Human Papillomavirus (HPV): Genital Warts and Recurrent Respiratory Papillomatosis (RRP)

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Purpose

This course describes human papillomavirus (HPV) and associated conditions (genital warts and recurrent respiratory papillomatosis), including risk factors, diagnosis, symptoms, treatments, and preventive measures.

Goals

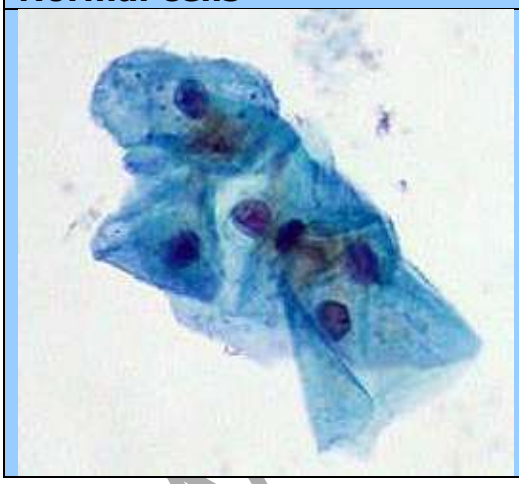
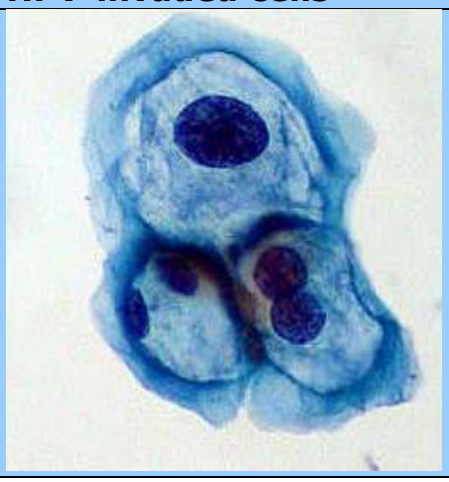
Upon completion of this course, the healthcare provider should be able to:

- Explain characteristics of human papillomavirus (HPV).
- List at least two low-risk HPV and two high-risk HPV.
- Describe at least 3 common sites of condylomata acuminata (genital warts).
- Explain diagnostic procedures used to diagnose genital warts.
- List and describe at least 6 treatment options for genital warts.
- Describe the difference between Gardasil® and Cervarix®.
- Describe symptoms related to recurrent respiratory papillomatosis (RRP).
- Describe at least 4 treatment options for RRP.
- List and describe 3 types of HPV-related cancers.

Introduction

There are hundreds of varieties of papilloma virus, infecting humans, birds, animals, and some reptiles. The papillomaviruses are non-enveloped DNA viruses that replicate in keratinocytes, which are found

in the squamous epithelia of the basal layer of the skin and in some mucosal surfaces, such as inside the cheek and the vagina. Papillomavirus are generally species-specific with about 100 different varieties affecting humans, about 40 spread by sexual or skin-to-skin contact. Up to 80% of sexually active people become infected with human papillomavirus (HPV). HPV is classified as low-risk if it usually does not cause cancer and high risk if it does. However, there are about a dozen low-risk HPV that result in genital warts, which can be a devastating disorder, as well as recurrent respiratory papillomatosis (RRP). Another 15 high-risk HPVs are linked to cancers involving the anus, cervix, vulva, vagina, penis, head, and neck. The CDC estimates that 80% of females have been infected with HPV by age 50. Males also carry infection. HPV is often asymptomatic and self-limiting, clearing within 2 years in about 90% of those infected. However, for the other 10%, HPV can cause serious morbidity. HPV is an increasing public health concern because prevalence has increased 4-fold over the past 20 years.

