Plantar Warts: Epidemiology, Pathophysiology, and Clinical Management

Dexter Jordan Witchey, MPAS, PA-C; Nichole Brianne Witchey, MPAS, PA-C; Michele Marie Roth-Kauffman, JD, MPAS, PA-C; Mark Kevin Kauffman, DO, MS

From Gannon University in Erie, Pennsylvania (Mr Witchey, Ms Witchey, and Dr Roth-Kauffman); and Lake Erie College of Osteopathic Medicine in Bradenton, Florida (Dr Kauffman).

Financial Disclosures: None reported.

Support: Funding for this article was provided by the Cooney-Jackman Endowed Professorship.

Address correspondence to Mark Kevin Kauffman DO, MS, Med Ed, 4800 Lakewood Ranch Blvd, Bradenton, FL 34212-4953.

Email: mkauffman@lecom.edu

Submitted May 17, 2017; revision received August 15, 2017; accepted August 23, 2017.

Verrucae plantaris (plantar warts) are common cutaneous lesions of the plantar aspect of the foot that are caused by the human papillomavirus (HPV). Ubiquitous in our environment, asymptomatic infection with HPV occurs frequently, with most infections controlled or cleared by cellular and humoral immune responses. However, certain populations have been observed to manifest plantar warts at higher rates compared with the general population, placing them at increased risk for wart-induced pain and complications. Plantar warts shed HPV, which can then infect other sites in the plantar region or spread to other people. Although controlling risk factors is useful in preventing infection, the pervasive nature of HPV makes these preventive measures frequently impractical. This literature review outlines the current knowledge regarding the relationship between plantar wart pathophysiology, HPV transmission, and epidemiologic characteristics. Given the high propensity for treatment resistance of plantar warts and no established, practical, and reliable method of prevention, HPV prophylaxis for populations that demonstrate high rates of plantar warts may be of benefit in controlling the spread of lesions.

J Am Osteopath Assoc. 2018;118(2):92-105
doi:10.7556/jaoa.2018.024

Keywords: HPV, human papillomavirus, plantar wart

Plantar warts, or *verrucae plantaris*, are cutaneous lesions on the plantar aspect of the foot that are caused by the infection of keratinocytes with the human papillomavirus (HPV).[1] Human papillomavirus is pervasive.[1] While most people are asymptomatic carriers of HPV, 2% of the general population seeks medical care for warts annually.[1-3] Plantar warts exhibit an annual incidence of 14%.[4] The majority of cases occur in children and adolescents.[5,6] However, other populations, such as immunocompromised patients, are at increased risk for acquiring plantar warts, which can lead to pain, embarrassment, and, in rare cases, cancer.[6,7]

Once a plantar wart is established, it sheds HPV via desquamated epithelial cells. The viral particles can subsequently infect other sites and hosts.[8] Viral transmission is facilitated by current therapeutic strategies for plantar warts that are based on retroactively treating the wart. Current treatment methods have been used with variable success, as the lesions are notoriously resistant to treatment and recur frequently.[3,9,10] Also, few of these treatment methods actually address the root of the problem—HPV

infection.[11] The only preventive measures that have been established involve controlling exposure to HPV, which is often impractical given its ubiquitous nature.[5,12] Given the high propensity for treatment resistance of plantar warts and no established practical and reliable method of prevention, medically based HPV prophylaxis for populations that demonstrate high rates of plantar warts may be of benefit in controlling lesion spread and transmission.[13,14]

This review of literature outlines the current knowledge regarding the relationship between plantar wart pathophysiology, HPV transmission, and epidemiologic characteristics. Diagnostic considerations are reviewed, as well as currently available treatment modalities with their respective advantages, disadvantages, and success rates.

Etiology

The cause of plantar warts, HPV, is not a single virus but rather a group of nonenveloped DNA viruses that are categorized into more than 150 types according to similarities within their DNA sequences. These types are then further classified into species. Species are categorized into 1 of 5 genera, including α, β, γ, μ, and ν.[11,15,16] The species of HPV can also be broadly categorized according to whether they preferentially cause cutaneous or mucosal lesions or both.[8,16]

The types of HPV that have been isolated from plantar warts include HPV-1, -2, -3, -4, -27, -29, -57, -60, -63, -65, -66, and -69.[15,17,18] In one randomized controlled trial, 88% of plantar warts were caused by HPV-1, -2, -27, or -57.3[18] Most plantar warts are attributed to HPV-1, however.[19] While most plantar wart–causing HPV types belong to the categories of cutaneous or mucosal/cutaneous lesions, there are rare instances, such as in immunocompromised persons, in which a mucosal HPV type can cause cutaneous lesions, including plantar warts.[16,20] Human papillomavirus is species specific to human hosts, and humans are the primary reservoir of the virus.[1,21,22] The virus is transmitted via contact with HPV particles.[4,23,24]

Pathophysiology

Human papillomavirus can survive months to years on surfaces.[21,24,25] Infection of a host requires direct contact with viral particles, which can occur through either direct contact via a plantar wart or indirect contact via fomites, such as flooring, socks, shoes, towels, and sports equipment.[4,23] There is no systemic dissemination or viremic phase to HPV infection. As such, contact with body fluids, except those directly from the plantar wart itself, does not transmit HPV.[14,21] Preexistent microtrauma of the epidermal barrier of the plantar aspect of the foot allows entry of the virus on contact.[5,26-29] Once in contact with a host, HPV gains entry to the basal epithelial layer, where actively dividing stem cells are located.[29,30] In the basal epithelium, the virus binds with cellular receptors and is subsequently taken up by the now-infected cell.[8,31] After an incubation period of 1 to 20 months, viral DNA is then established within the host cell, usually without integration into the host cell genome.[24,29,30]

Once infection occurs, 3 outcomes are possible: clearance of the infection with resultant immunity to that particular HPV type, latent infection, or clinically manifested infection as a plantar wart.[4] After infection, if the virus is not cleared, the host basal keratinocyte is stimulated to divide and replicate viral DNA via HPV E1 and E2 proteins.[29,30] This process produces numerous stem cells that each contain 20 to 100 copies of the viral DNA.[11,29] The basal stem cells contain very low levels of viral proteins, which enhances the virus's ability to evade the host's immune response.[11,27,30] As the basal cells undergo normal differentiation into keratinocytes, they progress toward the outer surface of the epithelium. At the same time, the viral genome promoter region is activated, leading to increased production of viral proteins that enhance HPV genome amplification within each differentiating cell. It is thought that E5, a membrane protein produced via the

viral DNA template, serves to enhance signaling from growth factor, which in turn maintains the cell's capacity for DNA replication.[29,30] Once viral DNA copies are sufficient, L1 and L2 viral coat proteins are expressed by surface keratinocytes.[11] Protein E2 recruits viral DNA copies to the host cell nucleus, where the viral DNA is packaged into capsids composed of proteins L1 and L2.[11,30] The infectious viral particles can then be released in high numbers from desquamated keratinocytes on the surface of the plantar wart to infect other sites or hosts.[8]

