Narrative Review:
Treatment of Warts in Children With Focus on Recalcitrant Warts: A Narrative Review

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ABSTRACT

Context: Warts are benign cutaneous and mucosal growths caused by human papillomavirus. Warts are the most common skin diseases seen by pediatric dermatologists. Warts are often self-limited, especially in children, but some lesions are not resolved despite repeated treatments and referred to as recalcitrant warts.

Evidence acquisition: Electronic databases such as Google Scholar, PubMed, and Scopus were searched during 2000-2018 and a review was conducted for articles published in English on pediatric warts by focusing on recalcitrant warts.

Results: If warts are asymptomatic and being in a location that causes no cosmetic or other problems, observation is the ideal management course. Most parents and children prefer treatment for their warts. There are three modalities of treatment: medical, surgical, and immunotherapy.

Conclusions: Treatment of warts is a therapeutic challenge that depends on the patient's age and the type of warts. Despite treatment according to evidence-based guidelines, a significant proportion of warts are failed to respond. This condition is an unsolved problem in practice. The management for treating these lesions has remained unclear and a wide range of the second line of treatments has been developed.

1. Context

Definition

Warts are benign cutaneous and mucosal viral-induced lesions caused by Human Papillomavirus (HPV). HPV is a coiled, double-stranded DNA virus that infects host squamous cells. Warts may be present in different forms according to epithelial surface reaction and HPV type responsible for the infection. Common warts, plantar warts, flat or plane warts, and genital warts are some of the most common types of HPV infection (1). Hands, feet, elbows, knees, and face are the most frequent sites for cutaneous warts in chil-

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dren. Although there is no clear definition for recalcitrant warts in literature, it can be defined as warts that are failed to respond to therapies after five treatments over 6 months (2).

Epidemiology

Warts are the most common skin diseases seen by pediatric dermatologists (3). About 10% to 22% of children develop warts, with the incidence peaking during adolescence (2-6). Up to one-third of non-genital warts are converted to recalcitrant warts, especially the plantar, periungual, and subungual types (2). Warts infection is more common in girls than in boys (1). HPV 27, 57, 2, and, 1 are the most frequently detected HPV types in cutaneous warts among the general population (7). The natural progression of warts is the spontaneous disappearance of warts after two years without treatment in 40% of children (8). Approximately one-third does not resolve and become recalcitrant despite repeated treatments (9-12). Children with recalcitrant warts potentially may play the role of reservoirs for HPV transmission. Rarely, oncogenic genotypes have been linked to cases of early squamous cell carcinoma on the genitals in toddlers (13). Genital warts that develop in a child older than 3 years of age may be a red flag for sexual abuse.

Diagnosis

The clinical appearance of common wart is hyperkeratotic flesh color papules which tend to occur on sites subject to trauma, as noted above. Warts can be tender and have a tendency for pinpoint bleeding when their surface is pared away, and this feature distinguishes warts from calluses, corns, actinic keratoses, nevi, or acrochordons. Flat warts are smooth with flat tops and can have a yellow-brown color. Warts in immunocompromised children may need to be biopsied. Intermediate warts can show the manifestation of both common warts and flat warts. Epidermodysplasia Verruciformis (EV) is a genetic dermatologic condition in which there is a mild defect of cell-mediated immunity leading to persistent HPV infection and increased lifetime risk of development of cutaneous dysplasia and malignancy (14). EV lesions develop in early childhood and continue to develop new lesions throughout life (15). No definitively effective treatment exists for EV.

In childhood, the rate of spontaneous resolution of HPV-induced warts is high, half of the primary school children will be free of warts within one year (16). One option is to observe the lesions because the majority of common warts resolve spontaneously within 2 to 3 years.

The American Academy of Dermatology lists the indications for the treatment of warts as follows: the patient's seeking for treatment, presence of symptoms such as pain, bleeding, itching and burning, disfiguring lesions, or disability due to lesions, large numbers or large-sized lesions, immunocompromised health status, patient's desire to prevent the distribution of warts to themselves or others. The number and location of warts as well as the age of the child all guide treatment choices for the management of common warts. Often, more than one round of monotherapy is necessary. If monotherapy fails, combination therapy may be effective, but usually requires several office visits, further increasing frustration on the part of children and their parents (17). For this reason, patients and their parents must be educated about the recalcitrant nature of warts and should be reassured that the appropriate measures are being taken to eliminate the lesions using methods that are least likely to cause discomfort and long-term cosmetic sequelae (17). There are different therapeutic approaches, including observation and treatments, but combination therapy can be more effective (18).

2. Evidence Acquisition

Performing the review, the international electronic databases such as Google Scholar, PubMed, and Scopus were searched. We conducted a review of articles published on pediatric warts during 2000-2018. The keywords included wart in children, pediatrics, recalcitrant wart, treatment of wart, and treatment of recalcitrant wart. All studies written in English about children wart were included. After removing duplication and abstracts, among 75 studies related to warts, we selected all studies about children wart by focusing on recalcitrant warts. Also, all studies either case-control, cross-sectional, clinical trials, and review articles were included. Other irrelevant articles were excluded.