Normal cells	HPV-invaded cells
	

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Condylomata Acuminata (Genital warts)

HPV types 6 and 11 cause most cases of condylomata acuminata, more commonly referred to as genital warts. Condylomata (warts) may occur throughout the perineal area. Genital warts are spread through sexual contact, but the incubation period varies widely, from 6 weeks to 6 months and even years in some cases, so a person who develops genital warts cannot assume that the last sexual partner spread the infection if the person has had multiple sexual partners. However, about two-thirds of those infected develop lesions within 3 months of contact. Sexual contact may be vaginal, anal, or oral.

Genital warts in children may be an indication of sexual abuse although they may also have developed the infection from direct physical/manual contact.

Infection of more than one site is common. People who have not yet developed lesions may transmit the infection as well as those in remission, so practicing safe sex is essential for those with suspected or diagnosed genital warts. However, reducing visible lesions through treatment decreases the overall viral load and lowers the risk of transmission.

Condylomata may vary in appearance: pearly, filiform, fungating, cauliflower-like, or plaque-like. They may also be flat, verrucous (irregular wart-like), or lobulated.

Site	Discussion
Vulva/Urethra SOA Amsterdam, Wikimedia Commons	Lesions may involve the vulva and the urethra as well as the vagina and cervix. In some cases, lesions may spread to surrounding tissues and involve the anus. While HPV that causes genital warts has a low risk for cancer, that's not the same as NO risk, so women with lesions should be monitored frequently with Pap smears.
Penis SOA Amsterdam, Wikimedia Commons	Lesions may involve only the penis but may also spread to the scrotum, groin areas, and inner thighs. Bleeding may occur from flat urethral lesions.
Anus	Lesions may develop internally or externally about the anus, especially in males who engage in anal sex with other males. According to studies, about 40% of heterosexual couples now also engage in anal sex, so this may be reflected in an increase in anal lesions in heterosexuals as well as

SOA Amsterdam, Wikimedia Commons	homosexuals.

Those with genital warts may also develop lesions on the lips, mouth, tongue, palate or throat (recurrent respiratory papillomatosis), so those diagnosed with genital warts should be examined for other lesions. An examination for internal lesions should always follow diagnosis of external lesions. For example, those with lesions of the vulva may also have urethral, vaginal, and/or cervical lesions. Screening for other sexually transmitted diseases (STDs) should also be done as the risk factors for HPV are the same as for other STDs: Young age, multiple sex partners, smoking and drinking.

Genital warts may result in severe emotional distress, especially if lesions are extensive. People may become depressed and withdrawn. Painful treatments may cause a sense of despair, so adequate pain control is important. People may have difficulty establishing relationships with other because of fear and shame related to their infection, or they may lose relationships.

Some people may benefit from support groups for those with STDs. A few may require referral to a psychologist for help in reducing anxiety. A number on online forums are available on the Internet to provide support and information to help people who are living with genital warts. The healthcare provider should set aside time to answer questions and education patients about treatment and safe sex practices, which includes the use of barrier protection, such as condoms.

Diagnosis is usually by genital and/or pelvic examination. For women, a colposcopy may show lesions that are not visible to the naked eye. Applying 3% to 5% acetic acid solution for 5 to 10 minutes helps to make lesions more visible so they can be more easily detected. Women who have cervical changes (lesions or dysplasia) consistent with HPV infection should have HPV DNA testing to determine the type of HPV infection and their risk of developing cervical cancer.

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About 10 to 15% of people are infected with more than one type of HPV, so one should never assume that a patient with low-risk HPV causing genital warts is not at increased risk of cancer.

Treatment is essential, and patients should not try to treat the condition themselves with over-the-counter medications. Therapeutic options may present some risks to the healthcare provider, and no treatment has a 100% cure rate, so patients must often undergo repeated, painful treatments. Patients should seek advice from clinicians experienced in treating genital warts, as a wide range of treatment options is available.

