External Genital Warts: Diagnosis, Treatment, and Prevention

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External genital warts (EGWs) are visible warts that occur in the perigenital and perianal regions. They are due primarily to non-oncogenic human papillomavirus (HPV) types, usually types 6 and 11. Physical examination assisted by bright light and magnification is the recommended approach for primary diagnosis. Biopsy is indicated when EGWs are fixed to underlying structures or discolored or when standard therapies are not effective. Recurrences are common, and there is no single treatment that is superior to others. Among women with atypical squamous cells, molecular HPV testing may be useful in determining who should be referred for colposcopy. Condoms may provide some protection against HPV-related diseases and thus are recommended in new sexual relationships and when partnerships are not mutually monogamous. Because the efficacy of cesarean section in preventing vertical transmission of HPV infection from women with EGWs to their progeny has not been proved, it is not recommended.

Genital human papillomavirus (HPV) infection is probably the most common of infections that can be sexually transmitted and is an important public health problem because of its clear association with cervical cancer in women and its potential association with other anogenital malignancies [1, 2]. HPV specifically infects and replicates in the lower levels of stratified epithelium; these infections manifest clinically as warty growths and dysplastic areas of cellular proliferation [3, 4]. HPVs are classified and referred to as “types” on the basis of their genetic similarities; the terms “serotype” and “strain” are not appropriate characterizations. Currently, >80 different HPV types have been sequenced and officially classified, ~30 of which have been found to infect genital epithelium [5, 6]. Seminal work has shown and clinical trial data continue to demonstrate that HPV types 6 and 11 are most often associated with external genital warts (EGWs) [7–25].

Clinical warts are the most common recognized clinical manifestation of genital HPV infection. Although HPVs infect the squamous epithelium at a variety of anatomical locations, the present review focuses on EGWs; these are visible warts that occur on the perigenital and perianal region: the penis, scrotum, and vulva; pubic, perineal, and perianal areas; and crural folds. We focus primarily on the available treatments, including studies published since our prior review [26], and factors that influence treatment decisions. In addition, we briefly review diagnostic criteria and issues pertinent to prevention, including approaches relevant to EGW-affected patients and their partners and the prevention of transmission, both sexual and perinatal.

BACKGROUND

Papillomaviruses infect virtually all vertebrates. Although there may be as many as 230 different HPV types according to data from partially sequenced virus
fragments, >80 HPV types have been officially sequenced and typed [5, 6]. HPV classification is based on genetic similarities in the virus capsid peptide L1; different types share <90% homology [6]. HPVs are nonenveloped, double-stranded DNA viruses that are tropic for epithelium; although the virus initially infects the basal cell layer, the virus life cycle is inextricably linked to the progressive differentiation of epithelial cells. Recent work has identified α6 integrin as a potential HPV binding site [27, 28]. The α6β4 complex is expressed on the basal cell layer of epithelium and, for one, is involved in anchoring these cells to their basement membrane [27, 29]. In vitro studies have shown that the binding of virus-like particles to these complexes induces cell proliferation through Ras-MAP kinase pathways [29]. Additionally, Joyce et al. [30] have demonstrated a heparin-binding region located within the carboxy-terminus of L1 that interacts with heparin and with human keratinocyte cell-surface glycosaminoglycans that resemble heparin in vitro; these regions may be important to virus binding in vivo.

More than 30 of the sequenced HPV types infect genital epithelium, and ~20 have been classified as “oncogenic” or “high risk” because of their association with cervical cancers (e.g., HPV-16 and -18) [1, 2, 11, 12, 31–37]. The oncogenic HPVs also appear to be commonly associated with other anogenital cancers [38]. The other HPV types are considered to be “low-risk” or “non-oncogenic” because they are rarely, if ever, associated with anogenital cancers [7, 12]. EGWs are generally due to low-risk HPV types, particularly HPV types 6 and 11; however, high-risk types have been found in a small proportion of patients, especially those with immunodeficiency [7–12, 39–45]. The prevalence of HPV infection varies, but experts generally agree that ~1% of the adult population have symptomatic EGWs, that most genital HPV infections occur during the first few years after the onset of sexual activity and are transient, and that more than half of the middle-aged adult population bear some evidence of historical infection (e.g., serum antibodies) [46–49]. Because epidemiological research has focused largely on cervical infection in women, we know more about HPV infection among women than among men and about cervical infection and its clinical correlates than about any other manifestation. For example, data from 8 studies that evaluated 4843 female and 135 male heterosexuals showed that infection is relatively common and that infection with low-risk HPV types is less common than infection with high-risk types [48, 50–55]. Population-based data have suggested that the incidence of genital HPV infections, including infections with low-risk types, decreases with age [48, 50]. Thus, detection of HPV infection among older women is more likely to reflect persistent infection, whereas detection among younger women more often represents recently acquired and probably transient infection [48, 50].