3. Results

There are three treatment modalities: medical, surgical, and immunotherapy. Treatment of warts is a therapeutic challenge for dermatologists because no particular therapy has been proven effective at achieving complete remission in each patient (16, 18). Treatment options should be made individually according to the experience of the physician, patient preference, and the application of evidence-based medicine (19).

Medical treatment

Salicylic acid

Salicylic acid (SA) is a keratolytic agent and may stimulate an immune response from the mild irritation occurred by SA. Topical therapy with salicylic acid as the first-line therapy (18) is safe and effective and shows no clear evidence to prove that other therapies have an advantage related to higher cure rates or fewer side effects (20). Topical therapy by SA is an effective therapy for non-genital cutaneous warts. This agent needs time to achieve a response and is inexpensive. Daily application of a 3% to 20% SA preparation is recommended according to the location of skin lesion. Over the counter preparation, SA is available as 11%-17% collodion base ±lactic acid.

A study demonstrated that topical 1% cantharidin, 5% podophyllotoxin, and 30% SA has achieved complete clearance of recalcitrant plantar warts (21). Studies demonstrated that there are not any major side effects with the use of SA for recalcitrant plantar warts (22-24).

Cantharidin

Cantharidin is derived from blister beetle and causes epidermal cell death. Topical cantharidin 0.7% solution is safe and effective for the treatment of recalcitrant flat warts (22).

Bleomycin

Bleomycin is a chemotherapeutic agent that can inhibit DNA synthesis in cells and viruses. It is an alternative therapy for warts that are resistant to other therapies or may be difficult to excise surgically. Diluted bleomycin (0.1-2 unite per lesion) is injected into the wart and supplementary injections can be given every 3 to 4 weeks until the clearance is achieved (19). The previous review has shown that bleomycin was effective as a third-line therapy for common and plantar warts (19). Scarring, change in pigmentary disorders, nail damage, and Raynaud's phenomenon were reported as the side effects of bleomycin (17, 25).

Retinoids

Systemic retinoids are other agents for the treatment of warts due to their ability to alter keratinization and accelerate the clearing of warts (26). Retinoids are potent immunomodulators. Oral and topical retinoids can be used as the second line of treatment for flat warts (19).

Fluorouracil

This agent may be used for both common and genital warts. It is safe to use on the face and poses minimal risk of scarring. This drug disrupts viral replication and epidermal cell turnover. Topical 5-FU is applied locally once-daily by the parents at home. The cure rate has been estimated to be approximately 50% (20). Application of 5-FU to the periungual region should be avoided because the medication can interfere with the growth of the nail, leading to a chemical onycholysis. It should not be used in children who suck their thumbs or in widespread warts due to the increased potential for systemic absorption.

Cidofovir

Topical cidofovir has been successfully used with negligible risk in children with refractory warts (27). A case report demonstrated that this agent is effective in treating recalcitrant warts in immunocompromised patients (28).

Sinecatechins (Veregen) ointment

This green tea derivative and a novel agent has been approved to be effective in the treatment of anogenital warts in immunocompetent adults and for the treatment of extragenital warts (29, 30). This agent is used 3 times a day for a maximum of 16 weeks. This ointment was well tolerated and associated with a decrease in the number and or size of warts (31).

Vitamin D3

Topical vitamin deregulates epidermal cell proliferation involves the formation of antimicrobial peptides. Some studies documented that intralesional and topical vitamin D3 is a safe, effective, and inexpensive therapeutic agent for recalcitrant warts (32-34).

Supplement therapy

Patients with persistent, progressive, or recurrent viral warts suffer from zinc deficiency. Studies with a careful dose adjustment of oral zinc sulfate may be helpful to treat these patients (35). The results of a study revealed positive clinical outcomes of the selected nutriceutical such as Coenzyme Q, vitamin E, selenium, and methionine associated with conventional protocols in the treatment of relapsing mucocutaneous human papillomavirus (11, 36). Another study has shown that nutraceutical agents containing Echinacea, methionine, and antioxidant/immunostimulating compounds are safe and useful in patients with cutaneous warts, and

capable of improving the response to conventional standard therapy (37).

Surgical and laser

Cryotherapy

Liquid nitrogen boils at -196°C under normal atmospheric pressure and on contact with lesion induces rapid freezing of tissue (2). The wart is frozen for 10-30 s until a 1-2 mm iceball halo surrounds the targeted area (17, 18). This treatment needs an average of three or four repeated treatments in the office. The highest cure rates are achieved by a frequency of two to three treatments weekly (38, 39). Cure rates for cryotherapy depend on the therapeutic regimen. Cryotherapy for plantar warts has been shown by cutting the hyperkeratotic surface and using two freezes with a complete melt in between (38, 39). For recalcitrant warts, at first, the lesion should be pared down with a scalpel then repeated cryotherapy is performed (new 2).