The induction of cellular replication throughout the process of viral genome amplification leads to the hyperkeratinized papule that constitutes a plantar wart.[31] Plantar warts tend to develop at areas of increased pressure on the sole of the foot, including the heel and metatarsal heads.[5,25,27] Such pressure points are regions of increased microtrauma to the epidermal barrier, which increases the likelihood of HPV invasion.[15,26] Owing to the pressure exerted on the forming plantar wart, the lesion tends to progress deeper into the skin (creating an "iceberg effect") as opposed to forming a rounded papule, which can contribute to their resistance to therapy.[1,26] As a result of normal sloughing of the epithelium, viral particles are released and may be transmitted to surfaces where the virus will lie until picked up by a new host or spread to adjacent sites (autoinoculation).[7,21] Thus, once a plantar wart develops, the host is susceptible to additional warts developing.[23]

Sixty-five percent to 78% of cutaneous warts have been shown to regress within 2 years.[32] In persons older than 12 years, the rate of spontaneous regression significantly decreases.[2,33] Wart regression relies on the development of an effective cellular immune response.[8,34] However, plantar warts may develop in an otherwise healthy person when HPV gains entry to the epithelium and evades the host's immune response.[35] In the most healthy persons, HPV infections are controlled by an immune response that begins on contact with the HPV particle.[1,8,27] The viral antigen is first taken up by Langerhans cells of the epidermis, which then enter the regional lymphatic drainage and thereby enter a lymph node. There they present the antigen to T cells, which are activated and induce an antigen-specific immune response in the area of viral penetration. The antigen-presenting cells activate keratinocytes to release inflammatory cytokines that promote migration of neutrophils and monocytes, activation and migration of helper T cells, maturation of B cells, and activity of natural killer cells. Tumor necrosis factor α, which is released from keratinocytes, improves the recognition of virally infected keratinocytes by T cells, which are then responsible for destroying the infected keratinocytes.[8] This response should lead to eradication of the infection and prevent a plantar wart from occurring or lead to regression of established plantar warts. If this process fails, a persistent plantar wart is established.[36] Humoral immunity, if established by antibody-producing B cells, prevents future reinfection by that HPV type.[27]

Epidemiology and Risk Factors

It is estimated that 40% of the population is infected with HPV, and in 7% to 12%, a wart develops.[5,14,24] Plantar warts exhibit an annual incidence of 14% in the general population.[4] Risk factors center about increased exposure to HPV, increased risk of epidermal barrier penetration, and inappropriate immune responses (**Table 1**). Plantar wart incidence varies with age, sex, race, and health status. Further, geographic, seasonal, behavioral, and socioeconomic factors are associated with variable rates of plantar wart incidence. It is estimated that only 0.84% of the United States population have plantar warts, whereas 12.9% of the Russian population has been shown to have plantar warts.[32] Furthermore, populations living in northern England have been noted to exhibit an increased incidence of plantar warts compared with populations in southern England.[44] Throughout all regions, rates of plantar warts are noted to increase during winter months.[39]

Two percent of the adult population and 6% of the pediatric population seek care for a plantar wart

annually.[3] Plantar warts occur most frequently in children and adolescents, although they are rare in patients younger than 5 years.[6,37] Young children experience a steady increase in warts as they age until a peak incidence between 12 and 16 years of age.[26] Silverberg and Silverberg[38] found that among children, 62.6% to 85.3% of whites and 14.7% to 37.4% of blacks had warts, and they reported that nonwhite skin type was associated with a lower incidence of warts. Children who are white, part of households with higher incomes, higher maximum levels of parental education, 2 parents, and family members with plantar warts have an increased risk of plantar warts.[4,38] Having classmates with warts also poses a risk of transmission.[4] In adulthood, there is a decline in rates of plantar warts in the general population.[3] Although adults experience fewer plantar warts, their lesions tend to have a longer duration and be more resistant to treatment.[2,26]

In terms of the sex distribution of plantar warts, incidence rates have been noted to change depending on patient age. The peak incidence of plantar warts occurs at age 13 years among females and at 14.5 years among males.[9,23] In childhood, girls have been noted to be at higher risk than boys.[1] However, among adults, men have higher rates of warts than women.[1,41] Throughout the lifetime, females tend to experience higher rates of plantar warts than males.[27]

Two of the most significant risk factors for developing plantar warts are (1) having a preexistent wart and (2) having close contact with someone who has a preexistent wart.[4,39] Plantar warts have a very high viral load, which increases the rate of viral shedding and the likelihood of contaminating adjacent body surfaces, inanimate communal surfaces, or close contacts.[23,24,39] Walking barefoot also increases the likelihood of contacting HPV, especially if one walks barefoot in an area where others have walked barefoot, such as pool decks or communal showers.[6,24,39] It is believed that the rough surfaces of a swimming pool promote microtrauma to the sole of the foot, and the warm, moist environment of a communal shower promotes viral survival and infectivity.[5,24] One study demonstrated a plantar wart incidence rate of 27% for communal shower users, compared with a 1.25% incidence rate for communal shower nonusers.[23] Communal locker room use alone has not been shown to increase plantar wart risk.[23]

Athletes have been observed to have higher rates of warts, including plantar warts, compared with the general population.[23] Hyperhidrosis of the feet is associated with increased risk of plantar warts.[45] Some athletes, such as gymnasts or dancers, have the predilection for practicing and performing barefoot on surfaces where others have also walked barefoot.[27] Such behavior could increase exposure to HPV.[13,27] Sharing equipment increases the risk of HPV infection and warts.[27,43]

