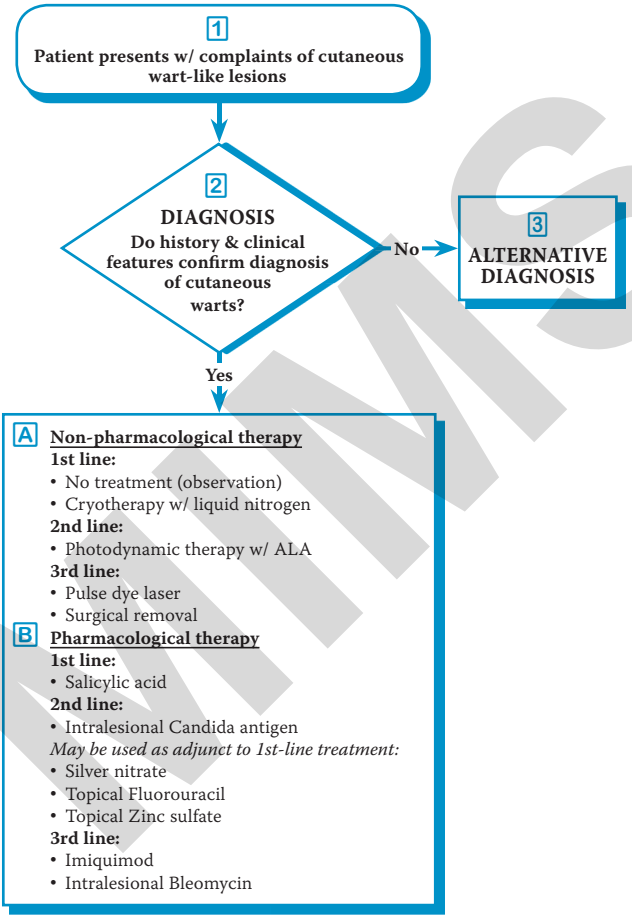
Warts - Cutaneous (1 of 10)



1 CLINICAL PRESENTATION

Cutaneous Warts

- Also called verrucae, they are benign proliferation of skin caused by human papilloma virus (HPV)
  - Most common warts on the hands & feet are due to HPV types 1, 2, 4, 27 & 57
- HPV is usually transmitted by contact w/ skin of an infected individual or by transmission of virus living in warm, moist environment
  - Autoinoculation may occur from traumatizing lesions by biting or scratching
  - Incubation period is unknown but may range from mth to yr
- Occur in 10% of children & young adults w/ greatest incidence in 12- to 16-yr-old children
  - May regress spontaneously w/in 2 yr in 40% of children
- May continue to increase in size & distribution & may become more resistant to treatment over time

2 DIAGNOSIS

History

May include but is not limited to:

- Duration of wart(s) & progression
- Location
- Current & past treatment modalities
- Family history of warts
  - Epidermodysplasia verruciformis is a rare familial disorder w/ HPV that can lead to squamous cell carcinoma
- Medical history
  - Eg immunosuppression [acquired immune deficiency syndrome (AIDS), organ transplant, etc], diabetes mellitus (DM), cold intolerance (may affect liquid nitrogen therapy)
- Medication history (eg corticosteroids, chemotherapeutic agents, etc)
- Pregnancy status
  - Warts may worsen in pregnancy & then regress afterwards
- Sunlight exposure
  - Sunlight may serve as cocarcinogen in transplant patients & patients w/ epidermodysplasia

Physical Exam

- Cutaneous warts are diagnosed by clinical appearance

Classification of Cutaneous Warts

Common Warts

- Most frequent type (approximately 70% of warts seen in clinical practice)
  - Typically found on hands but may appear anywhere on skin (eg palmar & plantar surfaces, neck, face & lips)
- Present initially as smooth, confined, flesh-colored papule
- Enlarge into grayish-brown, dome-shaped, hyperkeratotic nodule or papule
- Capillaries become trapped w/in the wart & may be viewed by debridement of wart surface
  - This may be used to differentiate from corns