Cryosurgery should be done with caution in children with facial warts because of the risk of dyspigmentation and scarring. The risk for scarring is greater on the face than elsewhere on the body. Cryotherapy may induce blisters, and, when performed over the digital nervous and vascular bundle, may cause nerve and vascular damage. Patients with bleeding diatheses are not candidates for cryosurgery, because of their risk for severe hemorrhagic bullae.

Pulsed dye laser

Treatment with a pulsed dye laser results is a necrotic wart that eventually sloughs off (40). Using this option, overall cure rates in previous studies were 48% to 93% for warts located at various sites (41-44). Pulsed dye laser therapy was reported to be as effective as cryotherapy or cantharidin therapy (45).

Curettage, cautery

This treatment is now less commonly used due to the need for local anesthetic injection, the risk of scarring, and high rates of recurrence (46). One of the advantages of curettage and cautery is providing tissue biopsy for histopathological examination when the diagnosis is uncertain.

CO_2 laser

CO_2 laser emits infrared light that is absorbed by water, nonselective thermal tissue destructive result. This laser may be useful for recalcitrant periungual and subungual warts. Fractional CO_2 laser-assisted topical imiquimod may provide benefits for recalcitrant warts in children (47).

Immunotherapy

Intralesional immunotherapy

This therapeutic method makes the immune system recognize certain viral and fungal antigens (48, 49). The probable mechanism is a delayed hypersensitivity reaction induced by these antigens, which increases the ability of the immune system to recognize and remove the HPV (50). Immunotherapy with Candida antigen is effective due to the high prevalence of immunity to Candida among the general population (51). Intralesional injection of Candida antigen was effective and safe for the treatment of recalcitrant and multiple warts (52). Candida antigen improves widespread cell-mediated immunity against the human papillomavirus (53, 54).

Complete clearance rates of 49% for mumps immunotherapy (MMR) and 70% for Candida immunotherapy were reported, compared with the 42% clearance rate for cryotherapy (55). The side effects were itching at the injection site (the most common), and influenza-like illness which lasted less than 24 hours and improved using nonsteroidal anti-inflammatory drugs (55). Intralesional immunotherapy is considered as the second-line therapy for plantar warts and third-line therapy for common and flat warts and MMR to be less painful and much safer than destructive methods for wart treatment (20, 56).

Another option for immunotherapy is PPD. Six sessions of treatment results in complete or near to complete resolution (57-59). PPD injection was effective against palmoplantar and periungual warts (60). Adverse effects with destructive techniques such as infection, wounding, ulcers, scarring, and hypo- or hyper-pigmentation seldom occur with utilizing intralesional antigen immunotherapy (54, 61, 62). Overall, intralesional immunotherapy is more successful in patients younger than 40 years probably because of weaker immunological responses with increasing age (63).

Squaric acid compounded as the dibutyl ester in acetone is another immunotherapy agent that is designed for home use by parents and complete clearance rates of 58% have been reported with home use and 68% with in-office use (22, 64, 65). Diphenlcyclopropenone (DCP) should be applied by a physician and clearance rates of up to 90% have been reported with DCP. Side

effects may include urticaria or severe eczematous reactions, necessitating discontinuation (66).

Autoimplantation therapy

Full-thickness excision of one wart is made, and after mincing it, the particles are introduced into a dermal pocket. Its mechanism of action is cell-mediated immunity stimulated by introducing a higher load of the same antigens at a location, then a strong immune system activation can occur (67). Post-inflammatory hypopigmentation and formation of an inflammatory nodule at the site of implantation are the potential side effects.

Occlusion with duct tape

This option is particularly attractive for use in children because it is painless, inexpensive, and carries no risk for toxicity. A study has shown that duct tape was associated with clearance of 85% of warts, while 60% of warts were cleared in the cryosurgery group (68). The mechanism is when duct tape is applied to a wart, the surrounding skin becomes moist and softens, promoting the maceration of warts. The bacteria trapped under the tape promote local inflammation that triggers an immune response that then acts against the wart virus.

Imiquimod cream 5%

This agent is a topical immune response modifier. Data suggest that imiquimod cream 5% may be an effective topical therapy in children for the treatment of recalcitrant subungual and periungual lesions. In a study, cure rates of 88.9% were reported for recalcitrant nongenital warts in children. The recommended regimen is a daily application for 5 days per week for up to 16 weeks (69). Imiquimod cream 5% can also be used as the first-line therapy for the treatment of flat warts. Side effects are limited to mild, transient erythema and pruritus, but erosions, ulcerations, and secondary bacterial infections also have been reported with the use of this agent (20, 47).

Oral immunotherapy

Studies have demonstrated that oral cimetidine alone or in combination with levamisole may be an effective treatment for warts and genital warts in children (70-78). Cimetidine stimulates Th1 cells to produce interleukin (IL)-2, IL-12, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ and their expression is correlated with improvement in cellular immunity and wart remission (79). Previous studies revealed that both cimetidine and ranitidine have clinically significant immunomodulatory effects (80), and ranitidine has only shown limited efficacy in a trial (81). Cimetidine needs to be informed of the significant risk for drug interactions.