Table 1.
Risk Factors for Plantar Wart Development

Risk Factor	Notes
Sex	Increased rate in girls[1]; increased rate in men[1]; increased lifetime risk in females[27]
Age	Rare in children aged <5 y[21]; children aged ≥5 y and adolescents most affected[6,37]; peak incidence at age 12-16 y[26]
Immune status	Increased risk in immunocompromised patients[16]
Race	More common in whites[4,38]
Activities	Athletics[23]; occupation (students, manual laborers)[6]; walking barefoot[24,39]; communal shower use[23]; locker room use[23]; swimming pool use[24]; bathroom use[26]; pedicure with improperly sanitized tools[40]
Environment	Close contact with an affected person (family members, classmates, teammates)[5]; dual-parent homes[38]; warm, moist environments[5,25]; sun exposure
Season	More common in winter months[39]
Socioeconomic status	High household income[38]; advanced level of education in household[38]
Trauma	Contact with rough surfaces,[26,39]; weight-bearing points most affected[39,41]; wet, macerated skin[26,39]; breaks in skin[39]
Preexistent wart	Autoinoculation[25,42]
Hygiene	Sharing unwashed shoes, socks, equipment, and other personal items[43,44]; using nail files and pumice stones used for warts on other areas of skin[19]; not changing socks daily[25]; contact with blood from a wart[14]; not wearing protective footwear in communal showers and locker rooms; poorly ventilated footwear and athletic clothing; poor personal hygiene

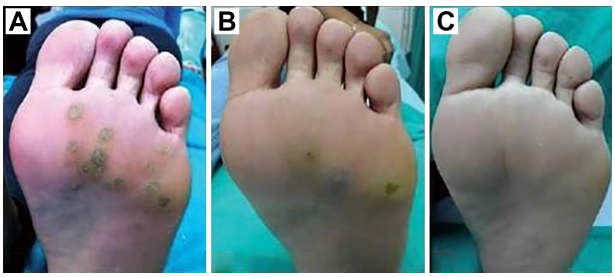

Figure 1.
Multiple plantar warts exhibiting full resolution with immunotherapy. (A) Before treatment; (B) after 2 injections of immunotherapy; (C) complete resolution after 4 injections of immunotherapy. Reprinted from Garg S, Baveja S. Intralesional immunotherapy for difficult to treat warts with *Mycobacterium* w vaccine. *J Cutan Aesthet Surg*. 2014;7(4):203-208. doi:10.4103/0974-2077.150740

Plantar warts present a significant problem to athletes, as the pain can affect the athlete's ability to ambulate.[19]

Immunocompromised patients have higher rates of plantar warts, along with increased severity and duration of the lesions.[15,16] In particular, cell-mediated immunodeficiency, including primary, secondary, and iatrogenic, has been noted to lead to increased rates of plantar warts.[16,42] Such patients may also be at increased risk of atypical HPV types as the etiologic agent of plantar warts.[15,20] For example, HPV-69, which is not typically isolated from plantar warts in the general population, has caused plantar warts in a patient infected with HIV.[20] Such lesions, especially plantar warts, have also been noted to undergo dysplastic changes and lead to verrucous carcinoma.[46-48] Malignant lesions tend to be more painful, friable, and erythematous than benign lesions.[19] Therefore, it is imperative that physicians consider that patients who present with large numbers of plantar warts or treatment-resistant plantar warts may have an underlying immunodeficiency and that patients with an established immunodeficiency and plantar warts may harbor a malignant neoplasm within the lesion.[20,39,42]

Clinical Presentation and Diagnosis

Patients with plantar warts most commonly present with pain or the sensation of a stone or swelling under their foot.[4,37] Pain most commonly occurs with activities that exert pressure on the soles of the feet.[19] Patients may also seek care because of their concern for transmitting the infection.[19,26] Patients may complain of a gradually enlarging wart on the plantar aspect of their foot or of increasing numbers of such lesions.[7,19]

Plantar areas of increased pressure, such as the heels or metatarsal heads, should be carefully examined. On gross inspection, plantar warts may appear as a singular rough, flesh-colored to yellow or grey-brown, hyperkeratotic papule, or a thickened "cobblestoned" plaque, termed a *mosaic wart,* which consists of multiple plantar warts that have coalesced (**Figure 1**).[7,36,37] A key feature of plantar warts is disruption of the normal skin lines, dermatoglyphics, which are reestablished on

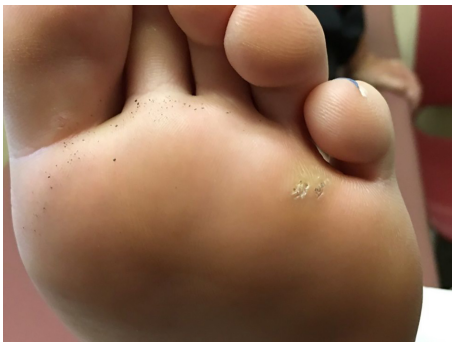

Figure 2.
Plantar wart underlying the left fourth metatarsal head. Note the presence of visible thrombosed capillaries and disruption of dermatoglyphics.

Table 2.
Currently Available Treatment Options for Patients With Plantar Warts

Treatment Method	Efficacy[a]	Advantages	Disadvantages
Wait and See	65%-78% spontaneous remission in 2 y[43,50]; 0%-58% cure rate[2,3]	Cost-effective and no side effects[3]; HPV-1 subtype has 58% cure rate[3]; children aged ≤12 y have higher spontaneous remission rate[2]	May take months to years; may recur; patient needs to alter behaviors to prevent spread of infection; not recommended for immunocompromised patients[45]; HPV-2, -27, and -57 have only a 7% cure rate[3]
Destructive			
Surgical removal (curettage,[26] cautery,[26] dissection, electrodissection)	65%-94% success rate[26,31,43]	May need only 1 treatment[7,25]; used on recalcitrant warts[7,13]; allows histopathologic examination[13]	Third-line treatment[51]; health care visit required; scarring and wart recurrence up to 30%[13,25,26]; prolonged recovery time[7]; adverse effects: pain, scarring, bleeding and infection[13,25]
Chemical cautery (silver nitrate,[26,31] phenol[31])	43%-85% cure rate[26,51,31,51]	First-line treatment[51]	Health care appointment necessary; adverse effects: excessive burns and irreversible tissue staining[26,51]
Salicylic acid (10%-60% salicylic acid [over-the-counter],[26,51] 70% salicylic acid [prescribed][9])	14.3%-84% cure rate[2,26,33]; 5%-92% cure rate[3,33,52]	First-line therapy[14,52]; safe[9,43]; self-applied[13,53]; cost-effective[7,26]; negligible pain[26,43]; well suited for use in children[2,14,26]; higher success rate in children aged ≤12 y[2]	Health care visit required for prescribed preparations; requires weeks to months of daily therapy; detailed instructions[5]; wart debulking[5,43]; risk of systemic toxicity in children[26,51]; prolonged treatment not recommended in children, pregnant woman, patients with diabetes, and patients with circulatory problems[14,31]; adverse effects: contact dermatitis, pain, erythema, blistering, skin irritation, burning sensation, and burns[5,31,51]
Formic acid	92% cure rate[26]	Cost-effective[31]	Adverse effects: infection[31]
Glycolic acid 5%	NA	Self-applied[53]; well tolerated in children[31]; no scarring[31]	NA
Pyruvic acid[31]	70% cure rate	NA	Adverse effects: hypertrophic scarring
Citric acid 50%[31]	64% cure rate	NA	NA
Monochloroacetic, bichloracetic, and trichloroacetic acid	46%-61% cure rate[31,45]	First-line treatment[7,51]; less pain[7,45]; appropriate for children[7]; used in recalcitrant warts[45]	Health care visit required; paring usually required[7]; may require multiple treatments; highly toxic and corrosive[31]; adverse effects: burning, pruritus, discomfort, stinging, dryness, fissuring, and contact sensitivity[10,51]
α-Lactalbumin-oleic acid[51]	45% cure rate	NA	Third-line treatment; health care visit required

