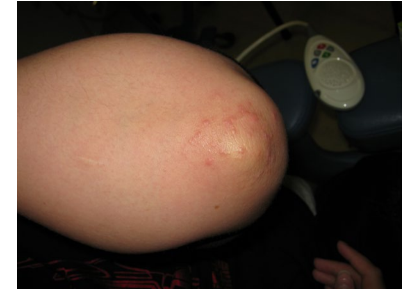
- Understand treatments for Warts in children
- Learn about treating Molluscum Contagiosum for kids
- Updates on newer treatments/innovations for Molluscum and Warts

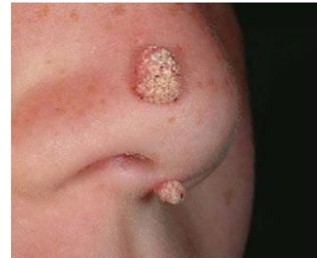
Warts

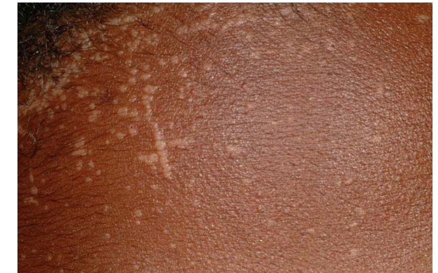
Types of warts in children

- Verruca vulgaris
- Plantar warts
- Flat warts (Verruca plana)
- Condyloma
- Filiform warts

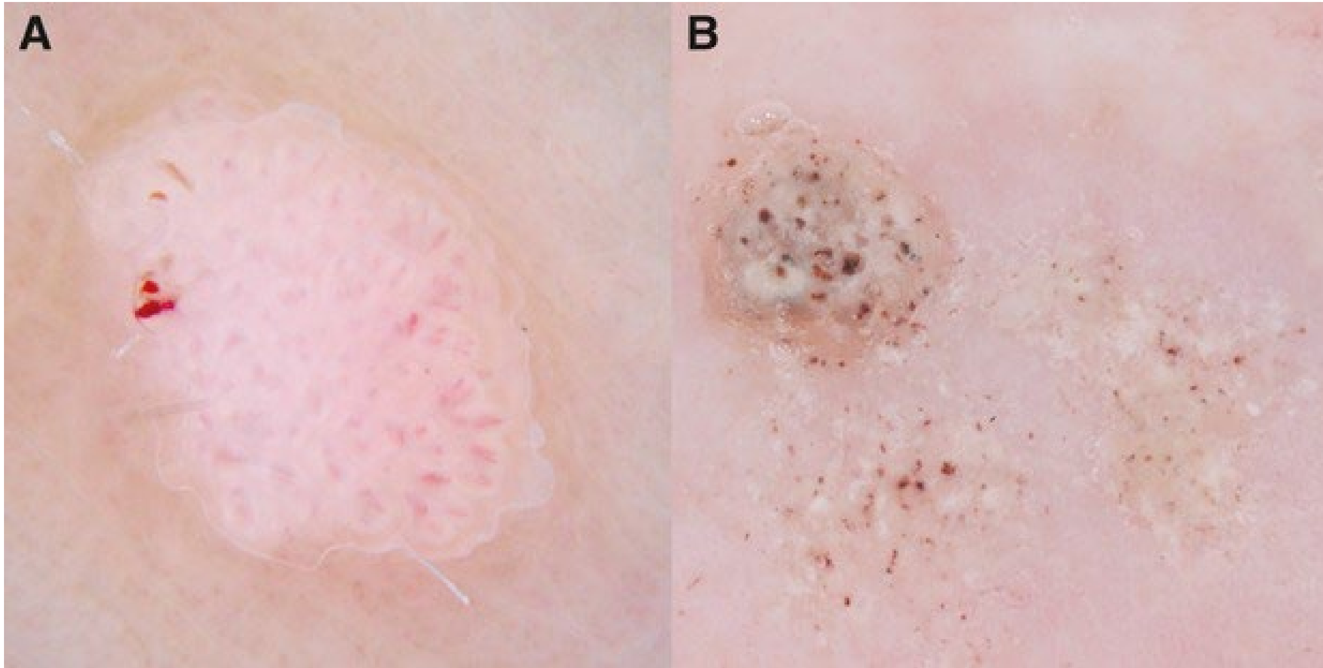








Warts Dermoscopy



- A. Verruca vulgaris with blood vessels and white halo
- B. Verruca with thrombosed capillaries

Pediatric Warts

- Caused by infection with human papillomavirus
- Transmitted by fomites on surfaces, from siblings, close contacts, walking barefoot at pools/gyms, sometimes congenital
- Extremely common in children
- Usually last more than a year
- Children with atopic dermatitis have higher risk of developing warts

A 4 year old girl presents to the clinic with several months duration of verrucous papules on the dorsal fingers. What is the most appropriate treatment?