Genital wart treatment options	
Observation	Small lesions may heal spontaneously without treatment in about 2 years, but they should be carefully monitored for changes or spread. Many people, however, want the lesions removed.
Cryosurgery	• Liquid nitrogen is used to essentially freeze the lesions. Cryosurgery is often used for cervical dysplasia to remove the surface tissue. • Cryosurgery can be used during pregnancy. • Clearance rate is about 75% effective.
Electrocauterization	A small electrical current is used to burn and cauterize the lesions. Smoke plumes may be infective, causing mucosal warts in the operator.
Laser therapy, carbon dioxide	Clearance rate is about 90% but up to 40% recur. The laser plume may be infective, causing mucosal warts in the operator.
Surgical excision	This is the most successful procedure and has the lowest recurrence rate. Cure rates with the initial excision range from 63% to 91%.
Infrared coagulation	Infrared light causes coagulation of the lesions and necrosis. Clearance rate is about 80%.
Podophyllin	This cytotoxic preparation can be used alone, but cure rate is only 20 to 50%. The cure rate improves if used in conjunction with cryotherapy. Intact lesions are treated with 10 to 25% concentration liquid applied to lesions one or two times weekly. The solution is applied one drop at a time with drying time between drops until the lesions are all

	covered. Only intact lesions are treated. After initial treatment, the area is washed 1 to 2 hours after application. After subsequent treatments, the area can be washed up to 4 to 6 hours after treatment. This medication is caustic so 25% solution should not be used near mucous membranes. Treatment protocol is the same for adults and children. Podophyllin is contraindicated during pregnancy.
Podophyllotoxin/ Podofilox (Condylox®)	This antimitotic agent is slightly more effective than podophyllin, and podofilox can be used for prophylaxis. Podofilox solution/gel (0.5%) is applied twice daily for 3 days with no treatment on the 4th day. This cycle is repeated for up to 5 weeks. The daily maximum dose is 0.5 ml solution or 0.5g gel, and maximum coverage <10 $cm^{2.}$ Podofilox is NOT for use on mucous membranes. Hands should be thoroughly washed after application to remove all residue. Pediatric dosage has not been established. Podofilox is not recommended for use during pregnancy, but it may be used during pregnancy if benefits outweigh risks
Trichloroacetic acid (TCA)	This caustic agent cauterizes skin, keratin, and other tissues although it causes less irritation and toxicity than other agents in the same class, but it is less effective and recurrence rate is high. TCA may be used during pregnancy if benefits outweigh risks.
5-Fluorouracil (Efudex®, Fluoroplex®)	5-FUO, an antineoplastic agent, is used to prevent recurrence in patients who are immunocompromised (such as those with HIV/AIDS). It is started within 4 weeks of ablation. Five percent cream is applied daily for 10 weeks or 1% cream twice daily for 2 to 6 weeks. Pediatric dosage has not been established. 5-FUO should not be used during pregnancy.
Kunecatechins	This botanical ointment is indicated only for

(Veregen®)	patients who are immunocompetent. It is used only for external lesions. It is applied three times daily with 0.5 strand of ointment used for each lesion. Pediatric dosage has not been established. Kunechatechins may be used during pregnancy if benefits outweigh risks.
Interferon alpha-n3 (Alferon N®)	This immunomodulatory agent is injected intralesionally. It is used for refractory cases of genital warts although recurrence rates are still 20% to 40%. The medication is injected (250,000 U) twice weekly for up to 8 weeks (to maximal dosage per treatment of 2.5 million U). Pediatric dosage has not been established. Interferon alpha-n3 may be used during pregnancy if benefits outweigh risks.
Imiquimod (Aldara®)	This immunomodifier induces secretion of interferon alpha and cytokines. Clearance rate is 50%. Five percent cream is applied 3 times a week for 16 weeks. It is usually applied at bedtime and washed off of the skin after 6 to 10 hours. Pediatric dosage for those >12 is the same as for adults but dosage has not been established for those <12.