Clinical manifestations of HPV infection include asymptomatic infection and dysplastic cellular changes that range from minor histological perturbations, such as koilocytosis, to pre-cancerous and malignant cellular changes. Studies of cervical HPV infection have suggested that infections are largely transient; most women clear the virus within 9 months–1 year of when it is first detected [48, 56, 57]. Two published studies have reported clearance rates for low-risk (HPV) type infections: Moscicki et al. [58] reported that 60% of women with low-risk HPV type cervicovaginal infection cleared infection within 10 months, and Franco et al. [50] reported that 12% per month of women similarly infected cleared infection. However, no studies have specifically determined whether infection duration for affected external genital tissues is comparable to those of cervicovaginal epithelium. Also, placebo-controlled trials have suggested that for some patients, EGWs may spontaneously clear without treatment, probably because of acquired cellular immune responses [26, 59–63]. Although some trials showed no regressions among placebo-treated patients, many trials have reported that as many as 40% of placebo-treated patients show spontaneous clearance [26, 62, 63]. Finally, the rapid emergence of HPV-related lesions among immunocompromised patient populations, specifically among organ transplant patients and HIV-infected men and women, suggests that HPV may be harbored in a latent form, in vivo [64–72]. However, to date, latent infection has not been shown conclusively.

Recurrent respiratory papillomatosis (RRP) is associated with low-risk HPV types. RRP can occur in adults but principally presents in children; among children, it is thought to be due to birth-associated exposure to HPV [73–79]. RRP is rare, is not malignant, and recurs often [77–79]. RRP can be life-threatening if papillomas grow to a size that obstructs the airway.

DIAGNOSTIC CONSIDERATIONS

Accurate diagnosis is an essential first step in treatment of EGWs. They can be flat, dome-shaped, keratotic, pedunculated, and cauliflower-shaped; they may occur singularly, in clusters, or as plaques [80–82]. Understanding the morphological presentation of these lesions is essential to accurate diagnosis of EGWs and their differentiation from other lesions that mimic them. As was previously mentioned, warts are not exclusive to external genital tissues. Sexual exposure can be associated with warts in the urethra and at the meatus, cervix, vagina, anus, and oral cavity. Cervical warts, however, require clinicians to rule out high-grade dysplasia using Papanicolaou (Pap) tests prior to treatment.

EGWs can be diagnosed through direct visual inspection with bright light and magnification [63]. The male urinary meatus and the fossa navicularis can be fully inspected with an otoscope and small spreader [83]. Biopsy is not recommended routinely.
However, when EGWs are not responsive to therapy or when neoplasia is suspected because of blue or black discoloration, sudden recent growth or increased pigmentation, or fixation to underlying structures, biopsy and histological evaluation should be performed [26, 63]. Patients should be referred to a specially trained clinician whenever neoplasia is suspected or when EGWs are recalcitrant [26, 63]. Specialized tests, including acetowhite testing and virus-typing assays, are not recommended routinely for accurate diagnosis [26, 63, 84]. There are no data to suggest that molecular testing for nucleic acids (e.g., hybrid capture assays) are effective, and they are not recommended in the routine diagnosis or management of EGWs [26, 63].

The differential diagnosis for EGWs includes a number of skin conditions: condyloma latum, seborrhiec keratoses, dysplastic and benign nevi, molluscum contagiosum, pearly penile papules, and neoplasms. Condyloma latum is due to secondary syphilis, an infection caused by Treponema pallidum, and can be diagnosed with dark-field microscopy and standard serological tests for syphilis [85]. Seborrhiec keratoses are common, localized hyperpigmented lesions that are rarely associated with malignancy [86]. Molluscum contagiosum is caused by a pox-virus, highly infectious, and common in immunodeficiency; lesions are usually umbilicated [87]. Pearly penile papules are angiofibromas that occur at the penile corona and are normal variants that require no treatment except reassurance [88].

High-grade intraepithelial lesions and cancers that may mimic EGWs include Bowen’s disease, Bowenoid papulosis, squamous cell carcinomas, Buschke-Lowenstein’s tumors, vulvar intraepithelial neoplasias (VINs), and dysplastic nevi. Bowen’s disease, an in situ squamous cell carcinoma, is confined to the epidermis and becomes invasive infrequently [9, 89, 90]. Associations between Bowen’s disease and both low- and high-risk HPV types have been reported [91, 92]. Bowenoid’s papulosis often presents as EGWs, but histological examination favors squamous cell carcinoma in situ and, for women, VIN [93–98]. Both low- and high-risk HPV types have been isolated from Bowenoid’s papulosis [97]. Also, Buschke-Lowenstein tumors, a rare and highly differentiated genital carcinoma, are associated with particular subtypes of low-risk HPV types [99–101]. Dysplastic nevi can be differentiated from benign nevi and EGWs; the former shows nonuniformity of color and irregular borders, is often accompanied by a reported history of recent growth in size or shape or increased pigmentation, and may be >6 mm in diameter [89].

TREATMENT

There are no data to indicate whether treatment for EGWs eliminates infectivity; thus, the primary goal of treatment is to ameliorate symptoms and remove symptomatic warts. Because of uncertainty over the effect of treatment on future transmission and the possibility of spontaneous resolution, an acceptable alternative for some patients is not to undergo therapy unless their lesions persist or enlarge.