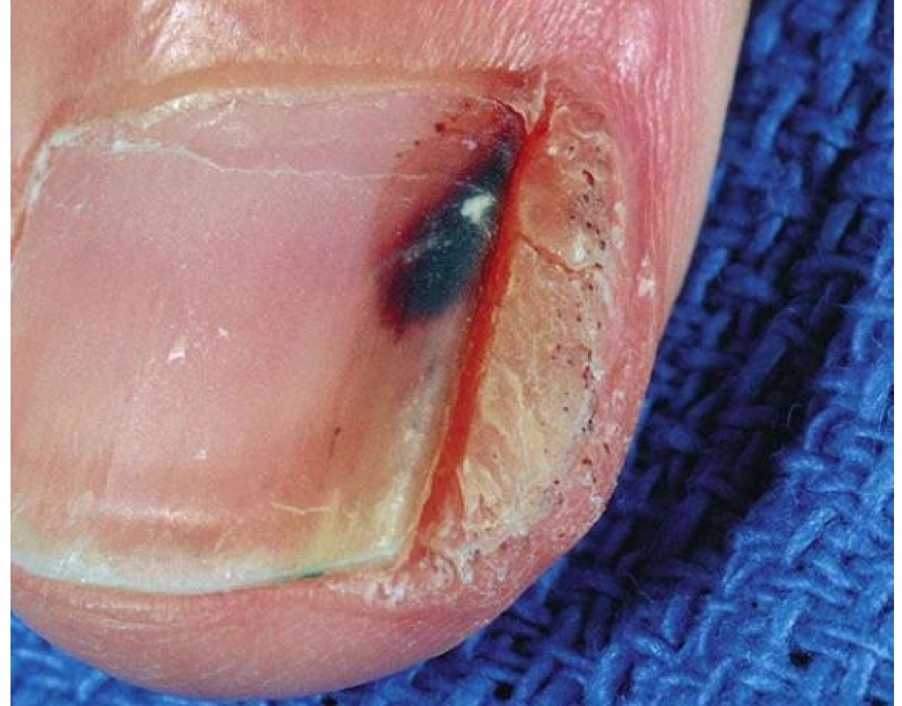
A. Liquid nitrogen

B. Cantharidin

C. Salicylic acid

D. Candida antigen injections

E. Imiquimod cream



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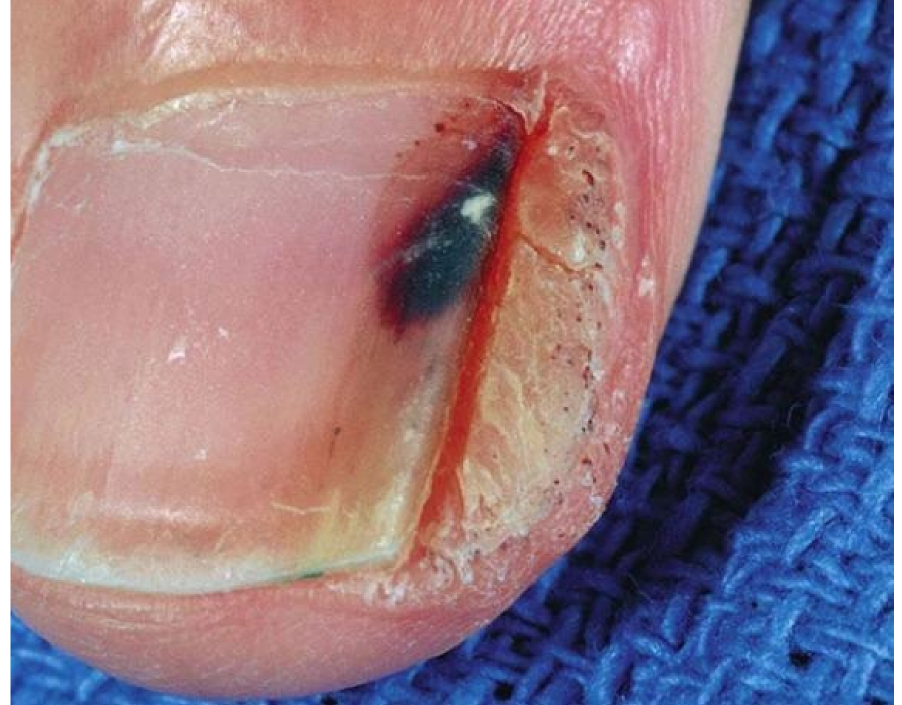