Levamisole was introduced as an anthelmintic agent but was found to have immunomodulatory effects. Levamisole can cause leukocytopenia or skin necrosis and should be accompanied by regular measurement of blood counts. It also should be reserved for the most severe cases in children.

Quadrivalent human papillomavirus vaccination

In a case study, the quadrivalent human papillomavirus vaccine was used in children aged 9-11 years who had resistance to treatment of extragenital warts for years (82). The vaccine was well-tolerated, with minimal complications, including local swelling, lasting only for a short time, in some children. They documented that the effects seem to be age-related. It is well known that papillomavirus-like particles, based on L1 capsid protein, can induce a specific CD8+ activation signal (83). Further placebo-controlled randomized studies are needed to perform in patients with different age groups.

Prevention

- The following recommendations can help stop warts from spreading:

- Avoid direct contact with warts.

- Don’t scratch or pick a wart.

- Wash your hands after touching a wart.

- Don’t bite your nails or suck fingers that have warts on them.

- Cover warts with a plaster when swimming.

- Take care not to cut a wart when shaving or clipping areas that have warts.

- Don’t share towels, flannels, socks, or shoes.

- Change your socks daily if you have a plantar wart.

- Don’t walk barefoot in public places if you have a plantar wart.

4. Conclusion

Recalcitrant warts are defined as lesions which are failed to resolve by repeated treatments. This condition is different from recurrent warts that resolve and then recur. The ideal treatment of warts in children is effective, painless, with no scars, no recurrence and to induce life-long immunity. Topical treatments such as 5% imiquimod or 5-FU creams should be tried before using intralesional injection and destructive treatments. Combination therapy may have a higher chance of cure. In doubtful cases, biopsies should be performed to exclude premalignant or malignant lesions that can mimic warts.

Ethical Considerations

Compliance with ethical guidelines

This paper was a review with no intervention.

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Authors contributions

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Conflicts of interest

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References

1. Plasencia JM. Cutaneous warts: Diagnosis and treatment. Primary Care. 2000; 27(2):423-34. [DOI:10.1016/S0095-4543(05)70204-9]

2. Leung L. Recalcitrant nongenital warts. Australian Family Physician. 2011; 40(1-2):40-2. [PMID]

3. Cobb MW. Human papillomavirus infecton. Journal of the American Academy of Dermatology. 1990; 22(4):547-66. [DOI:10.1016/0190-9622(90)70073-Q]

4. Larsson PA, Lidén S. Prevalence of skin diseases among adolescents 12-16 years of age. Acta Dermato Venereologica. 1980; 60(5):415-23. [PMID]

5. Kilkenny M, Marks R. The descriptive epidemiology of warts in the community. Australasian Journal of Dermatology. 1996; 37(2):80-6. [DOI:10.1111/j.1440-0960.1996.tb01010.x] [PMID]

6. Kilkenny M, Merlin K, Young R, Marks R. The prevalence of common skin conditions in Australian school students: 1. Common, plane and plantar viral warts. British Journal of Dermatology. 1998; 138(5):840-5. [DOI:10.1046/j.1365-2133.1998.02222.x] [PMID]

7. Bruggink SC, de Koning MNC, Gussekloo J, Egberts PF, Ter Schegget J, Feltkamp MCW, et al. Cutaneous warts-associated HPV types: Prevalence and relation with patient characteristics. Journal of Clinicla Virology. 2012; 55(3):250-5. [DOI:10.1016/j.jcv.2012.07.014] [PMID]

8. Massing AM, Epstein WL. Natural history of warts. A two-year study. Arch Dermatolology. 1963; 87:306-10. [DOI:10.1001/archderm.1963.01590150022004] [PMID]

9. Kwok CS, Gibbs S, Bennett C, Holland R, Abbott R. Topical treatments for cutaneous warts. Cochrane Database Systematic Review. 2012; (9):CD001781. [DOI:10.1002/14651858.CD001781.pub3] [PMID]

10. Atzori L PA, Ferreli C. Extensive and recalcitrant verrucae vulgares of the great toe treated with imiquimod 5% cream. Journal of the European Academy Dermatology and Venereology. 2003; 17(3):366-7. [DOI:10.1046/j.1468-3083.2003.00792_14.x] [PMID]

11. Keogh-Brown MR, Fordham RJ, Thomas KS, Bachmann MO, Holland RC, Avery AJ, et al. To freeze or not to freeze: A cost-effectiveness analysis of wart treatment. British Journal of Dermatology. 2007; 156(4):687-92. [DOI:10.1111/j.1365-2133.2007.07768.x] [PMID]

12. Hazard K, Karlsson A, Andersson K, Ekberg H, Dillner J, Forslund O. Cutaneous human papillomaviruses persist on healthy skin. Journal of Investigative Dermatology. 2007; 127(1):116-9. [DOI:10.1038/sj.jid.5700570] [PMID]