Plantar Warts

- More commonly found in adolescents & young adults
- Approximately 33% of patients w/ warts have plantar warts or its variants (mosaic or myrmecia)
  - Mosaic warts are coalesced warts on the plantar or palmar surface that form into a tile-like pattern
  - Myrmecia warts are dome-shaped, large & deep endophytic growths that are typically painful
- Typically found on wt-bearing areas of the foot
- Plantar warts tend to become calloused & grow into the foot
  - Usually found as multiple lesions which are firm & typically painful
- Capillaries become trapped w/in the wart & may be viewed by debridement of wart surface
  - This may be used to differentiate from corns

Filiform Warts

- Variant of common warts
- Commonly found on the face
- Characterized by long frond-like projections which can grow rapidly

Periungual Warts

- Occur anywhere along the nail margins, including the proximal nail fold & hyponychium
- May lead to onychodystrophy from nail matrix damage & onycholysis from nail bed warts
- Many times found in children who bite their nails but can also affect adults
- Tend to be hyperkeratotic papules that often show peeling & roughening of the surface

Flat Warts

- Flat-topped papules w/ minimal scaling & only slight elevation
- Typically present on the face & extremities of children
- Often small, 2-4 mm in diameter

Lab Exam

- Histology may be needed for warts resistant to therapy & for verrucous warts in immunocompromised patients

3 ALTERNATIVE DIAGNOSIS

- Callus
- Molluscum contagiosum
- Seborrheic keratosis
- Squamous cell carcinoma
- Acrokeratosis verruciformis
- Amelanotic melanoma
- Epidermal nevus
- Epidermodysplasia verruciformis
- Irritated acrochordon
- Lichen planus

PRINCIPLES OF THERAPY

- Many treatment options are available but there are very few well-controlled studies testing the efficacy of treatment options
- Patient or caregiver of child needs to be aware of advantages vs disadvantages of the treatments & that w/ any treatment, there may be recurrence of warts
- Different types of warts may need different site-dependent treatments
  - Begin treatment w/ the least painful method especially in children
  - Aggressive & destructive treatment regimens should be given for recalcitrant lesions & areas where scarring is not a concern
- Any of the non-pharmacological therapy or pharmacological therapy may be used alone or in combination
- There is no single therapy that has proven to achieve complete remission of warts in all patients
- Treatment should be made individually based on:
  - Patient's preference
  - Patient's desire for therapy
  - Age of the patient
  - Immunological status
  - Wart location, type, size & number
  - Degree of symptoms
  - Experience of the physician
  - Treatment availability
- Treatment decision should be made after discussion of appropriate options w/ the patient

A NON-PHARMACOLOGICAL THERAPY

No Treatment (Observation)

- Cutaneous warts in immunocompetent patients cause no harm & will usually resolve w/ no treatment w/in a month to 2 yr because of the patient's natural immunity
- May be a viable option if acceptable for the patient
- Many patients request treatment either because of social stigma or because of painful warts
  - It is easier to treat smaller fewer warts than to wait for these to enlarge or increase

Cryotherapy

- Works well for most warts, may be used as 1st-line therapy for flat & common warts & as 2nd-line therapy for flat & common warts on the face
  - Aggressive cryotherapy is effective & best results are achieved w/ treatment every 2 or 3 wk
- Recommended for light-skinned individuals
- Liqiud nitrogen, Nitrous oxide, Carbon dioxide or a mixture of Dimethyl ester & Propane is applied to each wart until 1-2 mm of surrounding skin has turned white
- **Action:** Damages the cell membranes & organelles by freezing affected cells
  - HPV is not destroyed but is released into the extracellular area which may produce an immunologic response
- Patient should be made aware that pain, dyspigmentation, hemorrhagic blister, nail dystrophy, tendon & nerve damage & recurrence of the wart can occur
  - Not recommended for young children because of pain