Initial therapy for Pediatric Warts

1. Observation: 2/3 of warts will spontaneously resolve in 2 years and 3/4 will resolve in 3 years

2. Over the counter salicylic acid 17% therapy

3. In office cryotherapy

Treatment Options for Verrucae

- Watchful monitoring
  - Younger patients, few lesions
- Destructive
  - Salicylic acid 17%
  - Duct tape (Soak/scrape and tape technique)
  - Compounded salicylic acid 17% and 5- fluorouracil (2- 2.5%)
  - Cryotherapy
- All with risks of scarring, dyspigmentation, repeated treatments with adherence and follow up

Treatment Options for Verrucae: Immunotherapy

- Immunotherapy
  - Oral: Cimetidine, Zinc
  - Intralesional: Candida Antigen
  - Topical: Imiquimod, squaric acid
  - HPV vaccine – some believe there is cross reactivity
- Immunotherapy can treat distant lesions not directly treated and prevent recurrence
- Less risk of scarring but not without side effects and need for regular therapy as well

Irritant Therapies: Duct Tape

- Occlude warts nightly with Duct Tape
- Duct tape causes maceration and irritation of warts
- Apply nightly
- Can be tricky on the palms/soles due to difficulty maintaining occlusion
- In one trial 85% (22/26) duct tape treated cases cleared vs 60% (15/25) of cryotherapy treated cases over 2 month period

WartPeel Cream

- Compounded 5- Fluorouracil cream and salicylic acid
- Apply nightly under occlusion
- Side effects: local irritation, 5 flurouracil can cause nail dystrophy if applied to periungual warts
- Compounded pharmacies (Nucara pharmacy- wartpeel.com uses a proprietary gel, similar from local compounded pharmacy, Skinmedicinals)

Oral Immunotherapy: Cimetidine for Warts

- Usually dosed at 30 mg/kg tid x 3 months (max of 300 mg per dose)
- Reported in case series with cure rates 56- 82%
- Randomized trials haven't found superiority over placebo, but a trend towards efficacy was suggested for younger patients
- Side effects of mild GI upset, dizziness, somnolence, gynecomastia for males

Chern E, Cheng YW. Treatment of recalcitrant periungual warts with cimetidine in pediatrics. J Dermatol Treat 2010
Rogers et al JAAD 1999

Oral immunotherapy: Zinc supplementation for Warts

- Zinc therapy was found to be beneficial in 13 out of 16 trials evaluating efficacy on warts
- Mechanism:? Correcting Zinc deficiency linked to warts
- Dose: 10 mg/kg daily up to 600 mg/day
- Simple, safe and cost effective
- Side effects: mostly mild GI

Song et al Clinical use of zinc in viral warts: a systematic review of the clinical trials J Dermatolog Treat 2022

Intralesional immunotherapy: Candida antigen injections for Warts

- Candida antigen injected 0.2 – 0.3 ml intradermally into the largest 2 warts
- Injection can be repeated every 4 weeks
- Second line therapy for recalcitrant warts
- Average of 3.78 treatments
- 48% had complete resolution, the remainder had partial resolution
- Side effects: pruritus at injection site, pain, erythema, edema, rarely hypersensitivity reaction

Clifton et al Immunotherapy for recalcitrant warts in children using intralesional mumps or Candida antigens Pediatr Dermatol 2003

Newer injectable treatments for warts

- In addition to candida, MMR, Tuberculin PPD and BCG have been studied as injectable immunotherapy treatment for warts
- HPV clearance relies on a cell mediated immune response
- Intralesional immunotherapy targets this response by introducing antigens at the wart site, inducing a T cell mediated systemic response

Newer injectable treatments for warts: MMR, PPD, BCG

- Studies of Candida antigen, MMR and PPD provided comparable complete response rates of injected warts
  - from 39-88% for candida
  - 26.5- 92% for MMR
  - 23.3 - 94.4% for PPD
- BCG appears to be inferior with clearance rates of 33.3-39.7%
- Randomized controlled trials are needed to better compare efficacy of intralesional immunotherapy options in pediatric populations

Fields et al Intralesional immunotherapy for pediatric warts : A review
Pediatric Dermatol 2020