A wide variety of therapies are available to treat EGWs. Some treatments are based on long-standing use and are supported by historical practice, smaller trials, and case-series data, whereas recently developed treatment modalities are supported by more rigorous research. Not all EGW therapies have been well studied, and not all are available in every treatment setting. Thus, effective treatment is dependent on an understanding of the underlying disease process and available treatment options.

Although there have been no clinical trials or observational studies that specifically addressed the factors that influence selection and treatment by patients with EGWs, 2 studies have examined the effectiveness of treatment guidelines. Clinical algorithms that follow formal treatment guidelines appear to improve wart clearance rates [102, 103]. Treatment guidelines offer structure to clinicians who are less experienced as well as support to experienced clinicians who treat particular outcomes infrequently. Clinical algorithms also provide a framework on which to base systematic evaluation of patient care outcomes. When EGWs remain after therapy, referral to a specialist continues to be advised [63]. However, EGWs recur frequently, and it is often unclear whether recurrences are due to recurrence, reinfection, or other factors—for example, individual immune responses or inadequate treatment.

Once treatment has been decided on, complete clearance of visible EGWs is the patient care goal. No currently recommended therapies treat HPV infection directly; however, IFN, a cytokine, and imiquimod, an immune response modifier, seek to treat infection by stimulating immune responses. In addition, cidofovir, an acyclic nucleoside phosphonate approved for treatment of cytomegalovirus infection, directly affects viral replication and is being tested currently for treatment of EGWs and other HPV-related outcomes [104–106].

Sex-specific differences in clearance and recurrence have been reported; it is likely that EGWs on smooth moist tissues, including the urinary meatus, respond better to treatment than those located on dry, cornified tissues [107–110]. However, only the most recent clinical trials have possessed enough statistical power to answer sex-specific questions about treatment outcome; the absence of these data in early studies is most often due to inadequate sample size.

Meatal EGWs are infrequently evaluated separately in clinical trial analyses, but where they have been reported, clearance rates appear to be similar to clearance rates reported for women in other studies [107–112]. If these data are representative, it seems likely that higher clearance rates may be related to the tissue type affected.

Treatments are often classified as either surgical or non-
surgical in nature or, more recently, are divided into provider- and patient-applied therapy groups. The clinical trial literature for these therapies has been reviewed extensively elsewhere [26, 62, 63, 113]. Surgical treatments include electrosurgery, surgical excision, cryotherapy, and laser surgery; these are classed together with other provider-applied treatments. Nonsurgical provider-prescribed and -applied therapies include podophyllin resin, IFN, and bi- and tri-chloroacetic acid (BCA/TCA). Patient-applied nonsurgical treatments include podophylloptox (podofilox), imiquimod (Aldara), and 5-fluorouracil (5-FU) cream. As with any pharmacological agent, the use of a nonsurgical treatment is contraindicated when there is any history of hypersensitivity to any product constituent. Data suggest that there is no single treatment modality that is vastly superior to other therapies [26, 62, 63, 113]. However, the randomized clinical trials data do suggest that podofilox, imiquimod, cryotherapy, podophyllin resin, BCA/TCA, and topically applied and intralesionally injected IFN are more effective than placebo and that, compared with one another, surgical treatments are largely equivalent [113].

**PATIENT-APPLIED THERAPIES**

*Podophyllotoxin/podofilox (Condylux).* Podofilox is an antimitotic agent that destroys warts by inducing tissue necrosis locally [26]. Podofilox is supplied in 0.5% gels, solutions, and creams; preparations ranging from 0.15% to 8% have been evaluated, as have a variety of treatment frequencies and duration, in randomized studies [23, 25, 114–119]. However, generally, podofilox is applied twice daily for 3 consecutive days and repeated for 2–4 cycles [24, 83, 120].

Unlike its parent agent, podophyllin resin, both podofilox gel and solution are devoid of the mutagenic flavenoids quercitin and kaempferol [26, 121]. Podofilox solutions and gels for the treatment of EGWs have been well evaluated historically and reviewed elsewhere. Prior placebo-controlled trials have shown that 45%–77% of patients attained clearance within 4–6 weeks of treatment [24, 26, 62, 63, 113, 120, 122]. Since our last report, one new study of podofilox gel has shown results that are not (statistically) significantly different from prior investigations; 37% of 167 patients treated with podofilox 0.5% gel showed EGW clearance, compared with placebo (table 1) [123].

Untoward outcomes have been reviewed extensively elsewhere; in brief, commonly reported side effects due to podofilox include local inflammation or irritation, most often erosion, burning, pain, and itching [26, 63, 113]. Symptoms uncommonly associated with podofilox include balanoposthitis (inflammation of the foreskin and glans in uncircumcised males), dyspareunia, bleeding, scarring, and insomnia; one case of preputial tightening has been reported [26, 63, 113, 124]. Recurrences have been reported for 4%–38% of patients followed in clinical trials [115, 120, 124]. Safety during pregnancy has not been evaluated; effective contraception for women of childbearing age is advised.

