Genital Warts
A Comprehensive Review

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ABSTRACT
External genital warts, also known as condylomata acuminata, are extremely common, with between 500,000 to one million new cases diagnosed each year in the United States alone. To date, more than 120 distinct subtypes of human papillomavirus have been identified. Human papillomavirus types 6 and 11 rarely give rise to cervical cancers, but are responsible for 90 percent of the cases of genital warts. The current treatment options are largely centered upon removal of the warts rather than elimination of the underlying viral infection. A wide range of therapies are presently in use, which are highly variable and can differ dramatically with respect to cost, side-effect profiles, dosing schedules, duration of treatment, and overall effectiveness. As of yet, no definitive therapy has emerged as the ideal standard of care in the treatment of genital warts, and therapy selection generally occurs in a patient-specific manner.
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External genital warts (EGW), also known as condylomata acuminata (CA), are one of the most common forms of sexually transmitted diseases affecting the general population.[1] It is estimated that anywhere between 500,000 to one million new cases are diagnosed each year in the United States alone, with clinically apparent warts presenting in approximately one percent of the sexually active population.[2,3] In 2004, the economic burden of human papillomavirus (HPV) was estimated at four billion dollars when accounting for direct costs of caring for genital warts as well as invasive cervical cancer.[4]

To date, more than 120 distinct subtypes of HPV have been identified, with approximately 40 different subtypes capable of infecting the anogenital tract.[1,5] These can be grossly subdivided into the following three categories: low risk, intermediate risk, and high risk, based on the likelihood of inducing intraepithelial dysplasias. HPV types 6 and 11 rarely give rise to cervical cancers and are thus considered low-risk subtypes. Infection by these genotypes is responsible for 90 percent of the cases of genital wart formation. In contrast, HPV types 16 and 18 are strongly associated with cervical dysplasia and are therefore considered to be high risk, oncogenic subtypes. Evidence for infection by these genotypes is found in up to 70 percent of squamous cell carcinomas (SCC) of the cervix.[6] HPV types 31, 33, 45, 51, 52, 56, 58, and 59 are typically thought to be of intermediate risk since they are often found in association with squamous neoplasms, but have been rarely linked to cervical SCC.[6] Patients with CA may be infected simultaneously by multiple HPV strains. While the specific nature of the infection certainly plays a role in predicting malignant progression, it has very little bearing on the diagnosis or treatment of genital warts.[7]

HISTORY
Historically, genital warts were believed to be cutaneous manifestations of syphilis or gonorrhea, and it was not until 1907 that Ciuffo definitively demonstrated the virus's infectious nature through the use of cell-free transmission experiments. By inoculating and injecting wart extracts into previously uninfected skin, Ciuffo induced novel papillomatous eruptions at the injection sites.[8] Subsequent investigation and experimentation revealed genital warts to be benign cellular proliferations of the anogenital skin and mucosa in response to a viral invasion. Recent advances in

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TABLE 1. Low-risk human papillomavirus subtypes versus high-risk human papillomavirus subtypes

	LOW RISK: HUMAN PAPILLOMAVIRUS SUBTYPES 6 AND 11	HIGH RISK: HUMAN PAPILLOMAVIRUS SUBTYPES 16 AND 18
Main pathologic association	75–90% cases of genital warts	70% cases of all invasive cervix cancer
Pathogenesis	Remain separate from host cell DNA, undergo independent replication	Integrate viral DNA with host's genome promoting transcription of oncoproteins that inactivate tumor suppressor genes
Associated with which types of verrucous carcinoma	Oral florid papillomatosis Buschke–Lowenstein tumor	Oral florid papillomatosis
Vaccination	HPV4	HPV2 HPV4

HPV 4: Gardasil (Merck & Co.), HPV2: Cervarix, (GlaxoSmithKline)

molecular biological techniques have allowed for the successful identification of the offending virus, HPV, as the source of genital wart outbreaks.[9]

EPIDEMIOLOGY

The prevalence of HPV infection has risen steadily in the past 35 years, with as many as 20 million people in the United States believed to be infected.[1,10] This phenomenon is often attributed to both an earlier age of initial sexual contact as well as an increase in the total number of sexual partners. Accordingly, nearly half of these new infections will occur in young adults ages 15 to 24 years.[11] HPV is a highly contagious virus and is transmitted predominantly through oral, anal, and genital sexual contact, although rare instances of vertical transmission and autoinoculation have been reported.[12] Furthermore, sexual contact with an HPV-infected individual results in a 75-percent chance of contracting the virus and developing CA. This high rate of transmission generates a 50-percent lifetime risk of acquiring EGW in sexually active individuals.[2] Additional risk factors include unprotected intercourse, use of oral contraceptives, a history of sexually transmitted infections, smoking, or immunosuppression.[13,14]