(continued)

Table 2 (continued).
Currently Available Treatment Options for Patients With Plantar Warts

Treatment Method	Efficacy[a]	Advantages	Disadvantages
Cantharidin	Cure rate up to 80%[26,45]	No application pain[26]; less scarring[26]; suitable for children[19]	Not available in United States[26,45]; health care visit required; annular ring may form around wart[26]; prolonged treatment should be avoided in children and patients with diabetes or circulatory problems[19]; adverse effects: blistering, wart recurrence, scarring, and postoperative pain[26,31]
Cryotherapy (liquid nitrogen)	6%-65% cure rate[2,3,45]	First or second-line treatment[9,51]; safe and cost-effective[41]; healing is usually quick[41]; HPV-1 has a 65% cure rate[3]; more effective in children aged ≤12 y[2]	Health care visit required; avoid in young children[5,14,37]; postoperative pain may limit mobility[7,43,44]; 30% wart recurrence[50]; may require multiple treatments[25]; may require wart paring[26,43,44]; therapy often fails in plantar warts and reoccurring warts[3,52]; aggressive therapy increases success and risk of adverse effects[45]; use cautiously in patients with poor circulation[26,31]; adverse effects: pigment changes, scarring, erythema, edema, pain, soreness, paresthesia, tendon and/or nerve damage, and blistering[2,5,25]
Hyperthermia (hot water, exothermic patches)[26]	NA	Cost-effective; self-administration[26]	Third-line treatment[51]; no proven efficacy[26]
Radiofrequency ablation[26] and infrared coagulation[5,31]	54% cure rate[31,45]	Safe[26,31]; decrease in pain sensation[45]; less tissue necrosis[26]	Third-line treatment[51]; health care visit required[26]; multiple treatments needed[31]; 10.8% wart recurrence rate[26]
CO_2 laser	64%-71% cure rate[26]	Used on recalcitrant warts[26,53] and for immunosuppressed patients[26]	Third-line treatment[51]; expensive[5]; nonselective tissue destruction[13]; wart debulking[45]; may need multiple treatments[5]; hazards related to laser plume[26,41]; adverse effects: scarring, postoperative pain, pigmentary changes, and prolonged healing time[5,26,51]
Erbium:YAG laser	75% cure rate[26]	Used on recalcitrant warts[13,53]; more precise thermal ablation[26]; cleaner laser plume[26]; may need only 1 treatment[26]	Third-line treatment[51]; expensive[5]; 25% relapse rate[26]; 7-10 d postoperative healing[26]; surrounding erythema for 2 mo[26]; wart paring[45]; adverse effects: scarring, pain, and pigmentary changes[5,45,51]
Neodymium:YAG laser	96% cure rate[31]	No wart recurrence reported[26]; cleaner laser plume[26]; used on recalcitrant warts[31,53]	Third-line treatment[51]; health care visit required; expensive[5,45]; may require wart paring[45]; may take multiple treatments[5]; adverse

(continued)

Table 2 (continued).
Currently Available Treatment Options for Patients With Plantar Warts

Treatment Method	Efficacy[a]	Advantages	Disadvantages
			effects: scarring, pain, and pigmentary changes[5,51]
Pulsed dye laser	32%-95% cure rate[9,13,26]; 47.6% cure rate[45]	Second-line therapy[9]; relatively painless[26]; well tolerated in children[31,45]; used on recalcitrant warts[13]	Health care visit required; expensive[5]; may take multiple treatments[5,13]; may require wart debulking[31,45]; 2-4 wk to heal[26]; plantar warts do not respond well[31,38]; adverse effects: pain, hemorrhagic bullae, pigment changes, scarring, and purpura[5,26,31]
Potassium-titanyl-phosphate laser	NA	No wart recurrence reported[31]; can treat recalcitrant warts[7,8,20,31]	Third-line treatment[28]; health care visit required; may require wart paring[45]; multiple treatments may be necessary[5]; expensive[5]; adverse effects: scarring, pain, and pigment changes[5,51]
Photodynamic therapy (5-aminolaevulinic acid)[26]	58%-95% cure rate[31,54]; 83% cure rate[45]	Used in recalcitrant warts[13,51]; minimally invasive[51,54]; little to no scarring[26]	Third-line treatment[51]; health care visit required; expensive[19]; required local anesthesia[19]; may need multiple treatments[19]; adverse effects: burning sensation, pain, pruritus, tingling, erythema, and pigment changes[51,54]
Antiviral			
Glutaraldehyde 10%[26]	72% cure rate[31,51]	First-line treatment[51]; self-application[26]; painless[19]; suitable for children[19,31]	Required wart debulking[14]; adverse effects: skin staining, dryness, fissuring, deep necrosis, and contact sensitivity[14,31]
Formaldehyde	61%-80% cure rate[26,31]	Painless[19]; suitable for children[19]	Third-line treatment[51]; wart paring[14,26]; avoid in patients with eczema or allergies[26,31]; adverse effects: skin sensitization[19,26]
Antiviral drugs (cidofovir, didanosine, stavudine, efavirenz, abacavir, valaciclovir)	75%-98% cure rate[31]	Successful in immunosuppressed patients[26,31]; improved immune status[26]; well tolerated in children[31]	Health care visit required; adverse effects: local irritation and decline in renal function[31]
Antimitotic			
Bleomycin[7]	16%-97% cure rate[14,26,45]	Used on recalcitrant warts[5,14]; may need only 1 treatment[26,45]; avoids dermal exposure[26]; commonly used on plantar warts[7]	Second- or third-line treatment[9,51]; expensive[7]; long treatment length[14,45]; systemic drug exposure[26]; contraindicated in pregnant or breastfeeding women, children, immunosuppressed, and patients with vascular disease[19,26]; adverse effects: pain, burning,