Duct Tape Occlusion

- Suitable for children w/ warts because it is painless, nonthreatening & inexpensive
- **Action:** Host immune system is stimulated through local irritation produced by the duct tape
- Duct tape is applied to the affected areas & removed after 6 days
  - An emery board or pumice stone is used to scrub the wart after soaking in water & left open to the air overnight
  - 6-day cycle is repeated the following morning for up to 2 mth
- A study showed 85% cure rate in children treated
  - This study did not follow patients long enough to see if recurrence occurred

A NON-PHARMACOLOGICAL THERAPY (CONT'D)

Infrared Coagulation
- Cheaper, safer & more convenient alternative to CO_2 laser treatment
- Direct application of infrared contact coagulators allows adjustable tissue necrosis w/o tissue adhesion
- Produces remissions w/ only 10.8% recurrence rate

Lasers

Carbon Dioxide Lasers
- Useful in resistant warts & in treating immunocompromised patients
- **Action:** Nonselective thermal tissue destruction
- Adverse effects include postoperative pain, prolonged healing time & scarring
- HPV has been transmitted to healthcare workers from smoke plume

Flashlamp-Pumped Pulsed Dye Laser
- Used for facia & perianal warts in children & for recalcitrant warts
- **Action:** Selective microvascular destruction of dilated capillaries in warts which results in necrotic warts that eventually slough off
- Mixed results in treating warts
- Causes minimal postoperative pain & heals in 2-4 wks
- Decreased risk of scarring & decreased risk of transmission via smoke plume to healthcare workers

Erbium:Yttrium/Aluminum/Garnet (Er:YAG) Laser
- Has a smaller zone of thermal damage giving more accurate thermal ablation & minimal scarring
- Warts are successfully eliminated in 75% of patients
- HPV DNA has not been detected in the laser plume

Neodymium:YAG (Nd:YAG) Laser
- Several reports showed remission w/ no recurrence
- A minimal load of potential infectious laser plume & toxic pyrolysis products are removed

Potassium-Titanyl-Phosphate (KTP) Laser
- Used for recalcitrant cutaneous warts
- No recurrence noted when warts are treated completely

Photodynamic Therapy
- Used to treat common warts on the hand, flat & plantar warts
- Moderately effective w/ Salicylic acid for recalcitrant warts
- **Action:** Uses 5-aminolevulinic acid (ALA) to stimulate porphyrin accumulation in the tissue which then acts as a photosensitizing agent
- Studies show that results are equal or better than other treatment modalities w/ less or no scarring

Surgical Removal
- Although the success rates are reported to be 65-85%, surgical excision by curettage & cautery is not recommended as a standard therapy
  - Can be painful & cause scars that are difficult to treat
  - No assurance that warts will not recur
  - Recurrence rates can be as high as 30%

Electrocautery
- Need to 1st anesthetize the area then remove verruca w/ surgical blade
  - Follow w/ carbonizing the surface w/ electrosurgical probe or hyfrecator tip
  - Repeat as necessary after removing charred tissue w/ moist gauze
- **Effects:** Large warts on the torso, plantar warts or resistant warts may respond well to a single treatment of electrocautery
- Scarring, pain & recurrence of warts can occur

Excision/Curettage
- Filiform warts benefit from snip or shave excision
- Surgical excision of wart should only be done if diagnosis is questionable
  - Recurrence of disease w/in scar tissue, scarring, delayed or inadequate healing may occur
- Curettage of verrucae may be acceptable when treating isolated warts
- Not recommended for plantar warts due to development of painful scars

B PHARMACOLOGICAL THERAPY

Antimitotic Agents

Bleomycin (Intralesional)