VIROLOGY

HPV is a group of nonenveloped, double-stranded deoxyribonucleic acid (DNA) viruses belonging to the family *Papovaviridae*.[3] Viral replication is restricted to the basal cell layer of surface tissues. The virus will penetrate both the cutaneous and mucosal epithelium in search of the appropriate cellular host. It will subsequently invade and infect the basal keratinocytes of the epidermis. The mucosa can be infected anywhere along the genital tract, including the vulva, vagina, cervix, and perianal regions in females as well as the penile shaft, scrotum, periurethral, and perianal regions in males. Infected regions will be marked by a proliferation of viral DNA and the formation of a warty papule or plaque.[3]

The viral genome is composed of six early-open reading frames (E1, E2, E4, E5, E6, E7) and two late-open reading frames (L1, L2). The early-open E genes are important for regulatory function and encode proteins involved in viral replication and cell transformation. In contrast, the late-open L genes encode viral capsid proteins. Differences in the L1 genotype lead to slightly altered patterns of viral DNA replication, which are thought to account for the various HPV subtypes.[12] Specifically, low-risk HPV subtypes will remain separate from the host cell DNA and thus undergo replication independently. In contrast, high-risk HPV subtypes will incorporate their DNA directly into the host cell's genetic material. The integration of viral and host cell DNA often results in the dysregulation and uncontrolled activation of the E6 and E7 genes, which promotes the transcription of oncoproteins. These will bind and inactivate tumor suppressor genes p53 and Rb, leading to increased cell proliferation and a greater risk of malignant progression (Table 1).[15,16]

DERMATOPATHOLOGY

Histopathologically, the hallmark of an HPV-infected cell is the development of morphologically atypical keratinocytes known as koilocytes. These are enlarged cells with eccentric, pyknotic nuclei that are often surrounded by a perinuclear halo. Generally, the epidermis will show a marked acanthosis with varying degrees of papillomatosis, hyperkeratosis, and parakeratosis as well as a complete effacement of the granular cell layer.[17] Rete ridges tend to be elongated and point inward toward the center of the wart, and the dermis

will often display an increased vascularization with the presence of thrombosed capillaries. In morphologically ambiguous lesions, definitive diagnosis can best be made through the use of electron microscopy and the immunohistochemical peroxidase-antiperoxidase stain.[18] These methods will enable the direct visualization of viral particles within the cells. Additionally, the use of MIB1, an antibody targeting cell proliferation protein Ki-67, may also be helpful in highlighting the presence of viral infection.[19]

CLINICAL PRESENTATION

Once infected with HPV, the virus typically requires an incubation period ranging anywhere from 3 weeks to 8 months prior to clinical manifestation. On average, physical symptoms begin approximately 2 to 3 months after initial contact.[20] The virus, however, is also capable of lying dormant within epithelial cells for prolonged periods of time. Infection may thus persist undetected for the duration of an individual's lifetime with no manifestation of clinically apparent warts. Many studies estimate the rate of subclinical HPV infection to be as high as 40 percent, as demonstrated by the identification of positive viral samples when conducting DNA analysis of seemingly uninfected genital skin.[21]

Following initial clinical manifestation, CA may increase in number and size or, alternatively, undergo a spontaneous regression. In fact, approximately 30 percent of all warts will regress within the first four months of infection. Unfortunately, long-term remission rates remain largely unknown, and the majority of genital warts will recur within three months of infection, even after undergoing the appropriate treatments.[22] Significant risk factors for long-term wart persistence include host immunosuppression, infection with high-risk HPV subtypes, and an older patient age.[22,23] Conversely, the presence of CD4+ lymphocytes in the dermis and the epidermis is generally thought to be associated with elevated rates of spontaneous regression, highlighting the critical role played by the immune system in determining the course of viral infection.

EGW typically present on the moist tissues of the anogenital area, although they may occasionally develop in the mouth or the throat after oral sexual contact with an infected partner.[3] CA have a highly variable appearance and may be flat, dome-shaped, cauliflower-shaped, or pedunculated.[13] EGW can manifest individually, as a solitary keratotic papule or plaque, but are more frequently found in large clusters. Often EGW begin as small, nondistinctive 1 to 2mm flesh-colored papules on the skin and may retain this presentation for the duration of the infection. Alternatively, CA may grow as large as several inches in diameter, leading to the painful disruption of normal intercourse and childbirth. The warty contour may also vary in color and appearance, ranging from white to pink, purple, red, or brown and from flat to cerebriform or verrucous.[24]

Lesions are rarely considered to be painful; however, they are often associated with severe discomfort, burning, and pruritis. Moreover, larger lesions may be subject to bleeding and irritation upon contact with clothing or during sexual intercourse. The vast majority of EGW can be accurately diagnosed with a careful clinical history and physical examination. In extremely mild or subclinical cases, the use of a 3 to 5% acetic acid solution (the acetowhite test) may be helpful in promoting wart visualization. Biopsy is rarely needed in order to achieve a correct diagnosis, yet it is often recommended for lesions suspected of being malignant or having an increased malignant potential. This includes lesions that are ulcerated, suddenly change in appearance, remain fixed to an underlying structure, or are recalcitrant to treatment.[13]