(continued)

Table 2 (continued).
Currently Available Treatment Options for Patients With Plantar Warts

Treatment Method	Efficacy[a]	Advantages	Disadvantages
			erythema, edema, scarring, Raynaud phenomenon, lymphangitis, tissue necrosis, and pigmentary changes[31,53]
Retinoids (tretinoin cream, etretinate, isotetinoin, acitretin)[13,26]	54%-85% cure rate[26,31]	Topical or oral[26]; prophylactic use for HPV[26]; self-applied[53]; cost-effective and accessible[31]	Third-line treatment[51]; health care visit required; high risk of wart recurrence[26]; contraindicated in pregnant and breastfeeding women[19]; adverse effects: pain, skin dryness, and skin irritation[19,31]
Vitamin D analogs (Maxacalcitol)[31]	59% cure rate[26]	NA	NA
Dithranol 2% cream[11]	56%-71% cure rate	NA	Long treatment duration
Podophyllin	67%-81% cure rate[26,31,50]	Self-application[26]; cost-effective[26]	Inconsistent formulation[26]; contraindicated in pregnant and breastfeeding women[19]; adverse effects: pain, burning, blistering, and intense inflammatory reaction[26,31,41]
Podophyllotoxin	84.1% cure rate[26]	Self-administered[26,50]	Affects normal skin[31]; 79% recurrence rate[26,50]; can have a systemic effect[31]; contraindicated in pregnant and breastfeeding women[31]; adverse effects: pain, erythema, edema, and ulceration[19,50]
Immunotherapy			
Zinc sulfate or zinc oxide	28%-87% cure rate[26,31,51]	Used on recalcitrant warts[26,50]; safe and accessible[31]; effective in those with zinc deficiency; well-tolerated[50]; oral or topical[31]; self-administered[26]	Third-line treatment[51]; adverse effects of oral products: nausea, vomiting, and abdominal pain[31,50]; adverse effects of topical products: inflammation, pruritus, and pigmentary changes[50,51]
Echinacea[52]	Up to 86% cure rate	Self-administered	Adverse effects: mild allergic reaction
Propionium bacterium parvum[50]	80% cure rate	NA	Health care visit required; multiple treatments required; adverse effects: mild local reaction
Autoimplantation[50]	66%-73.3% cure rate	Resolution of distant warts	Health care visit required
Contact sensitizers (DCP,[26,31] SADBE,[7] diphenylcyclopropenone[7])	44%-88% cure rate[26,31]; completely cured in a single patient[51]	DCP is cost-effective[26]; used for treatment of multiple warts[26,50]; no wart recurrence[31]; used in recalcitrant warts[13,50]	Third-line treatment[51]; health care visit required; not typically stocked by family physicians[7]; multiple treatments required; reduced clearance or prolonged treatment in immunosuppressed[13,31]; SADBE is expensive[50]; not suitable for children[13]; adverse effects: pigment

(continued)

Table 2 (continued).
Currently Available Treatment Options for Patients With Plantar Warts

Treatment Method	Efficacy[a]	Advantages	Disadvantages
			changes, pain, erythema, edema, regional lymphadenopathy, pruritus, mild burning, desquamation, blistering, multiforme-like reaction, urticaria, allergic contact dermatitis, eczematous eruption, and flu-like symptoms[13,53]
Intralesional injection of interferon	44.4%-62% cure rate[13,26,50]	Used on recalcitrant warts[5,13]; minimal scarring[19]; well tolerated in immunosuppressed[31,50]	Second- or third-line treatment[9,51]; health care visit required; not commonly used on plantar warts[19]; adverse effects: pain, headaches, fever, malaise, myalgia, fatigue, chills, pruritus, burning, and flu-like symptoms[50,51]
Intralesional injection of an antigen (eg. mumps, candida, tuberculosis, leprosy, bacillus Calmette-Guérin, *Trichophyton*)	22%-93.33% cure rate[31,32,55]; 10%-30% cure rate[34]; 100% clearance in an immunocompromised patient[50]	Used on recalcitrant warts[5,13,32]; wart resolution elsewhere[32,55]; safe in children[26,32]; cost-effective[50,55]; first-line therapy in patients with mumps or candida and >5 warts or wart >1 cm[26]; minimal scarring and pain[51]; no recurrence[34]	Second- or third-line treatment[51,55]; health care visit required; not for patients with hypersensitivity to antigen, pregnant women, or immunosuppressed[50,55]; multiple treatments needed; adverse effects: pain, pruritus, flu-like symptoms, erythema, edema, induration, ulceration, scarring, nodule formation, lymphadenopathy, site tenderness, blistering, numbness, paresthesia, fever, myalgia, and delayed-type hypersensitivity reaction[32,51,55]
5-Fluorouracil	30%-95% cure rate[26,31,51] 95% cure rate in plantar warts[52]	Used on recalcitrant warts[51]; minimal destruction of healthy surrounding tissue[52]	Third-line treatment[51]; health care visit required; 16% wart reoccurrence[52]; contraindicated in pregnant and breastfeeding women[19]; adverse effects: pain, erythema, irritation, inflammation, pigment changes, allergic contact dermatitis, perilesional maceration, photosensitivity reaction, ulceration, and erosion [26,31]
H2 receptor antagonists (cimetidine, ranitidine)	26%-87% cure rate[26,31]	Safe in all age groups[26,31]; appropriate for immunosuppressed[50]; used on recalcitrant warts[26]	Third-line treatment[51]; not FDA-approved for children aged <16 y[50]; health care visit required; treatment could take >12 wk[26]; insufficient evidence to support use; adverse effects: headache, dizziness, diarrhea, rash, urticaria, alopecia, gynecomastia, breast soreness, arthralgias, and myalgias[50]

(continued)

Table 2 (continued).
Currently Available Treatment Options for Patients With Plantar Warts