13. Weitzner JM, Fields KW, Robinson MJ. Pediatric bowenoid papulosis: Risks and management. Pediatric Dermatology. 1989; 6(4):303-5. [DOI:10.1111/j.1525-1470.1989.tb00914.x] [PMID]

14. Gül Ü, Kılıç A, Gönül M, Çakmak SK, Bayis SS. Clinical aspects of epidermodysplasia verruciformis and review of the literature. International Journal of Dermatology. 2007; 46(10):1069-72. [DOI:10.1111/j.1365-4632.2006.03014.x] [PMID]

15. Crequer A, Picard C, Patin E, D'Amico A, Abhyankar A, Munzer M, et al. Inherited MST1 deficiency underlies susceptibility to EV-HPV infections. PLoS One. 2012; 7(8):e44010. [DOI:10.1371/journal.pone.0044010] [PMID] [PMCID]

16. Bruggink SC, Eekhof JAH, Egberts PF, van Blijswijk SCE, Assendelft WJJ, Gussekloo J. Natural course of cutaneous warts among primary schoolchildren: A prospective cohort study. Annals of Family Medicine. 2013; 11(5):437-41. [DOI:10.1370/afm.1508] [PMID] [PMCID]

17. Nanette B, Silverberg MD. Pediatric warts: Update on interventions. Pediatric Dermatology. 2019; 26-33. https://www.mdedge.com/dermatology/article/192293/infectious-diseases/pediatric-warts-update-interventions

18. Sterling JC, Handfield-Jones S, Hudson PM, British Association of Dermatologists. Guidelines for the management of cutaneous warts. British Journal of Dermatology. 2001; 144(1):4-11.[DOI:10.1046/j.1365-2133.2001.04066.x] [PMID]

19. Brodell RT, Johnson SM. Warts: Diagnosis and management: An evidence based approach. New York: Martin Dunitz: 2003. [DOI:10.3109/9780203011584]

20. Gibbs S, Harvey I, Sterling JC, Stark R. Local treatments for cutaneous warts. Cochrane Database Systematic Reviews. 2004; (3):CD001781. [DOI:10.1002/14651858.CD001781] [PMID]

21. López-López D, Agrasar-Cruz C, Bautista-Casasnovas A, Alvarez-Castro CJ. [Application of cantharidin, podophyllotoxin, and salicylic acid in recalcitrant plantar warts. A preliminary study (Spanish)]. Gaceta medica de Mexico. 2015; 151(1):14-9. [PMID]

22. López López D, Fernández JMV, Iglesias MEL, Castro CÁ, Morales CR, Sánchez MMG, et al. Safety and effectiveness of cantharidin-podophylotoxin- salicylic acid in the treatment of recalcitrant plantar warts. Dermatologic Therapy. 2016; 29(4):269-73. [DOI:10.1111/dth.12356] [PMID]

23. Moed L, Shwayder TA, Chang MW. Cantharidin revisited. Archives of Dermatology. 2001; 137(10):1357-60. [DOI:10.1001/archderm.137.10.1357] [PMID]

24. Silverberg NB, Lim JK, Paller AS, Mancini AJ. Squaric acid immunotherapy for warts in children. Journal of American Academy of Dermatology. 2000; 42(5 Pt 1):803-8. [DOI:10.1067/mjd.2000.103631] [PMID]

25. Vanhooteghem O, Richert B, de la Brassinne M. Raynaud phenomenon after treatment of verruca vulgaris of the sole with intralesional injection of bleomycin. Pediatric-Dermatololy. 2001; 18(3):249-51. [DOI:10.1046/j.1525-1470.2001.018003249.x] [PMID]

26. al Aboosi M. Treatment of plane warts by tretinoin induced irritant reaction. International Journal of Dermatology. 1994; 33(11):826-7. [DOI:10.1046/j.1525-1470.2001.018003249.x] [PMID]

27. Fernandez-Morano T, del Boz J, González-Carrascosa M, Tortajada B, de Troya M. Topical cidofovir for viral warts in children. Journal of the European Academy of Dermatolog Venereology. 2011; 25(12):1487-9. [DOI:10.1111/j.1468-3083.2010.03961.x] [PMID]

28. De Socio GVL, imonetti S, Rosignoli D, Minga P, Baldelli F. Topical cidofovir for severe warts in a patient affected by AIDS and Hodgkin's lymphoma. International Journal of STR & AIDS. 2008; 19(10):715-6. [DOI:10.1258/ijsa.2008.008065] [PMID]

29. Clouth A, Schöfer H. Treatment of recalcitrant facial verrucae vulgares with sinecatechins (green tea catechins) ointment. Journal of European Academy and Dermatology Venereology. 2015; 29(1):178-9. [DOI:10.1111/jdv.12341] [PMID]

30. Alcántara González J, Pérez Carmona L, Ruano del Salado M, Calzado Villarreal L. Extragenital warts treated with sinecatechins ointment. Actas Dermo-Sifiliográficas (English Edition). 2015; 106(2):139-40. [DOI:10.1016/j.adengl.2014.12.005]