Topical immunotherapy for warts: Squaric acid

- Universal allergen
- Not mutagenic like dinitrochlorobenzene
- Less erythema and pruritus than diphencylopropenone
- Requires sensitization - usually on upper medial arm with SADBE 2-5%
- 2-4 weeks later clinic follow up to assess response and demonstrate how to apply lower strength SADBE (from compounding pharmacy) directly on the warts
- Apply at home 2-7 times per week for up to 2-4 months

Advantages and Disadvantages of Squaric Acid

- Advantages:
    - non painful
    - less frequent office visits for child family
- Disadvantages
    - can cause significant pruritus and blistering
    - requires compounding pharmacy
    - physician can become sensitized

Topical imiquimod for warts

- FDA approved for genital warts in patients 12 years or older
- Can be used off label for flat warts on the face
- Apply three times weekly for several months
- Case reports but not great data

Devices for warts

- Several over the counter devices that contain compressed gases to treat warts at home:
  - dimethyl ether
  - nitrous oxide
  - devices employ an applicator that is either metal, polyethylene sponge/foam or polypropylene

Devices for warts

- Study compared nitrous oxide device with a dimethylether propane based product
- Randomized patients with common or plantar warts into two groups
- After 3 applications, superior cure rates were found with the nitrous oxide device

- Walczuk et al Efficacy and Safety of Three Cryotherapy Devices for Wart Treatment: A Randomized Controlled, Investigator- Blinded, Comparative Study. *Dermatology and Therapy* 2018

Laser treatments for Warts

- Pulsed Dye Laser (595 nm, 5-7 mm spot size, fluence 9-14 J/cm2, pulse duration 0.45-1.5 ms without cooling)– destroys dilated superficial capillaries in warts, heat may kill wart virus
- Nd:YAG laser (1064 nm)
- CO_2 Laser (10600 nm)– excises/coagulates lesion and destroys cells
- Paring the wart prior to the procedure makes the laser procedure more effective
- Topical lidocaine before treatment
- Smoke evacuator and N95 masks due to aerosolization of HPV

Gupta D Laser Surgery for Dermatologic Conditions in Pediatric Patients Dermatol Clinics 2022

Innovative treatments for Warts in WHIM patients

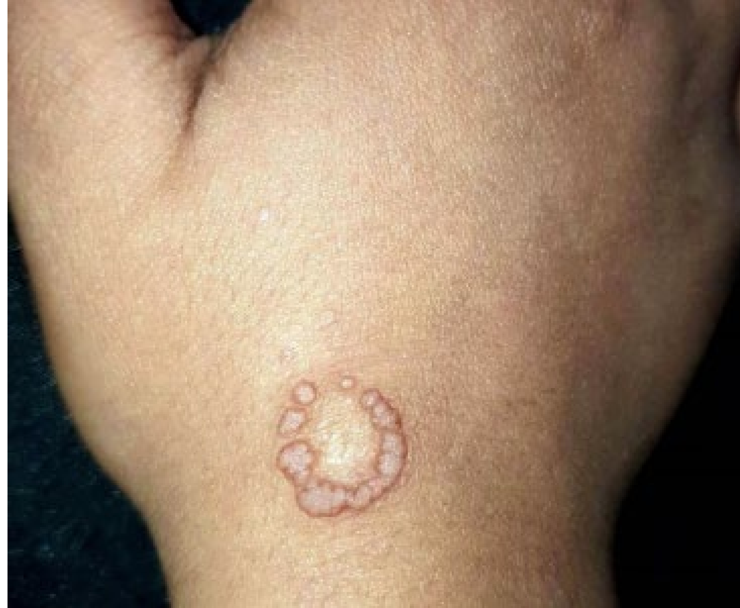
- Plerixafor (injection) & Mavorixafor (oral)- selective reversible antagonist of CXCR4 receptor that increases mobilization and trafficking of white blood cells from the bone marrow
- Has been used to treat WHIM syndrome (Warts Hypogammaglobulinemia, Infections and Myelokathexis Syndrome), warts decreased by 75%
- WHIM is an autosomal dominant primary immunodeficiency syndrome due to gain of function mutations in CXCR4 gene

- Plerixafor for the Treatment of Whim Syndome NEJM 2019, Results of a phase 2 trial for oral CXCR4 antagonist, mavorixafor for treatment of WHIM syndrome Blood 2020