COMPLICATIONS OF UNTREATED HPV INFECTION

Both low-risk (subtypes 6 and 11) and high-risk (subtypes 16 and 18) HPV subtypes have also been associated with the very low-grade, well-differentiated squamous cell carcinoma known as verrucous carcinoma (VC).[25] Verrucous carcinoma is divided into clinico-pathological types based on the anatomic area of involvement: oral florid papillomatosis (oral cavity), giant condyloma of Buschke and Löwenstein (anogenital area), and carcinoma cuniculatum (palmoplantar surface). These tumors tend to spread by local invasion and, therefore, rarely metastasize.[26] While a direct causal relationship between HPV and VC has yet to be defined, it is hypothesized that HPV's viral oncogene expression promotes the degradation of the p53 tumor suppression gene, thereby lowering the threshold for tumor formation.[27] Histologically, VC can vary from benign-appearing pseudoepitheliomatous hyperplasia-like lesions to invasive SCC. Additionally, presence of vacuolation and prominent keratohyalin granules in the stratum granulosa cells, which are hallmark features of genital warts, was discovered to be variable in histological studies of VC.[28,29] One can differentiate VC and SCC by comparing the immunoperoxidase staining pattern of expression of certain oncogenes. For instance, VC and SCC cells can stain positively for bcl-2, Ki-67, and p53. However, nuclei of VC stain positive for p53 and Ki-67 in the lower third of the epidermis, primarily in the basal proliferating cells. The nuclei of SCC stain positive throughout the full thickness of the epidermis for these markers.[30]

Additionally, while most HPV infections clear spontaneously, in 10 to 20 percent of women these infections persist and these females are at risk for progression to grade 2/3 cervical intraepithelial neoplasm and, if left untreated, can eventually develop invasive cancer of the cervix.[31] Penile cancer, which is 10 times less common than cervical cancer, also has a high correlation rate with high-risk HPV infection and history of EGW. A case-control study involving more than 100 men with penile cancer reported that the risk of penile cancer in men with a history of EGW was 5.9 times that of men with no such history (95% CI 2.1–17.6).[32]

THERAPY

The current options available for the treatment of CA are largely centered upon removal of the warty growth rather than elimination of the underlying viral infection. There is little evidence to suggest that existing treatments are

effective in the long-term eradication of genital warts or that they play any significant role in hindering potential malignant wart evolution. A wide range of therapies are presently in use, which are highly variable and can differ dramatically with respect to cost, side-effect profiles, dosing schedules, duration of treatment, and overall effectiveness (Table 2). As of yet, no definitive therapy has emerged as the ideal standard of care in the treatment of genital warts, and therapy selection generally occurs in a patient-specific manner. For the purpose of this review, treatment options are reviewed in order of grading of recommendations (based on AHCPR, 1994).[33]

Podophyllotoxin 0.05% solution or gel and 0.15% cream (Grade A). Podophyllotoxin is a purified extract of the podophyllum plant, which binds to cellular microtubules, inhibits mitotic division, and induces necrosis of warts that is maximal 3 to 5 days after administration. Shallow erosions occur as the lesions necrotize and heal within a few days.[34] This treatment option is generally thought to be safe, effective, and can be self-administered. Podophyllotoxin is available as a solution, cream, or gel and must be applied twice daily for three consecutive days of the week, for a maximum of four weeks. Typically, the solution is recommended for penile lesions, whereas cream or gel vehicle preparations are thought to be more comfortable for application to anal or vaginal lesions.[35]

Randomized, placebo-controlled trials have demonstrated successful clearance rates ranging between 45 to 77 percent.[36,37] Podophyllotoxin is also associated with rates of recurrence as low as 38 percent.[38] Warts that have not resolved after four courses should be treated by alternative means. Adverse effects tend to be fairly common, especially with the first course of therapy and include pain, inflammation, erosion, burning, or itching at the application site. These are frequently thought to be the result of excessive treatment administration on the part of the patient.[39] Despite its significantly safe drug profile, podophyllotoxin has not yet been thoroughly evaluated for teratogenecity and is not recommended for use during pregnancy.[40]

Imiquimod 5% cream (Grade A). Imiquimod (imidazoquinolinamine) 5% cream is a patient-applied topical immunomodulatory agent, which first received its indication for the treatment of external CA in 1997. It has since been used in the treatment of a variety of skin conditions, including basal cell carcinomas and actinic keratoses.[41] Although its precise mechanism of action remains unclear, imiquimod is believed to activate immune cells by binding to the membranous toll-like receptor.[7] This leads to the secretion of multiple cytokines, such as interferon-α, interleukin-6, and tumor necrosis factor-α, which are critical in the induction of an inflammatory response promoting wart clearance.[42,43] In addition, imiquimod-treated patients have been shown to have a decrease in viral load measured by HPV DNA, a decrease in messenger ribonucleic acid (mRNA) expression for markers of keratinocyte proliferation, and an increase in mRNA expression for markers of tumor suppression.[44]

For the treatment of CA, imiquimod is applied at bedtime three times per week for up to 16 weeks. Commonly encountered local inflammatory side effects, such as itching, erythema, burning, irritation, tenderness, ulceration, and pain, have been long-standing issues with the 5% cream. Occasionally, patients may experience systemic side effects of headaches, muscle aches, fatigue, and general malaise.