31. Deeb M, Levy R, Pope E, Lara-Corrales I. Sinecatechins ointment for the treatment of warts in children. Pediatric Dermatology. 2019; 36(1):121-4. [DOI:10.1111/pde.13653] [PMID]

32. Raghukumar S, Ravikumar BC, Vinay KN, Suresh MR, Aggarwal A, Yashovardhana DP. Intralesional Vitamin D3 injection in the treatment of recalcitrant warts: A novel proposition. Journal of Cutaneous Medicine and Surgery. 2017; 21(4):320-4. [DOI:10.1177/1203475417704180] [PMID]

33. Moscarelli L, Annunziata F, Mjeshtri A, Paudice N, Tsaloukos A, Zanazzi M, et . Successful treatment of refractory wart with a topical activated vitamin d in a renal transplant recipient. Case Reports in Transplantation. 2011. [DOI:10.1155/2011/368623] [PMID] [PMCID]

34. Labandeira J, Vázquez-Blanco M, Paredes C, Suárez-Penaranda JM, Toribio J. Efficacy of topical calcipotriol in the treatment of a giant viral wart. Pediatric Dermatology. 2005; 22(4):375-6. [DOI:10.1111/j.1525-1470.2005.22425.x] [PMID]

35. Raza N, Ahmed Khan D. Zinc deficiency in patients with persistent viral warts. Journal of the College of Physicians and Surgeone Pakistan. 2010; 20(2):83-6. [PMID]

36. De Luca C, Kharaeva Z, Raskovic D, Pastore P, Luci A, Korkina L. Coenzyme Q(10), vitamin E, selenium, and methionine in the treatment of chronic recurrent viral mucocutaneous infections. Nutrition. 2012; 28(5):509-14. [DOI:10.1016/j.nut.2011.08.003] [PMID]

37. Cassano N, Ferrari A, Fai D, Pettinato M, Pellè S, Del Brocco L, et al. Oral supplementation with a nutraceutical containing Echinacea, methionine and antioxidant/immunostimulating compounds in patients with cutaneous viral warts. Giornale Italiano di Dermatologia e Venereologia. 2011; 146(3):191-5. [PMID]

38. Bunney MH, Nolan MW, Williams DA. An assessment of methods of treating viral warts by comparative treatment trials based on a standard design. British Journal of Dermatology. 1976; 94(6):667-79. [DOI:10.1111/j.1365-2133.1976.tb05167.x] [PMID]

39. Bourke JF, Berth-Jones J, Hutchinson PE. Cryotherapy of common viral warts at intervals of 1, 2, and 3 weeks. British Journal of Dermatology. 1995; 132(3):433-6. [DOI:10.1111/j.1365-2133.1995.tb08678.x] [PMID]

40. Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. British Journal of Dermatology. 1992; 127(3):262-5. [DOI:10.1111/j.1365-2133.1992.tb00125.x] [PMID]

41. Hruza GJ. Laser treatment of epidermal and dermal lesions. Dermatologic Clinics. 2002; 20(1):147-64. [DOI:10.1016/S0733-8635(03)00053-6]

42. Goldman M, Fitzpatrick RE. Cutaneous laser surgery: The art and science of selective photothermolysis. Maryland

Heights: Mosby Year Book; 1999. https://books.google.com/books?id=DfBsAAAAMAAJ&q

43. Borovoy MA, Borovoy M, Elson LM, Sage M. Flashlamp pulsed dye laser (585 nm). Treatment of resistant verrucae. Journal of the American Podiatric Medical Association. 1996; 86(11):547-50. [DOI:10.7547/87507315-86-11-547] [PMID]

44. Tan OT, Hurwitz RM, Stafford TJ. Pulsed dye laser treatment of recalcitrant verrucae: a preliminary report. Lasers in Surgery and Medicine. 1993; 13(1):127-37. [DOI:10.1002/lsm.1900130120] [PMID]

45. Robson KJ, Cunningham NM, Kruzan KL, Patel DS, Kreiter CD, O'Donnell MJ, et al. Pulsed-dye laser versus conventional therapy in the treatment of warts: A prospective randomized tria. Journal of American Academy Dermatology. 2000; 43(2 Pt 1):275-80. [DOI:10.1067/mjd.2000.106365] [PMID]

46. Duthie DA, McCALLUM DI. Treatment of plantar warts with elastoplast and podophyllin. BMJ. 1951; 2(4725):216-8. [DOI:10.1136/bmj.2.4725.216] [PMID] [PMCID]

47. Park SM, Kim GW, Mun JH, Song M, Kim HS, Kim BS, et al. Fractional laser-assisted topical imiquimod 5% cream treatment for recalcitrant common warts in children: A pilot study. Dermatologic Surgery. 2016; 42(12):1340-6. [DOI:10.1097/DSS.0000000000000885] [PMID]