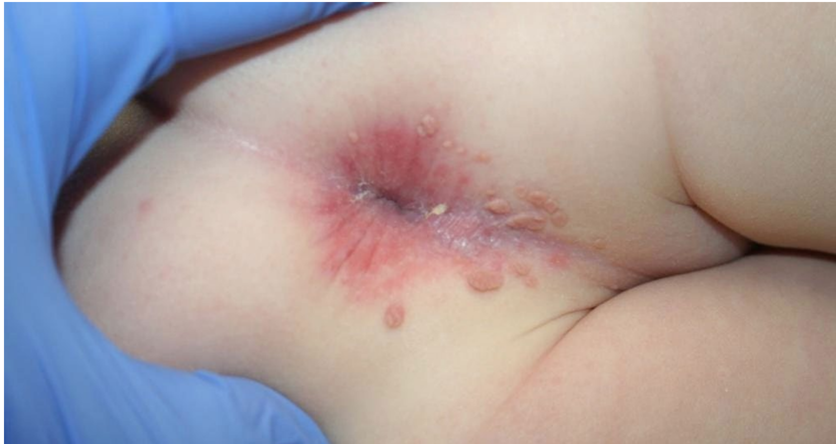
VP-102 Phase 2 study for the treatment of common warts

- Device containing cantharidin 0.7%
- Open label trial, participants > 2 years with one to six common warts were administered VP-102 topically once every 2 weeks with and without wart paring.
- Clearance at day 84 was 19% in device only group and 51.4% in group with paring and device

Ring warts after cantharidin treatment



Condyloma Acuminta



- Anogenital tract
- Mostly perianal
- Penis, scrotum, vulva
- Vaginal and cervical lesions require internal exam
- Challenging because of the concern of tranmission

Condyloma Acuminata

- Most common HPV types 6, 11 (low risk) but also HPV 16,18 (high risk)
- Transmission may be:
  - Vertical (perinatal or prenatal)
  - Benign non-sexual heteroinoculation
  - Autoinoculation
  - Sexual Abuse

Condyloma Acuminata

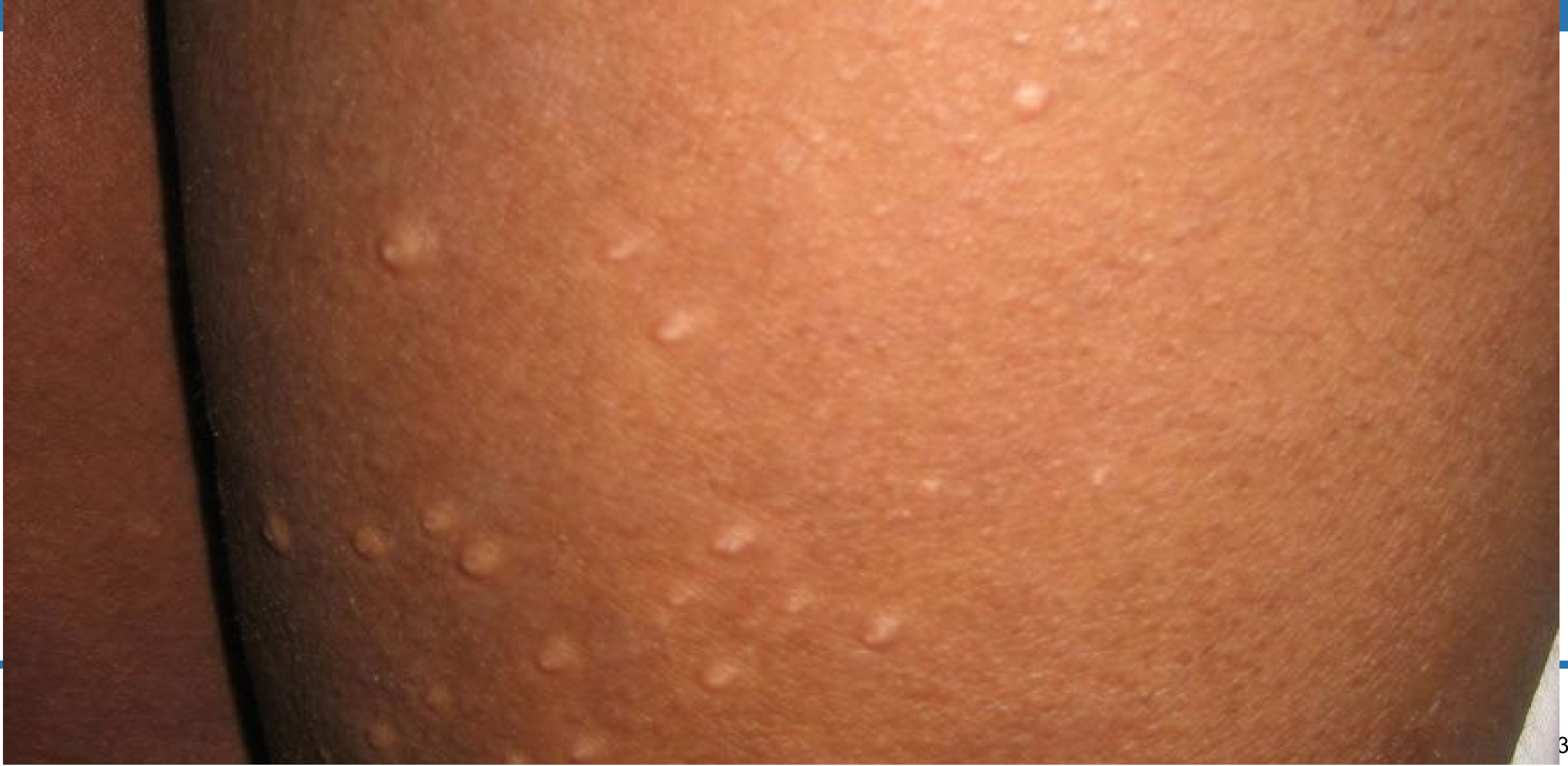
- Obtain detailed history about age of onset, maternal genital infection history, caregivers and close contacts wart history
- Complete physical exam for evidence of physical and sexual abuse
- May need to enlist help of child protective services
- May need to screen for other sexually transmitted diseases