*Imiquimod/imidazoquinolinamine (Aldara).* Aldara is an imidazoquinolinamine derivative (1-[2-methylpropyl]-1H-imidazo[4,5-c]quinolin-4-amine) that has no in vitro antiviral activity but does induce macrophages to secrete cytokines (e.g., IL-2 and IFN-α). In vivo studies have shown enhanced cytolitic and lymphoproliferative responses after administration [163, 164, 167, 168]. It has been tested in animals and humans [126, 163–165, 167]. Imiquimod has been studied extensively and is a new therapy relative to other EGW treatments.

Imiquimod is applied topically, and both 1% and 5% preparations have been studied; 5% cream is more efficacious and has been approved for EGW treatment by the US Food and Drug Administration [109, 126, 165]. In 3 randomized placebo-controlled trials of 5% cream, 37%–54% of treated patients showed clearance within 16 weeks (table 1) [102, 126, 165]. Unlike many early EGW clinical trials, these studies were designed with enough power to detect differential effects among subgroups. For example, Edwards et al. [126] reported that women were nearly twice as likely to show complete clearance compared with men; however, these relationships have not been replicated by others [102].

Imiquimod is dispensed as an individual dose and is applied directly to the affected area at bedtime, 3 times/week for up to 16 weeks [83]. Patients are advised to wash the affected area with mild soap and water on awakening, to remove residual drug [83].

Mild to severe erythema has been associated with EGW treatment that uses 5% imiquimod cream [126]. In addition, localized erosion, itching, and burning sensations are often associated with imiquimod; irritation, induration, scabbing, tenderness, and pain have been reported less frequently [113, 126]. Recurrences have been reported in 13%–19% of clinical trial subjects who were treated with 5% imiquimod cream. As with other EGW treatments, safety during pregnancy has not been tested; effective contraception is advisable for women of childbearing age.

**PROVIDER-APPLIED THERAPIES**

*Podophyllin resin.* Podophyllin resin is an antimitotic agent that, like podofilox, destroys warts by inducing tissue necrosis locally. Podophyllin resin is one of the oldest nonsurgical EGW treatments available. It is compounded as a 10%–25% suspension in tincture of benzoin; to avoid the risk of systemic absorption and possible toxicity, podophyllin should not be used for areas >10 mm² [26, 63].

Podophyllin resin has been evaluated extensively, relative to
Table 1. Summary of randomized controlled trials for and select uncontrolled studies of external genital wart therapies: percentage of patients showing wart clearance, recurrence by end of study, guideline-based recommended use, and safety during pregnancy.

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<tr>
<td><strong>Recommended</strong></td>
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<tr>
<td>Patient-applied</td>
<td></td>
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<tr>
<td>Podophyllotoxin gel</td>
<td>37 [123]</td>
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<tr>
<td>Imiquimod 5%</td>
<td>27–54 [102, 109, 126, 127]</td>
<td>13–19 [109, 126]</td>
<td>Unknown</td>
<td>Comparisons to placebo [109, 126]; effectiveness data suggest that, in clinic settings, effectiveness is comparable to reported efficacy [102]</td>
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<tr>
<td><strong>Provider-applied</strong></td>
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<tr>
<td>Cryotherapy</td>
<td>27–88 [13, 107, 111, 128, 129]</td>
<td>21 [107]</td>
<td>Yes [130, 131]</td>
<td>Compared with podophyllin resin, TCA, and electrosurgery; comparisons have been made with and without IFN as an adjunct therapy</td>
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<tr>
<td>Podophyllin resin (20%–25%)</td>
<td>23–72 [110, 124, 132–135]</td>
<td>23–65 [110, 124, 132–135]</td>
<td>No, contains flavenoid mutagenic flavenoids, quercetin and kaempferol [121]</td>
<td>Compared with podophyllotoxin, cryotherapy, electrosurgery, TCA, and surgical excision; comparisons have been made with and without IFN as an adjunct therapy</td>
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<tr>
<td>BCA/TCA</td>
<td>63–70 [128]</td>
<td></td>
<td>Yes</td>
<td></td>
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<tr>
<td>Electrosurgery</td>
<td>61–94 [107, 137]</td>
<td>22 [107]</td>
<td>Yes</td>
<td>Compared with IFN, cryotherapy, and podophyllin resin</td>
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<tr>
<td><strong>Not recommended</strong></td>
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<tr>
<td>IFN Topical</td>
<td>33–90 [143, 144]</td>
<td></td>
<td>No</td>
<td></td>
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<tr>
<td>Topical IFN: 1.0 × 10⁶ IU/g and 0.15 × 10⁶ IU/g gel vs. placebo as adjuvant therapy to prevent recurrences</td>
<td>Not applicable [145]</td>
<td>IFN gel, 54–62; placebo, 75 [145]</td>
<td>No</td>
<td>Topical IFN-g was somewhat more effective in preventing recurrences compared with placebo for 1 million IU/g concentration RR, 0.82; 95% CI, 0.60–1.14; for 0.15 million IU/g concentration RR, 0.72; 95% CI, 0.51–1.04 [145]</td>
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<td>Intralesional</td>
<td>17–63 [146–154]</td>
<td></td>
<td>No</td>
<td></td>
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<tr>
<td>Topical 5 fluorouracil</td>
<td>10–50 [162–164]</td>
<td>50 [162]</td>
<td>No</td>
<td>Case series, vulvar application [165], compared solution and cream preparations [166]</td>
</tr>
<tr>
<td>Cidofovir (S-1-(3-hydroxy-2-phosphonyl-methoxypropyl) cytosine)</td>
<td>33 [105]</td>
<td></td>
<td>Unknown</td>
<td>HIV-infected patients; genital ulcers related to treatment reported for 8/10 treated patients [105]</td>
</tr>
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</table>