In the pivotal clinical study, wart clearance was achieved in 56 percent of patients. More women (77%) than men (40%) cleared their warts, with the male study population comprising predominantly circumsized men. Females had a shorter median time to clearance (8 weeks) compared to males (12 weeks). A low recurrence rate (13%) was found.[45]

Although multiple clinical studies have validated the efficacy and safety of the currently indicated dosing regimen for imiquimod 5% cream for CA, the lengthy duration and sporadic frequency can affect patient compliance. Only one dose-response study exploring a daily treatment regimen with the imiquimod 5% cream has been published with results showing poor patient tolerance secondary to severe local inflammatory side effects. Of the 64 patients enrolled in this study, 13 were withdrawn prior to completion.[46]

Imiquimod 3.75% cream (Grade A). Recently, the FDA approved the use of a 3.75% formulation of topical imiquimod cream for the treatment of EGW.[47] Two Phase III, double-blind, placebo-controlled studies have shown imiquimod 3.75% to be significantly more effective than placebo, achieving a 33-percent clearance rate in a protocol evaluation and a 28-percent clearance rate in an intention-to-treat study. Furthermore, recurrence rates were relatively low, with up to 85 percent of subjects achieving complete clearance at a 12-week follow-up evaluation.[48]

Primary cure rates for the 3.75% formulation are not as high as the 5% counterpart; however, the newer product is thought to have several considerable benefits with respect to patient compliance. Importantly, the treatment regimen for 3.75% imiquimod is significantly shorter, with daily application required for a maximum of eight weeks. Additionally, the 3.75% cream is thought to have a markedly less aggressive side-effect profile with the main complaints including itching, burning, or pain at the site of application. Unlike the 5% cream, no systemic symptoms have yet been associated with the therapy.[48]

Sinecatechins 15% ointment (Grade A). Sinecatechins is a botanical extract approved in 2006 by the United States Food and Drug Administration (FDA) for the treatment of genital warts, making it the first botanical to officially receive medical approval.[49] The active ingredient is a green tea extract containing sinecatechins, which is thought to possess antioxidant, antiviral, and antitumor effects. Although the precise mechanism of action remains unclear, sinecatechins is thought to modulate the inflammatory response through the inhibition of transcription factors AP-1 and NF-κB, both of which are induced by reactive oxygen species.[50] They have also been shown to downregulate the expression of cyclooxygenase-2, which has been linked to activation of the prostaglandin E2 system and subsequent epithelial dysplasia.[51]

TABLE 2. Treatment modalities for genital warts

TREATMENT TYPE	MECHANISM OF ACTION	ADMINISTERED BY	PREGNANCY SAFETY	LEVEL OF EVIDENCE	CLEARANCE %	RECURRENCE %	COMMENTS
TOPICAL							
Podophyllotoxin	Anti-wart lignans	Patient	Unknown	A	45–77[34,36]	38–65[38]	Cost-effective home treatment
Imiquimod 5% cream	Induces secretion of cytokines that reduce HPV DNA viral load	Patient	Unknown	A	56[45]	13[45]	Lengthy duration and sporadic dosing frequency can affect compliance
Imiquimod 3.75% cream	Induces secretion of cytokines that reduce HPV DNA viral load	Patient	Unknown	A	28–33[48]	15[48]	New formulation with more intuitive dosing regimen
Sinecatechins 15% ointment	Possess antitumor, antiviral, antioxidant effects	Patient	Unknown	A	58[55]	6–9[55]	Can often take 16 weeks to elicit positive response
Podophyllin	Anti-wart lignans	Patient	No	C	42–50[67]	46–60[58]	Not generally recommended for EGW treatment
5-FU	Inhibits key enzyme in DNA replication	Physician	No	C	10–50[48]	50[48]	Sometimes used for urethral warts
DESTRUCTIVE AND SURGICAL							
TCA	Chemically destructive acids	Physician	Yes	B	70[49]	18[50,51]	High clearance rates with relatively low morbidity
Cryotherapy	Dermal damage induced by cold temps initiate immune response	Physician	Yes	B	79–88[12]	25–40[12]	Treated areas can take several weeks to heal, requires multiple treatments
Electrosurgery	Thermal coagulation	Physician	Yes	B	94[58]	22[58]	Long-term effectiveness comparable to cryotherapy
Scissor excision	Physical removal of diseased tissue	Physician	Yes	B	72[60]	19–29[60]	Outdated treatment modality, utilized with large lesions causing obstruction
CO_2 laser	Infrared light energy vaporizes lesions	Physician	Yes	B	23–52[12]	60–77[12]	Treatment of choice in immunocompromised
SYSTEMIC							
Interferon	Interferes with viral replication	Physician	No	C	17–67[56,57,58]	9–69[56,57,58]	Topical use has higher clearance rates versus placebo; systemic use has comparable clearance rates versus placebo