- Reserved for recalcitrant warts or those that may be difficult to surgically excise
- **Actions:** Selectively affects squamous cell & reticuloendothelial tissue
  - Inhibits DNA & protein synthesis in cells and viruses & triggers apoptosis
  - Causes acute tissue necrosis that may stimulate an immune response
- Adverse effects: Pain, burning, erythema, swelling in the injection site, Raynaud's phenomenon, lymphangitis, hyperpigmentation
- Disadvantage: High cost
- Not recommended in pregnancy, children, immunocompromised patients & patients w/ vascular disease

Retinoids

- Tretinoin is useful for flat warts
- **Actions:** Disrupt epidermal growth differentiation thereby reducing the bulk of warts
  - Alter keratinization & accelerates the clearing of warts by inducing an irritant dermatitis
  - Can downregulate HPV transcription in affected cells
- Administered topically or systemically; protect normal skin by using barrier cream
- Use sun protection measures, not recommended in pregnancy

Immunomodulators

Candida Antigen (Intralesional & Intradermal)

- Immunotherapy that is nonscarring
- May be used on most verrucae warts esp plantar or facial warts
- Suitable for recalcitrant warts
- May serve as 1st-line treatment for immune individuals w/ >5 warts or >1-cm warts
- Considered an effective 2nd-line treatment in immune individuals w/ warts that failed cryotherapy
- **Actions:** Enhances the immune response at the wart site to suppress HPV infection
  - Since most people have been exposed to Candida, they will mount an immune response when Candida antigen is injected into the base of the wart
- A study showed that 74% of the patients had resolution of injected warts & 78% of these patients also had resolution of all noninjected warts
- Patients may experience a delayed-type hypersensitivity reaction

Cimetidine

- H2-receptor antagonist which acts as an immunomodulating agent at high doses
- **Actions:** Inhibits suppresor T-cell function while increasing lymphocyte proliferation thus enhancing cell-mediated immune responses
- May be considered for use in recalcitrant warts & in children who cannot tolerate destructive therapy

Diphenylcyclopropenone (Diphencyprone)

- Usually reserved for recalcitrant warts
- May start treatment w/ 2% soln then decrease or increase as required
- **Actions:** Sensitizing agent that causes a type IV delayed-hypersensitivity reaction directed against protein of viral or human origin enhancing wart regression
- Cure rate may be approximately 80%
- Less destructive, less time consuming, cost effective & can be used for concurrent treatment of multiple warts
- Some patients may not tolerate the induced hypersensitivity reaction

Fluorouracil (Topical)

- Used topically as an antiproliferative agent for flat warts
  - Used in recalcitrant warts; as an adjunct to laser excision
- **Actions:** Destroys cells by inhibiting DNA & RNA synthesis
- Effective in treating plantar warts in 92% of patients

B PHARMACOLOGICAL THERAPY (CONT'D)

Squaric Acid Dibutylester (SADBE)
- A non-mutagenic contact sensitizer used to treat warts
- Has been used for the treatment of recalcitrant warts
- Cure rates have ranged from 58-84%
- More expensive & less stable than Diphenylcyclopropenone (Diphencyprone)

Zinc Sulfate
- May be used in recalcitrant warts
- **Action:** Enhances the immune system
- A clinical trial of Zinc sulfate PO reported to show complete clearance in 87% of the treatment group compared to placebo

Keratolytics

Podophyllotoxin
- **Actions:** Binds to the spindle during mitosis & blocks cellular division
- Less effective in cutaneous warts because of poor absorption through thick stratum corneum
- May be applied under occlusion after paring of the wart
- Effective but w/ risk of intense inflammation, sterile pustule formation or secondary infection
- Not recommended in children, pregnancy & lactation

Salicylic Acid
- Safe & effective for removal of warts w/ minimal discomfort
- Recommended as 1st-line therapy for flat warts on the face, plantar warts, flat & common warts on the hands in some guidelines
- **Actions:** Slowly destroys virus-infected epidermis by dissolving the keratin layer
  - Causes mild irritation that may produce an immune response
- **Effects:** Studies show approximately 75% cure rate
- Advantages include wide availability, convenience, minimal expense, negligible pain & reasonable efficacy
- Disadvantages: May take time before results can be observed
  - Complex instructions for home use (debride, soak, apply Salicylic acid daily)
  - Strict compliance should be observed
  - Potential risk of systemic toxicity in children
    - Can be avoided by using lower concentrations or on limited areas only
- Still suitable for children but precautions should be made
  - Prevent them from placing the treated areas in their mouths
- Not recommended for patients w/ peripheral neuropathy