**NOTE.** Newly published and reviewed studies are [102, 105, 123, 144]. BCA, bichloroacetic acid; CI, confidence interval; RR, relative risk; TCA, trichloroacetic acid.
other treatment modes (table 1) [26, 63, 113]. When compared, individually, with podofilox, cryotherapy, and electrosurgery or when used with intralesional IFN as an adjunct therapy, these treatments were statistically equivalent to podophyllin alone [113]. However, a variety of adverse effects including bone marrow suppression, hepatocellular dysfunction, neurological compromise, hallucinations, psychosis, nausea, vomiting, diarrhea, and acute abdominal pain have been reported over the past 20 years [83, 166, 169–178]. These untoward effects occurred in situations where the treatment area was extensive or on skin surfaces that favored systemic absorption. Together with the large number of alternative therapies now available, these reports of side effects have led some European experts to recommend against use of podophyllin in primary-care settings [83].

Recurrences have been reported for 23%–65% of clinical trial participants [110, 124, 132–135]. Podophyllin contains mutagenic flavonoids, quercetin, and kaempferol [121] and thus is not safe during pregnancy. Effective contraception for women of childbearing age is essential [26, 63, 113].

BCA/TCA. BCA/TCA is corrosive to the skin and mucous membranes; the acid denatures and precipitates proteins and kills EGW-affected tissues [179]. BCA/TCA is not readily absorbed through the skin [179], and, although BCA/TCA has rarely been studied, it is widely used in practice. Treatment concentrations are not standardized, but early studies reported the use of 85% and 95% concentrations [26, 128, 180].

Effectiveness in randomized clinical trials ranges from 63% to 70%, and no new studies have been reported during the past 2 years. BCA/TCA has been compared with cryotherapy and laser therapy in case series and randomized trials reviewed elsewhere [26, 62, 63, 113], and acid ablation is no more effective than cryotherapy (table 1) [113]. The rates of recurrences for patients treated with BCA/TCA remain unclear.

BCA/TCA may run onto adjacent, healthy skin if overapplied. Applying carefully and allowing drying time afterward will prevent the spreading of acid onto unaffected areas [26]. Local pain, ulceration, and scabbing have been reported [113]. BCA/TCA has been administered adjunctively with laser therapy during pregnancy; although 97% of treated women showed clearance, significant side effects attributable to this treatment combination included suprapubic catheterization in 7 of 32 treated women, premature labor in 2 women, premature rupture of membranes in 1 woman, and prolonged rupture of membranes in 2 others [180].

**SURGICAL TREATMENTS**

Surgical treatments directly ablate or excise wart-affected tissues, using curettage or tangential excision, electrocautery, or electrotherapy. Generally, anesthesia, analgesia, and infection control are priorities with all surgical treatments. The resulting surgical wound for most EGW excisions, if performed properly, should extend only into the upper regions of the dermis. Adequate local anesthesia and postprocedural prescription of mild analgesics should control discomfort during the procedure and during wound healing, respectively. Local anesthesia can be achieved rapidly by standard preparations (e.g., lidocaine); preparations that contain epinephrine both prolong the anesthetic effect and provide hemostasis [181].

When reviewing clinical trial data, it is important to remember that the duration of follow-up significantly affects efficacy estimates; the immediacy of results related to surgical treatments almost always favors these treatments. Nonsurgical therapies, no matter who applies them, almost always require time for the agent to act; thus, when compared with surgical procedures, their short-term efficacy is generally less favorable. No randomized clinical trials that have compared the efficacy of scalp and scissors excision against sham or no treatment have been reported. Generally, untoward effects of surgical treatments for EGWs include pain and the risk of infection. All surgical treatments can be used during pregnancy.

Surgical excision. Surgical excision that uses scalpel, curettage, or scissors directly removes wart-affected tissues. No new studies have been reported since the last guidelines were issued (table 1). Older clinical studies that compared these procedures against other forms of therapy suggested that 35%–72% of patients show clearance of visible warts immediately and, ~1 year after excision, 19%–29% of patients showed recurrences [138, 139]. Podophyllin resin appears to be less effective than surgical excision; however, when compared with laser therapy, surgical excision is about equally effective [138–140].