Appropriate Management of Condyloma Acuminata

- Non intervention (many infections resolve within a few years)
- Imiquimod 5% cream
- Podophyllotoxin
- Surgical and laser therapy
    - For very large or recalcitrant warts

Molluscum Contagiosum

Molluscum Contagiosum: dome shaped monomorphic papules central umbilication



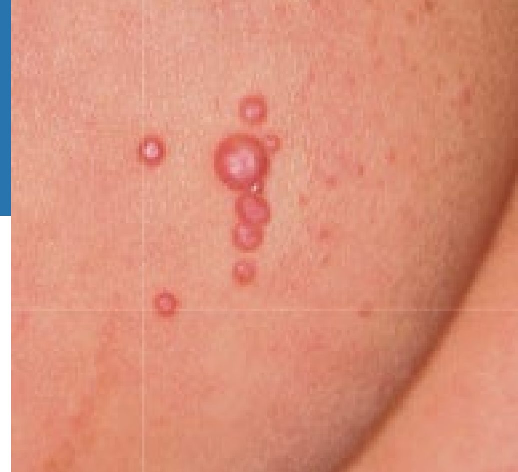
Molluscum contagiosum

- Poxvirus:
  - Affects younger patients
  - Multiple, easily autoinnoculates
    - Spread by skin to skin contact, water, fomites
  - More common in children with atopic dermatitis, impaired skin barrier
  - When suprapubic or genital location can be sexually transmitted (especially adolescents, adults)

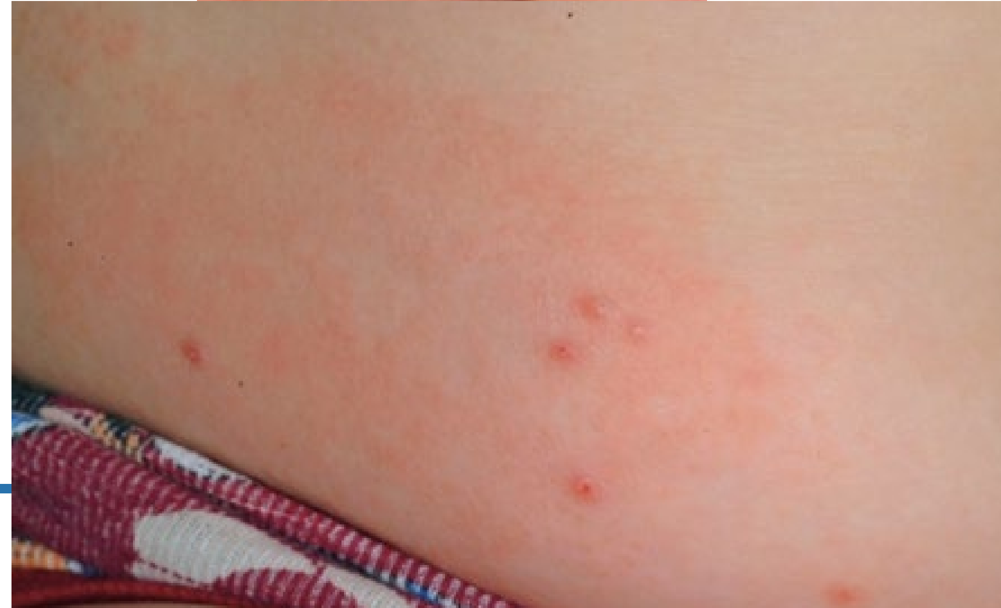
Molluscum contagiosum

- Poxvirus:
  - Generally resolves in months to years
  - Usually asymptomatic, itchy at times
  - Severe for immunocompromised patients (HIV – can be giant or extensive)