Skin Antiseptic & Disinfectant

Silver Nitrate
- **Action:** Chemically cauterizes epithelial tissues
- Clinical efficacy is moderate
- Caution in application should be exercised
  - May cause excessive burns & irreversible tissue staining

Virucidal Agents

Formaldehyde
- **Actions:** Disrupts the upper layer of epidermal cells & possibly damages the virions
- A study showed 80% clearance of warts
- Avoid in patients w/ eczema & allergies

Formic Acid
- A caustic acid
- A study showed 92% clearance rate w/ Formic acid/needle puncture technique compared to placebo

B PHARMACOLOGICAL THERAPY (CONT'D)

Virucidal Agents (Cont'd)

Glutaraldehyde

- **Action:** Hardens the skin & makes paring easier
- As effective as Salicylic acid w/ >70% cure rates
- May stain the skin brown & cause contact sensitivity

Imiquimod (Topical)

- Showed efficacy in treating recalcitrant plantar, periungual & subungual, & flat warts
- May be useful for lesions where scarring may be a problem, facial lesions, children w/ multiple lesions unresponsive to other therapies, & as an adjunct to laser therapy or intralesional Bleomycin
- **Action:** Topical immune response modifier that stimulates the production of interferons & cytokines that produces localized immune response at the site of application
- Less pain & trauma
  - Involves costly & lengthy treatment
- May cause erosions, pruritus, bacterial infection, fever & scarring
- Use sun protection measures to prevent exacerbation

PREVENTION

- Avoid direct contact w/ warts
- Wash hands thoroughly after touching warts
- Keep hands & feet dry
- Avoid going barefoot in public places
- Avoid picking warts to prevent spread of the virus
  - Don't use the same file, pumice stone or nail clipper used for skin w/ warts on healthy skin

Not all products are available or approved for above use in all countries.
Specific prescribing information may be found in the latest MIMS.

Dosage Guidelines

ANTIMITOTIC AGENTS

Drug	Available Strength	Dosage	Remarks
Bleomycin		Inj 0.5-1 u/mL soln intralesionally into wart **Max total dose:** 1.5 u/ treatment	**Adverse Reactions** • Pain at injection site; permanent nail dystrophy & Raynaud's phenomenon have been reported **Special Instructions** • Not recommended in children, pregnancy & lactation
Tretinoin (Retinoic acid)	0.01% cream, gel 0.025% cream, gel 0.05 % cream, gel, lotion, soln 0.1% cream 0.1% soln	Apply 12-24 hrly	**Adverse Reactions** • Usually resolve w/ decreasing frequency of application: Stinging, feeling of warmth, erythema, peeling • Edema, blistering, crusting of the skin, temporary hypo- or hyperpigmentation, photosensitivity **Special Instructions** • Start w/ weaker formulation & increase concentration as tolerated • Avoid exposure to excessive sunlight or UV radiation • Not recommended in pregnancy
	0.04% microsphere gel 0.1% microsphere gel	Apply 24 hrly at bedtime	

WARTS & CALLUSES PREPARATIONS

Drug	Available Strength	Dosage	Remarks
Podophyllotoxin (Podofilox)	0.15% cream, 0.5% soln	Apply 12 hrly x 3 days followed by 4 days of no treatment Repeat cycle as necessary **Max:** 4 treatment cycles	**Adverse Reactions** • Burning, pain, inflammation, erosion & pruritus, headache • Topical overdosage can cause serious systemic effects **Special Instructions** • Not recommended in children, pregnancy & lactation
Salicylic acid[1]	16-60% as soln, gel, cream or plaster	Apply as manufacturer suggests **Usual application:** Soak wart in water for 5-10 min 24 hrly, debride w/ nail file or pumice stone then apply Salicylic acid formulation	**Adverse Reactions** • Contact dermatitis occurs infrequently **Special Instructions** • Avoid contact w/ normal skin - Normal skin may be protected w/ petrolatum

[1]Salicylic acid combined w/ Lactic acid is available. Please see prescribing information for specific formulation in the latest MIMS.