Treatment Method	Efficacy[a]	Advantages	Disadvantages
Levamisole	60%-85.7% cure rate[50,51]	Appropriate for children[7]	Third-line treatment[51]; monitor for agranulocytosis, especially in patients with HLA-B27 genotype[50]; adverse effects: agranulocytosis, multifocal leukoencephalopathy, nausea, taste alteration, rash, alopecia, and flu-like symptoms[50]
Imiquimod 5% cream (Aldara)	27%-89% cure rate[26,31] 37.5% cure rate[26]	Well tolerated in immunosuppressed[31]; self-applied in adults[26]; used on recalcitrant warts[13,51]; no wart recurrence[26,52]	Third-line treatment[5,51]; low absorbance through intact skin[50]; expensive[26]; long treatment duration[13,26]; adverse effects: local inflammatory reaction, pain, erythema, edema, erosions, pruritus, bacterial infection, weakness, fever, and scarring[5,13]
Topical bacillus Calmette-Guérin	45%-92% cure rate[32,50]	Safe in children[32]; no wart recurrence in 6-9 mo[26]	Health care visit required; adverse effects: burning, erythema, fever, and edema[42]
Quadrivalent HPV vaccine (types 6, 11, 16, and 18)[26,54]	84%-90% cure rate[26]	Good prophylaxis[56]; safe[22,26]; cross-reactivity with low-risk HPV, HPV-2[35,54]; used for recalcitrant warts[50] and low- risk HPV[35,54]	Health care visit required; multiple administrations; specific plantar wart vaccine not available[26]; adverse effects: headache, injection site pain, and erythema[22]

[a] Efficacy based on trials. Warts may resolve spontaneously.

Abbreviations: DCP, diphencyprone; FDA, US Food and Drug Administration; HPV, human papillomavirus; NA, not available; SADBE, squaric acid dibutylester; YAG, yttrium/aluminum/garnet.

resolution of the plantar wart.[7,26,45] Another distinguishing characteristic of plantar warts is the presence of small black dots, formed by thrombosed capillaries within the lesion, that exhibit pinpoint bleeding when the wart is pared (**Figure 2**). Visualization of thrombosed capillaries and pinpoint bleeding along with the loss of normal dermatoglyphics differentiate a plantar wart from other cutaneous lesions, such as calluses or corns.[7,13] On palpation, plantar warts feel rough and are tender when squeezed along the sides.[27]

The overwhelming majority of plantar warts are histologically benign, with only rare instances of malignant transformation, such as verrucous carcinoma.[11,36,46-48] Thus, plantar warts are usually diagnosed clinically.[43] In cases of diagnostic uncertainty or treatment resistance, biopsy with histopathologic evaluation may be indicated.[39] On histopathologic analysis, increased numbers of mitotic figures can be noted among the basal and suprabasal keratinocytes, evidencing the rapid cell replication that is occurring at this level of the epidermis in the region of HPV infection.[49] The basal layer of cells also exhibits papillomatosis, in which the basal layer becomes increasingly convoluted. Cells of the stratum spinosum and stratum granulosum exhibit increased numbers of proteinaceous, basophilic, granular inclusion bodies, formed by keratohyaline.[11,26,36] Furthermore, there is hypertrophy of the keratinocytes, which leads to acanthosis (thickening of the epidermis).[11,26,36] Hypertrophy and increased numbers of keratinocytes also lead to hyperkeratosis, seen on histopathologic analysis as thickening of the stratum corneum.[11,26,27] The keratinocytes also exhibit cytoplasmic vacuoles and retain nuclei within the stratum corneum (parakeratosis).[16,26,27]

Management of Plantar Warts

Numerous treatment options for plantar warts exist (**Table 2**). Each therapeutic method has been met with varying rates of success and adverse effects.[9,26] Evidence for nearly all available treatments is lacking, and no treatment has been found to have consistent efficacy for all patients.[26] Owing to the generally benign course of plantar warts, treatment should be pursued if the wart is symptomatic or causes psychological distress, if there are many lesions or if lesions are large, if the patient requests therapy or is concerned about transmission to others or self, or if the patient is immunocompromised.[26,51] The treatment modality that is pursued should have a relatively benign side effect profile and low cost.[26]

Physicians may choose to initially pursue a wait-and-see approach for immunocompetent patients, with most plantar warts resolving within 2 years.[3,31] However, lack of treatment can allow the wart to persist longer.[50] A plantar wart is considered to be recalcitrant when it has been present for more than 6 months. Such warts are usually more resistant to treatment, suggesting that it may be beneficial to initiate therapy before wart recalcitrance.[2,26,42] The 2 most common treatments for plantar warts are topical salicylic acid and cryotherapy with liquid nitrogen.[9,14,52]

Salicylic acid is available in topical formulations both over the counter and by prescription.[9,26,51] It promotes wart regression by chemically debriding the wart of excess keratin and by inducing a local inflammatory response.[51] Salicylic acid therapy generally requires weeks to months of daily applications, along with paring of the hyperkeratotic wart.[2,3,7] It is generally considered the most common initial therapy, because many patients use over-the-counter, self-applied preparations before seeking care from a physician.[7,26] However, certain patients, such as those with diabetic peripheral neuropathy or peripheral vascular disease, should be cautioned against using self-guided, at-home plantar wart therapy.[53]

Cryotherapy with liquid nitrogen has been shown to be less effective than salicylic acid and is considered to be a second-line therapy for plantar warts by some.[3,9,51] Cryotherapy works by freezing the plantar wart, causing cell damage and leading to a local inflammatory response.[51] Liquid nitrogen is not available over the counter. Although other forms of cryotherapy, such as dimethyl ether and propane, are available without a prescription, these forms demonstrate even less efficacy. Cryotherapy is also associated with more significant adverse effects than salicylic acid, such as mobility-limiting pain.[7,43] Double-freeze therapy, in which the lesion is frozen until a 1- to 2-mm ice halo forms and then completely thawed and immediately refrozen, has demonstrated increased efficacy but with greater risk of adverse effects.[9,26,45] Treatment is repeated as needed every 2 to 3 weeks for up to 3 months.[9,51] Because of the pain associated with this therapy, it is not recommended for young children.[4]

Do not share towels, shoes, socks, equipment, or other personal items
Wear footwear in communal showers and locker rooms
Sanitize communal sports equipment with isopropyl alcohol, ethyl alcohol, or bleach
Wear well-ventilated footwear and athletic clothing
Maintain quality personal hygiene
Allow shoes to dry thoroughly between uses
Wash socks between uses
Receive the quadrivalent HPV vaccine
Treat current warts promptly
Cover current warts[3]
Avoid manipulating warts
Avoid trauma and maceration of the skin
Keep nail files and pumice stones used for current warts separate from those used for other body areas
Avoid walking barefoot
Change socks daily
Keep feet clean and dry
Check children's feet periodically
Avoid direct contact with warts on self or others
Avoid blood from a wart

Figure 3.
Recommendations to prevent plantar warts.
Abbreviation: HPV, human papilloma virus.