Electrosurgery. Electrosurgery uses electrical energy, in the form of thermal coagulation or electrocautery, to destroy EGW-affected tissues. Since our last review, we have found no new studies of electrosurgical methods for EGW removal (table 1) [26, 62, 113]. Our prior evaluation showed that electrosurgery was evaluated by use of case series reports; 3 comparisons, which used randomization of subjects, compared electrosurgery against IFN, cryotherapy, and podophyllin resin [26, 62, 63, 107, 113, 136, 137]. Overall, 61%–94% of electrosurgery-treated patients showed clearance in 3 comparative trials 3–6 weeks of treatment [26, 62, 107, 113, 136, 137]. In these trials, electrosurgery was found to be ~3 times more effective than intramuscular IFN and ~6 times more effective than subcutaneously injected IFN [113, 136]. Compared with podophyllin resin, electrotherapy is about twice as effective initially but equally effective 3 months after therapy [107]. Similarly, 2 randomized trials showed slightly greater efficacy for electrotherapy compared with cryotherapy; however, the differences in treatment arms did not persist after 3 months of follow-up [107, 137].
The loop electrosurgical excision procedure (LEEP) has been compared with laser treatment for EGWs; Schoenfeld et al. [182] reported that 24 (86%) of 28 lesions treated with LEEP and 21 (75%) of 28 lesions treated with a laser showed no HPV DNA within a 20-mm circumference of the treated lesion. In clinical studies, 14%–22% of patients have shown recurrences [107, 182].

Cryotherapy. Cryotherapy uses liquid nitrogen to freeze and kill EGW-affected tissues; after several days, the tissues from the treated area slough, and inflammation ensues, then subsides as healing is evident. No new studies have been reported since our last review; prior studies compared cryotherapy against TCA and evaluated its efficacy when used in combination with IFN, variable freeze-thaw-cycle patterns, and placebo (table 1) [26, 62, 63, 113]. Handley et al. [129] and Eron et al. [13] each reported data for comparison groups who received cryotherapy plus placebo; wart clearance was 40% at 3 months and 27% at 6 months, respectively, for these groups. Data have suggested that recurrence rates may be 38%–73% by 6 months after treatment [13, 129].

Laser therapy. Laser therapy uses focused, infrared light energy to vaporize EGW-affected tissues. Laser treatment is more complex and costly than other surgical treatments such as cryotherapy and electrosurgery and requires specialized equipment and additional clinical training to perform properly [26, 63]. Although some specialists offer laser treatment as an in-office procedure, there are circumstances in which in-hospital treatment and general anesthesia are indicated. For example, if EGWs are extensive and the treatment field is large, in-office laser treatment may not be feasible [26, 63]. Children and young adolescents may also require general anesthesia for treatment [26, 63].

No new clinical trials have been reported that have compared laser treatment for EGWs with other treatments or with groups that received sham or no treatment (table 1) [26, 62, 63, 113]. Clinical studies of laser treatment are problematic because of their small sample sizes and poor study design that cannot control adequately for the effects of confounders. Three-quarters of the randomized trials we reviewed previously evaluated adjunct therapies in combination with laser therapy [26, 62, 63, 113]. In those studies, the efficacy of laser treatment ranged from 23% to 52% for studies where follow-up ranged from 3 to 18 months [20, 140–142]. Recurrence rates for patients enrolled in studies that used a randomized controlled design ranged from 60% to 77% [20, 140, 141].

THERAPIES NOT CURRENTLY RECOMMENDED

IFNs. IFNs are proinflammatory cytokines that have broad antiviral effects. Intralesional and systemically administered IFNs have been evaluated extensively in randomized clinical trials and reviewed elsewhere [26, 63, 113]. Both preparations are associated with a systemic flulike syndrome, including headache, fever, myalgia, fatigue, nausea, and/or vomiting. Since the CDC sexually transmitted disease (STD) treatment guidelines were issued, one new clinical trial has evaluated topical IFN-β as an adjunct therapy to CO2 laser, electrotherapy, or liquid nitrogen treatment to prevent recurrence [144]. IFN is associated with a number of systemic untoward effects.

Intralesional IFN is injected directly into the base of each EGW. For this reason, the procedure is painful, and local anesthesia is recommended to minimize discomfort. Intralesional IFN has been found to be more effective than placebo in one trial [147] but was not of statistically greater benefit in a second [154]. As an adjunct therapy to podophyllin resin, intralesional IFN showed no greater added benefit than placebo after 11 weeks of follow-up [110].

Systemic IFN has not been shown to be effective as a primary or adjunct therapy for EGWs [113]. Bone marrow suppression has been reported in as many as one-quarter of treated patients. Anaphylactic reaction, bronchospasm, and depression have been reported in a few subjects. Because IFNs have no advantage over other standard therapies in treating EGWs and because there are significant constitutional side effects associated with their use, these preparations are not recommended forms of therapy.

Topical IFN as a primary treatment has shown inconsistent and widely varying clearance rates in the few trials that have been reported [143, 183, 184]. New data have suggested that 54%–62% of those treated with IFN gel as an adjunct to CO2 laser, electrocautery, and cryosurgery developed recurrences, whereas 75% of placebo-treated participants showed recurrences (i.e., for 0.15 × 106 IU/g, relative risk [RR], 0.72; 95% confidence interval [CI], 0.51–1.04; for 1 × 106 IU/g, RR, 0.82, and 95% CI, 0.60–1.14) (table 1) [144]. Topical IFN is associated with local burning and itching and sometimes with flulike syndrome, including fever, headache, and pruritis [113].