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
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Dosage Guidelines

IMMUNOMODULATORS		
Drug	**Dosage**	**Remarks**
Candida	Mixture of 1:1 Candida antigen & 1% Lidocaine: Inj 0.1 mL intralesionally or intradermally into each wart up to 1 mL/treatment Repeat every 4 wk x up to 3 physician visits	**Adverse Reactions** • Discomfort on administration, mild local reactions (eg pain, burning, blistering & peeling)
Cimetidine	20-40 mg/kg/day PO in 3-4 divided doses	**Adverse Reactions** • Generally well tolerated; GI effects (diarrhea, constipation, GI disturbances); CNS effects (dizziness, headache, tiredness); Rashes • Less commonly altered LFTs, rarely hepatotoxicity; reversible confusion in elderly & renal impairment • Rarely hypersensitivity reactions, hematologic effects, CV effects, pancreatitis **Special Instructions** • Use w/ caution in patients w/ impaired renal function & in patients on drug treatment or w/ illnesses that could cause falls in blood cell counts
Fluorouracil[1]	Apply 5% soln under occlusion 24 hrly x 1 mth	**Adverse Reactions** • Inflammatory reactions may occur w/ occlusion **Special Instructions** • May use porous dressing w/o increased reaction
Zinc sulfate	10 mg/kg/day	**Adverse Reactions** • GI effects (abdominal pain, dyspepsia, N/V, diarrhea, gastric irritation) • Copper deficiency w/ prolonged use **Special Precautions** • Monitor CBC & serum cholesterol to detect early signs of copper deficiency

[1]Fluorouracil combined w/ Salicylic acid & Dimethylsulfoxide is available. Please see prescribing information for specific formulations in the latest MIMS.

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Dosage Guidelines

SKIN ANTISEPTIC & DISINFECTANT			
Drug	**Available Strength**	**Dosage**	**Remarks**
Silver nitrate	0.5% soln	Apply to affected areas	**Adverse Reactions** • Skin discoloration, diarrhea, vomiting • W/ prolonged use: Electrolyte disturbances, convulsions, methemoglobinemia, argyria, sialorrhea **Special Instructions** • Contraindicated in patients w/ known hypersensitivity to Silver nitrate • Not suitable for application to the face, eyes, anogenital region or large areas • Avoid application on broken skin & avoid contact w/ normal skin

TOPICAL ANTIVIRALS			
Drug	**Available Strength**	**Dosage**	**Remarks**
Formaldehyde	0.75% water-miscible gel 3% soln	Apply to affected areas	**Adverse Reactions** • Contact dermatitis, sensitivity reactions, whitening & hardening of the skin **Special Instructions** • Contraindicated in patients w/ known hypersensitivity to Formaldehyde • Avoid contact w/ eyes, nose & mucous membranes
Glutaraldehyde	5% gel 10% soln	Apply to affected areas 2x daily	**Adverse Reactions** • Eye, skin & resp irritation **Special Instructions** • May worsen pre-existing asthma, inflammatory or fibrotic pulmonary disease • Protect the eyes & skin; prevent vapor inhalation during work
Imiquimod	5% cream	Apply 3x/wk at bedtime, leave on for 6-10 hr then wash off Continue treatment until wart clearance or a max of 16 wk	**Adverse Reactions** • Local skin erosion, erythema, excoriation, flaking, edema, headache

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