HPV=human papillomavirus, BCA=bichloroacetic acid, TCA=trichloroactetic acid; A=one double-blind, randomized,controlled trial; B=well-conducted clinical studies, no randomized,controlled trial; C=Evidence from expert committee reports/options and/or clinical experience of respected authorities, indicated absence of directly applicable studies of good quality

Sinecatechins 15% cream is applied topically to warts three times a day for up to four months. Typically, if an improvement is not seen within a few weeks, the treatment is stopped and another option is tried. Several randomized, double-blind, placebo-controlled trials have shown sinecatechins to be significantly more effective than placebo in the treatment of genital warts, with clearance rates as high as 58 percent. Recurrence rates are also relatively low, ranging between 6 to 9 percent at 12 weeks follow up.[51]

This botanical extract is associated with a number of adverse effects that are thought to occur in approximately 20 percent of users. These events are generally quite mild and typically include redness, burning, itching, and pain at the site of application. More severe reactions associated with this topical product's use, such as lymphadenitis, vulvovaginitis, balanitis, and ulceration are extremely rare, but have been reported.[51]

Trichloroacetic acid (TCA) 80–90% solution (Grade B). TCA is a chemically destructive acid that burns, cauterizes, and erodes the skin and mucosa. Generally prepared in 80 to 90% solutions, TCA necessitates administration by the physician. Successful treatment of warts can occasionally occur with as little as a single dose; however, more frequently, several applications are required.

TCA is an inexpensive, cost-effective treatment that does require prolonged usage and regimen adherence. The destructive nature of the product frequently extends beyond the superficial wart to encompass the underlying viral infection providing for clearance rates that have been estimated at 70 to 80 percent with high recurrence rates of 36 percent.[52,53] An obstetric study that evaluated the use of 85% TCA in 50 female subjects with external genital warts showed that all subjects were cleared of all lesions after a treatment period that ranged from 2 to 5 months. None of the patients had recurrence or new lesions during the first six-month follow-up period. In the second six-month follow-up period, nine patients (18%) were diagnosed with recurrent lesions. Although transient burning pain during therapy was commonly experienced, none of the patient population discontinued therapy.[54]

Additionally, the low danger of systemic absorption allows for safe application during pregnancy. The main side effects of acid treatments involve pain or burning during administration as well as destruction of the healthy tissue surrounding the wart. The latter can be minimized by washings with soap and sodium bicarbonate immediately following over-application, and dermal injury or scarring is rare.[55] Occasionally, tissue destruction can result in pain, ulceration, and crust formation. High success rates and relatively low morbidity make acetic acid therapy a recommended treatment option for CA.

Cryotherapy (Grade B). Cryotherapy is a process in which the abnormal tissue is frozen through the use of a cooling agent, such as nitrous oxide or liquid nitrogen. Temperatures must be exorbitantly cold so as to cause permanent dermal and vascular damage. This leads to the initiation of an immune repair response, resulting in the necrosis and clearance of the destroyed cells. Generally, this treatment is most effective when used for multiple small warts on the penile shaft or vulva.[56,57]

Cryotherapy is considered a fairly inexpensive and highly successful therapy, with a 79- to 88-percent clearance rate seen within the first three treatments.[12] This suggests a more efficacious outcome when compared with TCA.[52] Cryotherapy has various limiting factors. Variables in administration, such as the temperature utilized and time of contact, influence efficacy of treatment. Common side effects of cryotherapy include local tissue destruction, such as painful blistering, ulceration, infection, potentially permanent scarring, and loss of pigmentation, which can be slightly more severe than that of TCA.

Additionally, as with other lesion-directed therapies, cryosurgery does not treat subclinical lesions in the surrounding skin. The recurrence rate associated with this provider-applied methodology has been estimated to be between 25 and 40 percent. Other disadvantages of cryotherapy are that multiple outpatient visits are required and the pain associated with its application can limit its repeated use in certain subjects. However, the effects of cryotherapy are entirely local, making it the current therapy of choice for pregnant women with multiple warts.