Molluscum Contagiosum

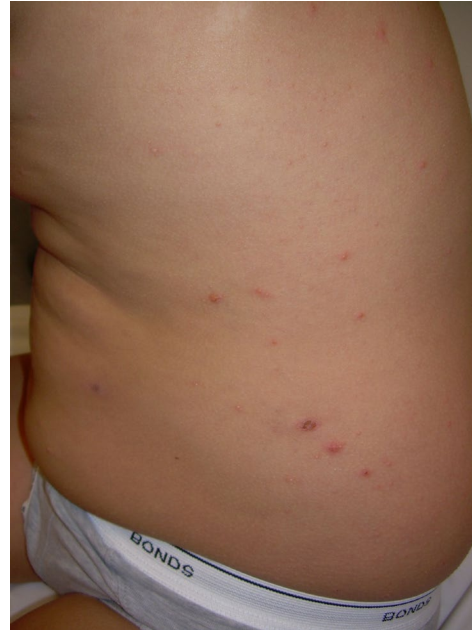


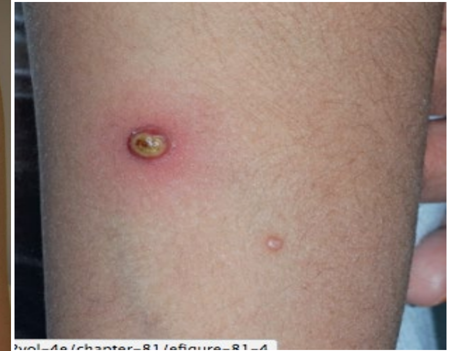
- Sometimes in linear array
- Koebner phenomenon
- May have “molluscum dermatitis”
- Eczematous patches and plaques surrounding molluscum



Molluscum Contagiosum

- BOTE sign
- ***Beginning Of The End***
- Often become inflamed or look infected prior to resolution
- “Pseduofuruncle”





Molluscum Dermoscopy

- Whitish to yellowish lobules surrounded by a crown of vessels

Dermoscopy for the Pediatric Dermatologist Pediatric Dermatol 2013

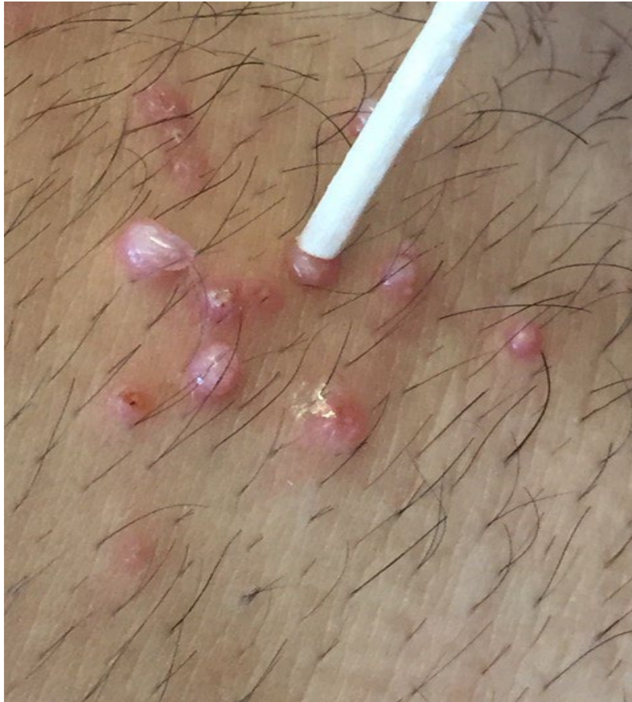
Molluscum Contagiosum Treatments (none are FDA approved)

- Watchful waiting
- Destruction
  - Cantharidin (extraction from blister beetle – *Cantharis vesicatoria* to induce vesiculation and an immune response)
  - Cryotherapy
  - Curettage
- Topical irritants
  - Tretinoin, zymaderm, molluscum Rx
- Immune therapy: oral cimetidine