48. Nofal A, Nofal E, Yosef A, Nofal H. Treatment of recalcitrant warts with intralesional measles, mumps, and rubella vaccine: A promising approach. International Journal of Dermatology. 2015; 54(6):667-71. [DOI:10.1111/ijd.12480] [PMID]

49. Na CH, Choi H, Song SH, Kim MS, Shin BS. Two-year experience of using measles, mumps and rubella vaccine as intralesional immunotherapy for warts. Clinical and Exp erimental Dermatology. 2014; 39(5):583-9. [DOI:10.1111/ced.12369] [PMID]

50. Zamanian A, Mobasher P, Jazi GA. Efficacy of intralesional injection of mumps-measles-rubella vaccine in patients with warts. Advanced Biochemical Research. 2014; 3:107. [DOI:10.4103/2277-9175.129701] [PMID] [PMCID]

51. Ohri LK, Manley JM, Chatterjee A, Cornish NE. Pediatric case series evaluating a standarized Candida albicans skin test product. Annals of Pharmacotherapy. 2004; 38(6):973-7. [DOI:10.1345/aph.1D518] [PMID]

52. Muñoz Garza FZ, Roé Crespo E, Torres Pradilla M, Aguilera Peirò P, Baltà Cruz S, Hernández Ruiz ME, et al. Intralesional Candida Antigen Immunotherapy for the Treatment of Recalcitrant and Multiple Warts in Children. Pediatric Dermatology. 2015; 32(6):797-801. [DOI:10.1111/pde.12667] [PMID]

53. Johnson SM, Horn TD. Intralesional immunotherapy for warts using a combination of skin test antigens: A safe and effective therapy. Journal of drugs in dermatology. 2004; 3(3):263-65. [PMID]

54. Clifton MM, Johnson SM, Roberson PK, Kincannon J, Horn TD. Immunotherapy for recalcitrant warts in children using intralesional mumps or Candida antigens. Pediatric Dermatology. 2003; 20(3):268-71. [DOI:10.1046/j.1525-1470.2003.20318.x] [PMID]

55. Johnson SM, Roberson PK, Horn TD. Intralesional injection of mumps or Candida skin test antigens: A novel immunotherapy for warts. Archives of Dermatology. 2001; 137(4):451-5. [PMID]

56. Rezai MS, Ghasempouri H, Asqary Marzidareh O, Yazdani Cherati J, Rahmatpour Rokni G. Intralesional injection of the measlses-mumps- rubella vaccine into resistant palmoplantar warts: A randomized controlled trial. Iranian Journal of Medical Sciences. 2019; 44(1):10-7. [PMID] [PMCID]

57. Amirnia M, Khodaeiani E, Fouladi DF, Masoudnia S. Intralesional immunotherapy with tuberculin purified protein derivative (PPD) in recalcitrant wart: A randomized, placebo-controlled, doubleblind clinical trial including an extra group of candidates for cryotherapy. Journal of Dermatological Treatment. 2016; 27(2):173-8. [DOI:10.3109/09546634.2015.1078871] [PMID]

58. Lahti A, Hannuksela M. Topical immunotherapy with tuberculin jelly for common warts. Archives of Dermatological Research. 1982; 273(1-2):153-4. [DOI:10.1007/BF00509040] [PMID]

59. Abd-Elazeim FMA, Mohammed GFA, Fathy A, Mohamed RW. Evaluation of IL-12 serum level in patients with recalcitrant multiple common warts, treated by intralesional tuberculin antigen. Journal of Dermatological Treatment. 2014; 25(3):264-7. [DOI:10.3109/09546634.2013.768760] [PMID]

60. Wananukul S, Chatproedpral S, Kittiratsacha P. Intralesional immunotherapy using tuberculin PPD in the treatment of palmoplantar and periungual warts. Asian Biomedicine. 2009; 3(6):739-43.

61. Mulhem E, Pinelis S, Hills, R. Treatment of nongenital cutaneous warts. American Family Physician. 2011; 84(3):288-93.

62. Nofal A, Salah E, Nofal E, Yosef A. Intralesional antigen immunotherapy for the treatment of warts: current concepts and future prospects. American Journal of Clinical Dermatology. 2013; 14(4):253-60. [DOI:10.1007/s40257-013-0018-8] [PMID]

63. Horn TD, Johnson SM, Helm RM, Roberson PK. Intralesional immunotherapy of warts with mumps, Candida, and Trichophyton skin test antigens: A single-blinded, randomized, and controlled trial. Archives of Dermatology. 2005; 141(5):589-94. [DOI:10.1001/archderm.141.5.589]

64. Lee AN, Mallory SB. Contact immunotherapy with squaric acid dibutylester for the treatment of recalcitrant warts. J ournal of the American Academy of Dermatology. 1999; 41(4):595-9. [PMID]

65. Pandey S, Wilmer EN, Morrell DS. Examining the efficacy and safety of squaric acid therapy for treatment of recalcitrant warts in children. Pediatric Dermatology. 2015; 32(1):85-90. [DOI:10.1111/pde.12387] [PMID]