5-FU cream. 5-FU cream as a treatment for EGWs has not been evaluated adequately; no randomized controlled trials have been performed [113]. Case-series data showed wart clearance in 10%–50% of treated patients within 3 months of treatment onset [158, 159, 162]. However, little is known about recurrences when 5-FU cream is used; in one study, EGWs recurred in 50% of the few patients that were followed beyond the initial study period [158]. 5-FU is a mutagen and teratogen and is contraindicated during pregnancy; thus, women of childbearing age should use effective contraception if 5-FU cream is prescribed [185, 186]. To date, no untoward outcomes have been reported when inadvertent exposure during pregnancy occurred [186, 187]. Experts have suggested that 5-FU not be used in the primary care setting [26, 83].

Cidofovir. Cidofovir is a nucleoside analog of deoxycti-
dine monophospate used systemically to treat cytomegalovirus and herpes virus infections [188]. It is being tested against HPV with use of intraleisionally injected and topical preparations. Cidofovir directly treats viral infection, and in vitro data suggest that viral polymerases are more sensitive to cidofovir than cellular polymerases [188]. Thus, interruption of cellular polymerases in transcribing human proteins is less likely. To date, one study has shown EGW clearance in 4 of 12 HIV-infected patients treated with topical drug, and case reports have also suggested clearance may be achieved with topical administration (table 1) [104–106]. Ulcerations at the treatment site have been reported [104–106]. Larger, more extensive studies of this investigational preparation are needed.

**COMFORT AND CARE ASSOCIATED WITH TREATMENT**

Almost all successful EGW treatments result in some disruption of skin integrity; for that reason, there are general patient education and comfort measures that may improve outcomes. Infection control is a priority whenever skin integrity is disrupted; surgical wounds and disruptions association with desiccation can provide additional portals of entry for infection.

Before the patient leaves the office, providers should assure themselves that patients are able to see their EGWs; for perianal, perineal, and vulvar warts, examination with a hand-held mirror should be possible. This is especially important for patients who elect to use patient-applied therapies. Patients should examine the areas being treated daily to detect any symptoms of infection, including increased redness, swelling, or discharge (green, yellow, brown, or frothy). Malodorous discharge or any other signs of infection, including fevers, should be reported to the clinician immediately.

Sitz baths, the use of warm water, and other traditional forms of pericare may aid in healing and minimize secondary irritation. After cleansing, heat sources (e.g., heat lamps and warm air from hair dryers) can be useful to aid in healing and alleviate discomfort. If heat lamps are used, they should be placed no closer than 18 inches from the perigenital region; low-wattage bulbs (e.g., 45–60-watt bulbs) and fewer than 10–15 min of use several times daily are advisable. If patients use hair dryers to dry the affected area, the dryer should be held ≥18 inches from the affected area, and heat should be adjusted to the lowest possible heat setting. Prophylactic antibiotics are not indicated.

**PREVENTION ISSUES**

**Education and counseling.** Education and counseling messages should seek to improve individuals’ understanding of their infection and should include key concepts that will enable them to better manage self-care after diagnosis and treatment. In general, patients should be educated about HPV infection and its manifestations, including EGWs. When EGWs are diagnosed, clinicians should discuss their origin, treatment, and outcomes that are associated with them. It is critical to dispel misunderstanding about this diagnosis—for example, the HPV types that are associated with EGWs rarely, if ever, cause cancers.

When one sex partner is symptomatic for HPV infection, questions about the source of infection and about fidelity often arise. Patients often express concern about disclosure and whether partners should be examined. Questions about molecular HPV testing often occur when one partner is asymptomatic. Symptomatic patients often want to know whether their partners should be examined, whether condoms will protect their partners, whether they will be persistently infectious, and whether infection can be transmitted to others through casual contact.

Examination of sex partners is not necessary for the management of EGWs, because there are no data indicating that reinfection from untreated partners plays a role in recurrences. However, partners of EGW-affected patients may benefit from examination to assess the presence of EGW, from STD and Pap smear screening, and from counseling about the implications of having a partner with EGW and their own future transmission potential [63]. It is important to convey that even if one partner has visible warts, the other may not, although both have likely been exposed in an ongoing sexual relationship [55]. HPV molecular testing for patients with EGWs or their partners has no real utility in the clinical setting at this time; one study has suggested that even if virus testing were performed, it is likely that only one partner would test positive for HPV DNA [55].

Educational resources are helpful to patients and providers; these include telephone resources sponsored by the CDC (STD, 800-227-8922 and 800-342-2427; Spanish, 800-344-7432). Also, the American Social Health Association sponsors a telephone hotline for HPV infection and cervical cancer prevention (919-361-4848), as well as a number of online resources through their Web site (http://www.ashastd.org or, more specifically, http://www.ashastd.org/hpvccc/index.html).