Salicylic acid and cryotherapy, while most common, are not suitable for treatment-resistant warts. Other treatment modalities have been used with variable benefit and minimal evidence for recalcitrant warts (**Table 2**). Although these step-up therapies have been shown to cause regression of recalcitrant plantar warts, their inadequacy lies in addressing the pathologic process of lesion development. The longer the plantar wart remains established, the greater its ability to transmit infection and cause pain and embarrassment.[9] Management of the plantar wart and implementation of behavioral modifications can decrease viral transmission and reduce the risk of warts. Thus, prevention of the lesion altogether by diminishing risk factors for HPV infection, maintaining the integrity of the epidermal barrier, and promoting the immune system's ability to clear early infections is the ideal, yet still elusive, approach to addressing plantar warts (**Figure 3**).

Conclusion

Plantar wart management strategies are met with high degrees of variability in success rates and often fail to adequately manage a recalcitrant wart. Because all currently available plantar wart management modalities address the lesion itself, none adequately manage the risk of transmission, which is intrinsic to the pathophysiologic mechanism by which the plantar wart develops and sheds viral particles.[9,23,26] On the basis of these considerations, further research is warranted in plantar wart prophylaxis. Preventing the lesion will reduce viral shedding and transmission and thereby reduce the risk of HPV infection and plantar warts among the population.

References

1. Krishna SK, Jethwa AS. Human papillomavirus infections in adults and children. *Am J Epidemiol Infect Dis*. 2013;1(2):11-19. doi:10.12691/ajeid-1-2-2
2. Bruggink SC, Gussekloo J, Berger MY, et al. Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial. *CMAJ*. 2010;182(15):1624-1630. doi:10.1503/cmaj.092194
3. Bruggink SC, Gussekloo J, de Koning MN, et al. HPV type in plantar warts influences natural course and treatment response: secondary analysis of a randomised controlled trial. *J Clin Virol*. 2013;57(3):227-232. doi:10.1016/j.jcv.2013.02.021
4. Bruggink SC, Eekhof JA, Egberts PF, van Blijswijk SC, Assendelft WJ, Gussekloo J. Warts transmitted in families and schools: a prospective cohort. *Pediatrics*. 2013;131(5):928-934. doi:10.1542/peds.2012-2946
5. Sudhakar GK, Pai V, Pai A, Kamath V. Therapeutic approaches in the management of plantar warts by human papillomaviruses: a review. *Asian J Biomed Pharm Sci*. 2013;3(26):1-4.
6. Ghadgepatil SS, Gupta S, Sharma YK. Clinicoepidemiological study of different types of warts. *Dermatol Res Pract*. 2016;2016:7989817. doi:10.1155/2016/7989817
7. Stulberg DL, Hutchinson AG. Molluscum contagiosum and warts. *Am Fam Physician*. 2003;67(6):1233-1240.
8. Sanclemente G, Gill DK. Human papillomavirus molecular biology and pathogenesis. *J Eur Acad Dermatol Venereol*. 2002;16(3):231-240. doi:10.1046/j.1473-2165.2002.00419.x
9. Bacelieri R, Johnson SM. Cutaneous warts: an evidence-based approach to therapy. *Am Fam Physician*. 2005;72(4):647-652.
10. Wortsman X, Jemec GB, Sazunic I. Anatomical detection of inflammatory changes associated with plantar warts by ultrasound. *Dermatology*. 2010;220(3):213-217. doi:10.1159/000275607
11. Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I.: Human papillomavirus molecular biology and disease association. *Rev Med Virol*. 2015;25(suppl 1):2-23. doi:10.1002/rmv.1822
12. Tlougan BE, Mancini AJ, Mandell JA, Cohen DE, Sanchez MR. Skin conditions in figure skaters, ice-hockey players and speed skaters, part II: cold-induced, infectious and inflammatory dermatoses. *Sports Med*. 2011;41(11):967-984. doi:10.2165/11592190-000000000-00000
13. Lynch MD, Cliffe J, Morris-Jones R. Management of cutaneous viral warts. *BMJ*. 2014;348:g3339.
14. Akram S, Zaman H. Warts and verrucas: assessment and treatment. *Pharm J*. 2015;294(7867). doi:10.1211/PJ.2015.20068680
15. King CM, Johnston JS, Ofili K, et al. Human papillomavirus types 2, 27, and 57 identified in plantar verrucae from HIV-positive and HIV-negative individuals. *J Am Podiatr Med Assoc*. 2014;104(2):141-146. doi:10.7547/0003-0538-104.2.141
16. Leto MDGP, Porro AM, Santos GFD Jr, Tomimori J. Human papillomavirus infection: etiopathogenesis, molecular biology and clinical manifestations. *An Bras Dermatol*. 2011;86(2):306-317.
17. Senger T, Schädlich L, Textor S, et al. Virus-like particles and capsomeres are potent vaccines against cutaneous alpha HPVs. *Vaccine*. 2010;28:1583-1593. doi:10.1016/j.vaccine.2009.11.048
18. Bruggink SC, de Koning MN, Gussekloo J, et al. Cutaneous wart-associated HPV types: prevalence and relation with patient characteristics. *J Clin Virol*. 2012;55(3):250-255. doi:10.1016/j.jcv.2012.07.014
19. Watkins P. Identifying and treating plantar warts. *Nurs Stand*. 2006;20(42):50-54.
20. Whitaker JM, Palefsky JM, Costa MD, King CM, Johnston JS, Barbosa P. Human papilloma virus type 69 identified in a clinically aggressive plantar verruca from an HIV-positive patient [case report]. *J Am Podiatr Med Assoc*. 2009;99(1):8-12.

21. Gearhart PA, Randall TC, Buckley RM, Higgins RV. Human papillomavirus. Medscape website. http://emedicine.medscape.com/article/219110-overview. Updated January 5, 2017. Accessed December 5, 2017.

22. Berry JM, Palefsky JM. A review of human papillomavirus vaccines: from basic science to clinical trials. *Front Biosci*. 2003;8:S333-S345.