Destructive treatments for Molluscum

- Cantharidin 0.7% solution - from compounding pharmacy, apply with wooden tipped end of cotton tipped applicators, wash off in 4-6 hours
- Cryotherapy: generally avoid in kids due to pain
- Curettage - topical numbing or sedation, curette out molluscum core
    - can be option for few molluscum in older child, least likely to cause post inflammatory hyper pigmentation for darker skin

Molluscum: Cantharidin treatment



- Example of treating molluscum with cantharidin on the wooden end of a cotton tipped applicator
- Apply a very small amount to each individual lesion
- Remind patient/family to wash off with soap and water in 4-6 hours

Topical treatments for Molluscum

- Topical retinoids: cause irritation
    - more helpful for facial molluscum, less effective on the body
  - Over the counter treatment options:
    - Zymaderm - plant based irritant with iodine, echinacea, thuja ,in tincture of M. alternifolia
    - Molluscum Rx - plant based irritant with procyanidins, myrrh and calendula

Imiquimod is INEFFECTIVE in treating Molluscum

- Two large, unpublished randomized trials of children (N=323 and 379) who were treated with imiquimod 5% cream or vehicle three times weekly for up to 16 weeks
- Complete clearance of molluscum in 24% & 24% of treatment groups vs 26% & 28% of placebo groups
- Imiquimod treated groups had more side effects with application site reactions, otitis media, conjunctivitis, leukopenia and lymphadenopathy

Aldara (imiquimod) cream, 5%. US FDA approved product information; Bristol, TN: Graceway Pharmaceuticals; October 2010.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020723s022lbl.pdf

Cimetidine for Molluscum

- H2 antihistamine that has immunomodulatory properties
- Data conflict on the efficacy
- Not a first line treatment
- 30-40 mg/kg/day for 2-3 months

- Dohil M Prendiville JS. Treatment of molluscum contagiosum with oral cimetidine: clinical experience in 13 patients Pediatr Dermatol 1996

What about Cantharidin for *facial* molluscum?

- 62 pediatric patients with facial molluscum treated with cantharidin 0.7% solution
- 20% had temporary post- treatment discoloration
- 10% had severe blistering or pain (similar to non facial sites)
- Study provides reassurance that cantharidin may be safe to use for facial molluscum lesions

- Jahnke MN et al Cantharidin for treatment of facial molluscum contagiosum: a retrospective review. J Am Acad Dermatol 2018

My approach to treating Molluscum:

- **Education** (brief showers, moisturizers, reassurance, **recommend watchful waiting)**
- If family/child want treatment:
  - In office cantharidin every 6 weeks until resolution
  - If very young/uncooperative try topical treatments
- Recalcitrant molluscum:
  - Curettage or cryotherapy in older children
  - Oral cimetidine in younger children

JAMA Dermatology | Original Investigation

Safety and Efficacy of VP-102, a Proprietary, Drug-Device Combination Product Containing Cantharidin, 0.7% (w/v), in Children and Adults With Molluscum Contagiosum

Two Phase 3 Randomized Clinical Trials

Lawrence F. Eichenfield, MD; Wendy McFalda, MD; Bradford Brabec, MD; Elaine Siegfried, MD; Pearl Kwong, MD; Mark McBride, PhD; Jayson Rieger, PhD; Cynthia Willson, RN; Matthew Davidson, PhD; Patrick Burnett, MD, PhD

IMPORTANCE Molluscum contagiosum (MC) is a common viral skin infection that primarily affects children. Cantharidin, a topical vesicant, has a long history of use for MC in compounded formulations, but the safety and efficacy of doses, regimens, and application methods have not been demonstrated in large-scale trials.

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 1383

VP-102: drug device containing 0.7% cantharidin

- Single use applicator, in office application, left on 24 hours
- Phase 3 trials: efficacious and safe
- Most frequent side effect: application site vesicles
- FDA approval expected to be soon?

On the horizon for molluscum: berdazimer 10.3% gel

- Topical nitric oxide releasing gel
- Phase 3 study
  - Vehicle- controlled, double-blind
  - 6 months and up
  - Once daily x 12 weeks
  - 32.4% in treatment group with complete clearance vs 19.7% in vehicle group
  - Browning et al JAMA Dermatol 2022

Conclusions: Warts and Molluscum

- Innovative and effective treatments are necessary for optimizing and improving treatments for Pediatric Warts and Molluscum

Thank you for your attention
Questions?

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