Electrosurgery (Grade B). Electrosurgery involves the use of high frequency electrical currents in the form of thermal coagulation or electrocautery to burn and destroy warty lesions. The desiccated tissue is subsequently removed by curettage. This technique is particularly efficacious when used in the treatment of smaller warts located on the shaft of the penis, the rectum, or the vulva; however, it is not recommended for large lesions as it may lead to permanent scar formation. Electrosurgery is an extremely effective technique, with randomized, controlled trials yielding clearance rates as high as 94 percent measured six weeks post-treatment. These rates, however, tend to normalize after three months, suggesting that electrosurgery is comparable to cryotherapy with regard to its long-term effectiveness.[58] Electrosurgery is also a fairly painful procedure and local or general anesthesia is usually required. Side effects tend to be relatively minimal and are typically limited to postprocedural pain, although the use of general anesthesia is always associated with a certain degree of elevated risk. It is important to note that electrosurgery is contraindicated in patients with cardiac pacemakers or other implanted cardiac devices due to the potentially fatal effects of current interference and the disruption of the pacemaker rhythms.[59]

Surgical scissor excision (Grade B). One of the oldest documented treatments for the removal of genital warts, surgical excision was considered for many years to be the primary available option. It involves the physical removal of diseased tissue from the body with scissors or a scalpel, followed by suturing the remaining healthy skin together. It is associated with up to a 72-percent clearance rate, which is evident immediately and often persisting over a year later. Although now considered to be somewhat outdated, this treatment option is still suitable for very large lesions that may be causing obstruction and are ineligible or

unresponsive to other forms of treatment. Examples include lesions involving the urethral meatus.[60]

Additionally, surgical excision remains the optimal procedure for the removal of neoplastic lesions suspected of malignant progression, which must be submitted for further histopathological examination. Surgical removal of large lesions is a painful process, which frequently results in bleeding and scar formation. The administration of local or general anesthesia is commonly recommended.

A recent and considerably more sophisticated surgical excision procedure for the treatment of genital warts is Mohs surgery. Although intended predominantly for cutaneous carcinomas, Mohs is a highly specialized technique in which the skin is removed in very thin layers and subject to immediate microscopic analysis for traces of pathology. In the continued presence of viral cell features, additional skin slices will be removed until the entire wart is excised and only healthy tissue remains.[61] The obvious benefit of this type of surgery is that it allows for the maximal preservation of healthy skin, resulting in minimal scar formation. However, it is a significantly more expensive and involved process and is only considered when the cosmetic appearance of the removal process is of significant concern.

Carbon dioxide (CO_2) laser therapy (Grade B). Carbon dioxide laser therapy relies upon the use of a concentrated beam of infrared light energy, which will heat and eventually vaporize the targeted areas. The intense light energy has the added benefit of providing immediate cauterization of any ligated vessels, ensuring a virtually bloodless procedure. The spatial confinement of the laser beam permits precise tissue ablation resulting in rapid healing with little or no scar formation.[62]

The efficacy of CO_2 therapy for CA remains contentious. Laser therapy is typically considered to be less effective than other forms of surgical treatment, with clearance rates ranging between 23 to 52 percent. Recurrence rates also tend to be elevated, reaching as high as 77 percent.[12] Side effects are generally mild and limited to the burning of tissue surrounding the lesion.[63] Despite these seemingly unfavorable results, the deep penetrating effect of the laser often allows for a greater and more complete viral attack than seen with other surgical treatment options. This renders it the treatment of choice for immunosuppressed individuals as well as for pregnant women with extensive lesions who remain unresponsive to TCA or cryotherapy.

Unfortunately, laser therapy is also a rather expensive and complicated treatment option. Specialized laser equipment must be purchased and subjected to continual upkeep, while physicians themselves are required to undergo additional training in order to utilize the equipment effectively. Furthermore, vaporization of viral lesions can lead to the release of HPV DNA into the surrounding environment. Appropriate measures must therefore be undertaken in order to ensure physicians and assisting personnel are protected from infection. This necessitates the use of specific, virus-resistant masks as well as a vacuum ventilation system in the examination room.[64] Additional risk factors for the transmission of genital warts through vaporization include treatment of malignant HPV subtypes, thinness of skin, and the degree of viral burden.[65]

Therapies not generally recommended. Due to low efficacy and toxicity, routine use of podophyllin, 5-fluorouracil (5-FU), and interferon therapy are not recommended for use in the primary care setting.[66] Podophyllin was the first topical treatment of genital warts; however, a lack of standardized drug preparation lead to samples that varied greatly in the active ingredient. This increased the likelihood for adverse skin reactions, such as burning, redness, pain, itching, or swelling. In extremely rare circumstances, over-application of podophyllin and excessive systemic absorption has been linked to the development of enteritis, bone-marrow suppression, abdominal pain, and neurological compromise.[67] Podophyllin fails to induce a lasting remission of genital warts and is generally considered less effective than podophyllotoxin, cryotherapy, or electrosurgery when used as individual modalities.[36,58]

5-FU is one of the oldest chemotherapeutic agents and has been effectively used in the treatment of cancer for more than 40 years. Although not officially approved by the FDA for use in the treatment of genital warts, topical 5-FU is still seen as a favorable option for urethral warts.[68–70] The administration of 5-FU has historically been associated with highly variable response rates, and side effects tend to be slightly more severe than those of imiquimod 5% cream with comparable clearance rates yet marginally higher rates of recurrence.[3,71]