23. Johnson LW. Communal showers and the risk of plantar warts. *J Fam Pract*. 1995;40(2):136-138.

24. Barna Z, Kádár M. The risk of contracting infectious diseases in public swimming pools: a review. *Ann Ist Super Sanità*. 2012;48(4):374-386.

25. Plantar warts. The American College of Foot & Ankle Orthopedics & Medicine website. http://www.acfaom.org/information-for-patients/common-conditions/plantar-warts. Accessed July 21, 2016.

26. Lipke MM. An armamentarium of wart treatments. *Clin Med Res*. 2006;4(4);273-293.

27. Cubie HA. Disease associated with human papillomavirus infection. *Virol J*. 2013;445:21-34.

28. Silverberg JI, Silverberg NB. Childhood atopic dermatitis and warts are associated with increased risk of infection: a US population-based study. *J Allergy Clin Immunol*. 2014;133(4):1041-1047.

29. Longworth MS, Laimins LA. Pathogenesis of human papillomavirus in differentiating epithelia. *Microbiol Mol Biol Rev*. 2004;68:362-372.

30. Doorbar J. Papillomavirus life cycle organization and biomarker selection. *Dis Markers*. 2007;23:297-313.

31. Sterling JC, Gibbs SS, Hussain H, Mustapa MF, Handfield-Jones SE British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. *Br J Dermatol*. 2014;171(4):696-712. doi:10.1111/bjd.13310

32. Singh S, Chouhan K, Gupta S. Intralesional immunotherapy with killed *Mycobacterium indicus* pranii vaccine for the treatment of extensive cutaneous warts. *Indian J Dermatol Venereol Leprol*. 2014;80(6):509-514. doi:10.4103/0378-6323.144145

33. Bavinck JNB, Eekhof JAH, Bruggink SC. Treatments for common and plantar wart. *BMJ*. 2011;342:d3119. doi:10.1136/bmj.d3119

34. Shaheen MA, Salem SA, Fouad DA, El-Fatah AA. Intralesional tuberculin (PPD) versus measles, mumps, rubella (MMR) vaccine in treatment of multiple warts: a comparative clinical and immunological study. *Dermatol Ther*. 2015;28:194-200. doi:10.1111/dth.12230

35. Landini MM, Borgogna C, Peretti A, et al. Identification of the skin virome in a boy with widespread human papillomavirus-2-positive warts that completely regressed after administration of tetravalent human papillomavirus vaccine. *Br J Dermatol*. 2015;173(2):597-600. doi:10.1111/bjd.13707

36. Cardoso JC, Calonje E. Cutaneous manifestations of human papillomaviruses: a review. *Acta Dermatovenerol Alp Pannonica Adriat*. 2011;20(3):145-154.

37. Sladden MJ, Johnston GA. Common skin infections in children. *BMJ*. 2004;329(7457):95-99.

38. Silverberg JI, Silverberg NB. The US prevalence of common warts in childhood: a population-based study. *J Invest Dermatol*. 2013;133:2788-2790.

39. Khondker L, Shah MOR, Khan MSI. Verruca: need to know about human papilloma virus (HPV) infection. *J Bangladesh Coll Phys Surg*. 2012;30(3):151-158.

40. Johnson IL, Dwyer JM, Rusen ID, Shahin R, Yaffe B. Survey of infection control procedures at manicure and pedicure establishments in north York. *Can J Public Health*. 2001;92(2):134-137.

41. Fallon LF Jr. Warts. *Gale Encyclopedia of Children's Health: Infancy Through Adolescence*. Farmington Hills, MI: Gale; 2006.

42. Leiding JW, Holland SM. Warts and all: human papillomavirus in primary immunodeficiencies. *J Allergy Clin Immunol*. 2012;130(5):1030-1048.

43. Farhadian JA, Tlougan BE, Adams BB, Leventhal JS, Sanchez MR. Skin conditions of baseball, cricket, and softball players. *Sports Med*. 2013;43(7):575-589. doi:10.1007/s40279-013-0022-4

44. Syrjänen S. Current concepts on human papillomavirus infections in children. *APMIS*. 2010;118:494-509.

45. Plantar wart. Dynamed. https://www.dynamed.com/resultlist?q=plantar+wart&filter=all. Accessed December 28, 2017.

46. Arican O, Ozturk P, Kurutas EB, Unsal V. Status of oxidative stress on lesional skin surface of plantar warts. *J Eur Acad Dermatol Venereol*. 2013;27(3):365-369. doi:10.1111 /j.1468-3083.2011.04419.x

47. Pempinello C, Bova A, Pempinellp R, Luise R, Iannaci G. Verrucous carcinoma of the foot with bone invasion: a case report. *Case Rep Oncol Med*. 2013;2013:135307. doi:10.1155/2013/135307

48. Bhatt Y, Singh S, Vaghani S, Doshi P. Verrucous carcinoma of the foot- a series of 4 cases. *Int J Biomed Res*. 2015;6(8):591-595.

49. Egawa K, Iftner A, Doorbar J, Honda Y, Iftner T. Synthesis of viral DNA and late capsid protein L1 in parabasal spinous cell layers of naturally occurring benign warts infected with human papillomavirus type 1. *Virol J*. 2000;268:281-293.

50. Sinha S, Relhan V, Garg VK. Immunomodulators in warts unexplored or ineffective? *Indian J Dermatol*. 2015;60(2):118-129. doi:10.4103/0019-5154.152502

51. Treat cutaneous warts on a case-by-case basis, taking into account patient factors and the available clinical evidence. *Drugs Ther Perspec*. 2012;28:15-19. doi:10.2165/11608610-000000000-00000

52. Bradley A, Boyle D, Rossidis M. Efficacy of topical agents (SE, 5-FU, and IMQ) for treatment of verruca plantaris: a systematic review. *Podiatr Med Rev*. 2013-2014;23:57-67.

53. Warts. American Academy of Dermatology website. https://www.aad.org/public/diseases/contagious-skin-diseases/warts. Accessed July 22, 2016.

54. Berman B, Bechtel MA, Cusack CAR, et al. Infection (viral). *J Am Acad Dermatol*. 2010;62(3)(suppl 1):S88-S117.

55. Garg S, Baveja S. Intralesional immunotherapy for difficult to treat warts with *Mycobacterium* w vaccine. *J Cutan Aesthet Surg*. 2014;7(4):203-208. doi:10.4103/0974-2077.150740

56. Bharti AC, Shukla S, Mahata S, Hedau S, Das BC. Anti-human papillomavirus therapeutics: facts & future. *Indian J Med Res*. 2009;130(3):296-310.