**Cervical cancer screening and EGWs.** As for all sexually active women, it continues to be recommended that women with EGWs and the female sex partners of patients with EGWs be screened regularly for cervical cancer with the Pap test [26, 63]. This recommendation is made irrespective of the sex of a woman’s partners [189, 190].

Although molecular HPV typing is not recommended for the diagnosis or treatment of EGWs, it has been shown to be effective in the triage of women with cervical Pap test findings that show atypical squamous cells of undetermined significance (ASCUS). ASCUS bears a limited but significant risk of occult
high-grade cervical intraepithelial neoplasia; 5%–20% of ASCUS Pap tests are due to high-grade disease [49, 191–196]. The commercially available Hybrid Capture-II HPV DNA detection test, which uses a battery of probes to detect any of a group of 13 high-risk types, has been reported in several studies to have high sensitivity and acceptable specificity for detection of high-grade squamous intraepithelial lesion. Although its cost effectiveness has not yet been determined, this strategy provides clinicians with a triage tool to decide who might best benefit from colposcopic evaluation [191, 193].

**Anal cancer screening and EGWs.** Anal cancer is a rare malignancy whose incidence has been increasing among some US populations, most especially among those at risk for HIV infection [66, 67, 69, 72, 197–209]. There is an increasing body of data documenting its association with high-risk types of genital HPV infection [69]. On the basis of analogies with the success of Pap smear screening for the prevention of cervical cancer and concerns over the increase of anal cancer among persons with HIV infection, there has been interest in the use of anal Pap smear screening in selected high-risk populations [210–212]. This interest is supported both by evaluations that have suggested that anal Pap smears have sensitivity similar to that of cervical smears [209, 213]. Anal Pap testing shows sensitivity and specificity similar to cervical screening that uses Pap tests to detect malignant cell phenotypes [202, 204, 205, 214–216]. To date, there has been no standard of care for treatment and follow-up for low- and high-grade anal dysplasias. However, because of limited information about key issues such as the natural history of high-grade anal squamous intraepithelial lesion and the efficacy and untoward effects of treatment for lesions detected prior to invasive cancer, anal cancer screening is not routinely recommended at this time, pending further studies.

**Preventing sexual transmission.** Abstinence is the only known method of preventing HPV infection completely. A recent report that reviewed the efficacy of condoms for specific sexually transmitted infections concluded that condoms appear to be effective in preventing HIV infection for men and women and gonorrhea in men but that existing data were inadequate to answer the question for most STDs [217]. Although condoms have not shown protection against HPV infection, per se, Adams et al. [217] concluded that condoms may afford some protection against EGWs for men and cervical neoplasia for women. Our review of the literature supports this conclusion; some studies show protection and others do not [48, 218]. Well-designed randomized, controlled studies to test condom efficacy in relation to sexual transmission of HPV infection are unethical; thus, it is unlikely that we can definitively quantify condom efficacy beyond what can be achieved by well-performed observational studies. However, given the evidence of condom efficacy for at least some STDs (e.g., HIV and gonorrhea) and their likely protective benefit for some manifestations of HPV infection, condoms are always recommended in new sexual relationships and when partnerships are not mutually monogamous [217].

**Disclosure.** Disclosure of newly diagnosed EGWs to current sex partners may be important, as noted above. However, once warts have resolved, it is not clear that productive infection persists or that partners are infectious. Although one clinical study has suggested that virions are cleared from symptomatic tissues when EGWs are removed [182], others have found virus after clearance [219]. Thus, because genital HPV infection is so common among persons who have been sexually active and because the duration of infectivity is unknown, the value of disclosing a previous diagnosis of EGW to future partners is unclear.

**Preventing perinatal transmission.** Patients are often concerned about the effect that HPV infection might have on reproduction. HPV infection does not induce infertility. Although there is clear evidence that HPV DNA can be recovered from the lower genital tracts of pregnant women [220–232], the relationship between HPV exposure among newborns and productive infection remains unclear [220–232]. Juvenile-onset RRP (JORRP) is a rare condition that is associated with high morbidity and is thought to be due to low-risk HPV types. The risk for conveying RRP to progeny is low; prevalence estimates range from 1 in 400 births [76, 233] and 0.36 (95% CI, 0.12–1.13) and 1.1 (95% CI, 0.58–2.13) per 100,000 resident children aged <18 years [78, 79]. To avoid exposure to the virus, delivery by cesarean section has been proposed by some [160], however, only a very limited cost-benefit analysis has been performed, and the true effectiveness of this procedure is unknown [161]. In addition, the morbidity associated with cesarean section is significant and, when conservative estimates are used, the risks associated with cesarean section are greater than the risk of rearing a child with JORRP [78, 79, 234]. Thus, cesarean section is not recommended for prevention of JORRP.

**OTHER RECOMMENDATIONS: PREGNANCY**

Several factors may promote growth of HPV-induced lesions in pregnancy, including promoting effects of pregnancy hormones and diminished immunoresponsiveness. There are few treatments that have been tested and recommended in pregnancy. Only BCA/TCA, cryotherapy, electrocautery, and surgical excision, including laser treatment, are recommended currently.

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