Historically, interferon therapy has been used predominantly for the treatment of malignant melanoma; however, recent evidence suggests that it may be useful as either an individual or adjuvant to surgical treatment of genital warts.[72,73] Interferon therapy can be administered systemically, via oral or intramuscular injection, as well as locally, via direct intralesional injections. Typically, 1 to 1.5 million units is used, and injections occur three times a week for a duration of three weeks. The use of interferon therapy for the treatment of genital warts remains somewhat controversial. A meta-analysis of 12 randomized clinical trials involving close to 1,500 subjects showed the local use of interferon to have a statistically higher complete response rate than placebo ($P<0.00001$). The rate of complete response of systemically used interferon and placebo had no perceivable discrepancy ($P>0.05$).[72,74] Due to its direct immune-boosting effects, interferon therapy is likely to promote the clearance of underlying virally infected cells in addition to targeting external lesions. This may ultimately lead to lower rates of recurrence and better long-term results, especially when used synergistically with other treatment modalities. The benefit of interferon therapy as an adjunct treatment remains unclear, with several studies indicating no advantage relative to placebo, while still others show a significant improvement in treatment results.[73,75] Although this therapy seems promising, further comprehensive research is needed in order to confidently evaluate its effectiveness.[72] Side effects generally include flu-

like symptoms, such as headache, nausea, vomiting, fatigue, and myalgia. On rare occasions, systemic interferon therapy has been linked to elevated liver enzymes, bone marrow suppression, bronchospasms, and depression. Intralesional injections are associated with significant pain upon administration, hence the use of local anesthesia is frequently recommended.[40] The use of interferon therapy is an extremely costly procedure and is typically considered the most expensive genital wart treatment. Given the ongoing controversy surrounding the effectiveness of this treatment, interferon therapy is generally considered a last-resort therapy reserved for severe cases that are unresponsive to other forms of treatment.[72]

PREVENTATIVE TREATMENTS—THE ROLE OF THE HPV VACCINE

Gardasil (HPV4). In the summer of 2006, the FDA approved the use of the first HPV vaccine, Gardasil (HPV4, Merck & Co.). The recombinant, quadrivalent vaccine was intended for the prophylactic treatment of girls and young women 9 though 26 years of age for the prevention of the following pathologies caused by HPV types 16 and 18: cervical, vulvar, and vaginal cancer, and condyloma acuminata. In addition, HPV4 is indicated for the prevention of precancerous or dysplastic lesions caused by HPV 6, 11, 16, and 18 (Table 3).[76] Gardasil triggers the formation of host antibodies to the HPV subtypes, which are directly responsible for approximately 90 percent of genital warts and 70 percent of cervical cancers.[77] Gardasil injections are administered in three separate doses and appear to be 99-percent effective in preventing genital wart formation in patients naïve to HPV infection.[78]

Four placebo-controlled, double-blind, randomized Phase II and III clinical studies evaluating more than 20,000 women ages 16 to 26 found that HPV4 reduced the incidence of definitive therapy (i.e., loop electrosurgical excision) by 16.5 percent (95% CI 2.9–28.2) and surgery to excise external genital lesions by 36.5 percent (95% CI 3.6–44.2), compared with placebo for all HPV-related diseases. Also, those individuals who were already infected with one or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV subtypes. Overall, HPV4 provided not only a sustained protection against low-grade lesions attributable to HPV subtypes 6, 11, 16, and 18, but also a substantial reduction in the burden of these diseases through 42 months of follow up.[79]

Long-term follow-up studies have confirmed the ongoing protective effects of Gardasil up to five years post-vaccination with no evidence of waning immunity.[80] Although some controversy persists with respect to the side effects of the vaccine, current evidence supports the fact that there is no causal link between vaccination and any serious adverse events, such as illness, hospitalization, permanent disability, or death.[79] The main side effects attributable to the HPV vaccine are mild and include fainting, swelling at the injection site, headache, nausea, and fever. Moreover, similar effects have been shown to occur with comparable frequency following the administration of placebo vaccines.[80] In fact, the main drawback of HPV4 is arguably the cost, which is known to be quite high and can pose a significant strain on public and private finances.

In the fall of 2009, the FDA expanded the therapeutic use of HPV4 in the prevention of genital warts to include boys and young men between the ages of 9 and 26 years.[81] The vaccine was shown to induce a similar immunogenic response in males when compared to females and appears to be equally beneficial in preventing wart development. It may also play a role in reducing precancerous lesions responsible for the development of anal and penile cancers.[79] Furthermore, expansion of the vaccination initiative to include males has the added benefit of reducing the viral burden of HPV by directly targeting the viral pool. Eliminating the potential reservoir for viral incubation is a critical and necessary step in eventually eradicating the virus.[82]