66. Upitis JA, Krol A. The use of diphencyclopropenone in the treatment of recalcitrant warts. Journal of Cutaneous Medicine and Surgery. 2002; 6(3):214-7. [DOI:10.1007/s10227-001-0050-9] [PMID]

67. Thappa Dm, Chiramel MJ. Evolving role of immunotherapy in the treatment of refractory warts. Indian Dermatology Online Journal. 2019; 7(5):364-70. [DOI:10.4103/2229-5178.190487] [PMID] [PMCID]

68. Focht DR, Spicer C, Fairchok MP. The efficacy of duct tape vs cryotherapy in the treatment of verruca vulgaris. Archives of Pediatrics and Adolescent Medicine. 2002; 156(10):971-4. [DOI:10.1001/archpedi.156.10.971] [PMID]

69. Grussendorf-Conen EI, Jacobs S. Efficacy of imiquimod 5% cream in the treatment of recalcitrant warts in children. Pediatric Dermatology. 2002; 19(3):263-6. [DOI:10.1046/j.1525-1470.2002.00083.x] [PMID]

70. Gooptu C, Higgins cR, James MP. Treatment of viral warts with cimetidine: An open-label study. Clinical Experimental Dermatology. 2000; 25(3):183-5. [DOI:10.1046/j.1365-2230.2000.00608.x] [PMID]

71. Parsad D, Pandhi R, Juneja A, Negi KS. Cimetidine and levamisole vs cimetidine alone for recalcitrant warts in children. Pediatric Dermatology. 2001; 18(4):349-52. [DOI:10.1046/j.1525-1470.2001.01951.x] [PMID]

72. Franco I. Oral cimetidine for the management of genital and perigenital warts in children. Journal of Urology. 2000; 164(3):1074-5. [DOI:10.1016/S0022-5347(05)67254-0]

73. Chern E, Cheng YW. Treatment of recalcitrant periungual warts with cimetidine in pediatrics. Journal of Dermatology Treatment. 2010; 21(5):314-6. [DOI:10.3109/09546630903164891] [PMID]

74. Orlow SJ, Paller A. Cimetidine therapy for multiple viral warts in children. Journal of the American Academy of Dermatology. 1993; 28(5):794-6. [DOI:10.1016/S0190-9622(09)80278-8]

75. Fischer G, Rogers M. Cimetidine therapy for warts in children. Journal of the American Academy of Dermatology. 1997; 37(2):289-90. [DOI:10.1016/S0190-9622(97)80150-8]

76. Bauman C, Francis JS, Vanderhooft S, Sybert VP. Cimetidine therapy for multiple viral warts in children. Journal of the American Academy of Dermatology. 1996; 35(2):271-2. [DOI:10.1016/S0190-9622(96)90351-5]

77. Rogers CJ, Gibney MD, Siegfried EC, Harrison BR, Glaser DA. Cimetidine therapy for recalcitrant warts in adults: Is it any better than placebo? Journal of the American Academy of Dermatology. 1999; 41(1):123-7. [DOI:10.1016/S0190-9622(99)70421-4]

78. Yilmaz E, Alposy E, Basaran E. Cimetidine therapy for warts: A placebo-controlled, double blind study. Journal of the American Academy of Dermatology. 1996; 34(6):1005-7. [DOI:10.1016/S0190-9622(96)90279-0]

79. Alsutany HA, Alshibly IK. Immunomodulating activity of cimetidine in Iraqi children and adolescents with common warts. Medical Journal of Babylon. 2014; 11(3):547-56.

80. Elenkov IJ, Webster E, Papanicolaou DA, Fleisher TA, Chrousos GP, Wilder RL. Histamine potently suppresses human IL-12 and stimulates IL-10 production via H2 receptors. J ournal of Immunology. 1998; 161(5):2586-93. [PMID]

81. Karaman G, Sendur N, Sevk E. Ranitidine therapy for recalcitrant warts in adults: A preliminary study. Journal of the Eur opean Academy of Dermatology Venereology. 2001; 15(5):495-6. [DOI:10.1046/j.1468-3083.2001.03408.x] [PMID]

82. Abeck D, Fölster-Holst R. Quadrivalent human papillomavirus vaccination: A promising treatment for recalcitrant cutaneous warts in children. Acta Dermato Venereologica. 2015; 95(8):1017-9. [DOI:10.2340/00015555-2111] [PMID]

83. Bellone S, El-Sahwi K, Cocco E, Casagrande F, Cargnelutti M, Palmieri M, et al. Human papillomavirus type 16 (HPV- 16) virus-like particle L1-specific CD8+ cytotoxic T lymphocytes (CTLs) are equally effective as E7-specific CD8+ CTLs in killing autologous HPV-16-positive tumor cells in cervical cancer patients: implications for L1 dendritic cellbased therapeutic vaccines. Journal of Virology. 2009; 83(13):6779-89. [DOI:10.1128/JVI.02443-08] [PMID] [PMCID]

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