Cervarix (HPV2). In the fall of 2009, the FDA licensed a recombinant, bivalent HPV vaccine (HPV2, GlaxoSmithKline) for use in females ages 10 though 25 years. Cervarix is directed against two oncogenic types, HPV 16 and 18, which are associated with cervical cancer, cervical intraepithelial neoplasia grade 1 or worse, and adenocarcinoma *in situ* (Table 3). The efficacy of HPV2 was evaluated in two Phase II and III randomized, double-blind, controlled clinical trials involving more than 18,000 female subjects who were followed for a mean of 35 months. Efficacy against HPV 16- or 18-related cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma *in situ* was 93 percent (95% CI 79.9–98.3). Comparable to the HPV4 safety data, injection-site pain, redness, and swelling were reported significantly more in the HPV2 group as compared to placebo. Fatigue, headache, and myalgia were the most common general symptoms. The dosing and administration schedules are similar to HPV4 where the second dose is administered 1 to 2 months after the baseline dose, and the third dose is administered six months after the baseline dose.[83]

Overall, the American Cancer Society and Advisory Committee on Immunization Practices recommend routine vaccination of girls age 11 or 12 years with three doses of either HPV2 or HPV4. The vaccination series can be started beginning at the age of nine.[4,84]

Thus far, there is only one randomized, observer-blinded, head-to-head study comparing these two vaccines in a single, well-defined population of more than 1,100 healthy women ages 18 to 45 years. Results of this study showed that HPV-16 and HPV-18 neutralizing antibodies induced by HPV2 were higher than those induced by HPV4 across all age strata ($p<0.0001$). The observed differences in immune response induced by the two vaccines could be due to differences in formulation, particularly with regard to adjuvant factors that enhance the immune response to vaccine antigens. Although the clinical importance of this difference in immune response is unknown, they may represent determinants of duration of protection against HPV-16 and 18.[85]

TABLE 3. Quadrivalent versus bivalent human papillomavirus recombinant vaccine

	QUADRIVALENT HUMAN PAPILLOMAVIRUS RECOMBINANT VACCINE (GARDASIL, MERCK & CO.)[68]	BIVALENT HUMAN PAPILLOMAVIRUS RECOMBINANT VACCINE (CERVARIX, GLAXOSMITHKLINE)[73]
Year of FDA approval	2006 for females, 2009 for males	2009 for females
Vaccination for HPV types	• 6 and 11 (genital wart formation) • 16 and 18 (oncogenic)	16 and 18 (oncogenic)
Sex/age indications	• Females/9–26 years old • Males/9–26 years old	Females/9–years old
Clinical prevention	• Cervical, vulvar, and vaginal cancers • CIN grade 1 or worse • Cervical adenocarcinoma • Cervical adenocarcinoma *in situ* • Genital warts	• Cervical cancer • CIN grade 1 or worse • Cervical adenocarcinoma *in situ*
Dosing regimen	Three separate intramuscular injections (baseline, two months, six months)	Three separate intramuscular injections (baseline, one month, six months)
Adverse reactions	• Mild injection site reactions (pain, swelling, erythema, pruritis) • Headache • Gastroenteritis • Nasopharyngitis • Dizziness • Diarrhea	• Mild injection site reactions (pain, swelling, erythema, pruritis) • Fatigue • Headache • Myalgia • Gastroenteritis • Arthrlagia
Pregnancy category	B	B
Comments	99% effective in preventing genital wart formation in patients naïve to HPV infection	93% effective in preventing HPV 16 or 18-related CIN grade 2 or worse or adenocarcinoma *in situ*

Pregnancy Category B=It is not known whether this vaccine can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity. CIN: cervical intraepithelial neoplasia

CONCLUSION

External genital warts and their associated HPV infections are considered among the most common sexually transmitted diseases affecting the general population. It is estimated that one percent of the sexually active population of the United States, or 3 to 6 million people, acquire symptomatic genital wart infections each year.[24] Approximately 90 percent of genital warts are related to infection with HPV subtypes 6 and 11, which have a very low malignant potential and rarely progress to cancerous lesions. However, those warts associated with HPV subtypes 16 and 18 may be predisposed to oncogenic transformation.[6]

Current treatment options focus predominantly on removal of the external wart rather than attacking the underlying viral infection and have thus proven somewhat inadequate in achieving effective long-term results. Therapies can be categorized as topical, surgical, or immunomodulatory and can differ quite significantly in terms of cost, duration of therapy, dosing schedules, and adverse effects. As of yet, there is little evidence to suggest that one class of treatments is not more effective than another nor has a single therapy emerged as the gold standard for treatment. Selection of a therapeutic modality typically depends on the needs and desires of the individual patient.

Given the strikingly high prevalence of genital warts among the population, and the lack of adequate therapies, HPV vaccines such as HPV4 and HPV2 may play a significant role in reducing the burden of disease by preventing viral infection and transmission. Studies evaluating the effectiveness of HPV vaccines in preventing genital wart infection have shown it to be both safe and extremely successful in both sexes. This supports the need for further research into the development of similar vaccines targeting additional subtypes of HPV. As vaccination against HPV continues to gain popularity and a broader therapeutic

population base, it may prove to be instrumental in the treatment and eventual eradication of genital warts.

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