While a cure for genital warts has remained elusive, preventive vaccines have been developed and are now recommended for all girls, ages ≥9-26 (usually given at ages 11-12 before sexual activity). Vaccination is now also recommended for boys/men as well, especially homosexual males. Two vaccines are available.

HPV vaccines	
Gardasil®	Gardasil® is indicated for prevention of HPV types 6, 11, 16, and 18, so it is effective for prevention of both cancer (cervical, vulvar, vaginal, and anal) and genital warts. This vaccine is administered in 3 separate doses: initial, 2 months later, and 6 months later.
Cervarix®	Cervarix® is indicated for prevention of HPV types 16 and 18, so it is not effective for prevention of genital warts. This vaccine is administered in 3 separate doses: initial, 2 months later, and 6 months later.

People bringing their children for vaccination or coming for vaccinations themselves should be advised to choose Gardasil® over Cervarix® because of the devastating effects of genital warts. People may be unaware of the difference between the coverage of the two vaccines. However, some parents, especially those who believe that this vaccine may encourage promiscuous behavior, may be reluctant. The best method to ensure compliance with recommended vaccinations is education.

Recurrent respiratory papillomatosis (RRP)

The same types of papillomaviruses that cause genital warts can also cause recurrent respiratory papillomatosis (RRP), in which condylomata grow in the throat, resulting in hoarseness and/or dyspnea. The condylomata occur primarily in the larynx and about the vocal cords but may spread to the trachea, bronchi, and even to the lungs. The condition is referred to as "recurrent" because the warts tend to regrow after surgical removal. At one time the disease was thought to affect only children, but that is not the case. Women with genital warts can pass the infection to a newborn, sometimes causing the child to have RRP. Delivering by Caesarean does not eliminate risk to the neonate although it may reduce the rate of transmission. Those most at risk are first-born children of young mothers (<20) with active condylomata. HPV types 6 and 11 are responsible for almost all juvenile RRP cases.

RRP may occur at any age in adults, but those most commonly affected are males in their 30s. These cases are almost all caused by HPV types 6 and 11 as well. About 5% of adults harbor HPV in their respiratory tracts, but only a small number (1:1000) develop RRP, suggesting that the disease may be related to an immune deficiency.

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Researchers believe that most cases of adult RRP were not acquired at birth but are acquired through sexual activity.

Symptoms vary depending on the size and location of lesions. Infants and young children may exhibit a weak cry, dysphagia, cough, and inspiratory stridor. Respiratory symptoms are often misdiagnosed as asthma or croup. Adults usually present with chronic hoarseness, dysphonia, or aphonia. In some people, symptoms develop slowly, but in others severe obstruction may occur within days.

Diagnosis is done with laryngoscopy and biopsy of lesions. There is no curative treatment for RRP, but a combination of surgery and intralesional antiviral medication may slow regrowth. About 3% to 5% develop squamous cell carcinoma. Children often experience remission at puberty, but by this time many have had up to 20 surgical interventions for treatment. Juvenile RRP tends to be more severe and aggressive than adult RRP. Adult females in remission may experience recurrence with pregnancy.

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RRP treatment options	
Resection	Microdebridement is usually now preferred to carbon dioxide laser because of less damage to surrounding tissue. In some cases, an emergency tracheostomy may be needed during surgery.
Intralesional injection with cidofovir	Cidofovir injected into the surgical site is effective in reducing rates of regrowth and has replaced intralesional injections of interferon. Patients may need a series of injections. A study of 13 patients showed 77% experienced remission after 3.5 injections. Recommended dosage has not been established.
Photodynamic therapy.	Studies indicate this treatment slows the rate of condyloma growth. Dihematoporphyrin ether (DHE) is administered 2 to 3 days prior to surgery and then argon laser light to the affected area with laryngoscope or bronchoscope activates the drug.
Dietary supplements	An active ingredient (Indole 3-carbonal) found in cruciferous vegetables has been found to help reduce lesions. Adults: 200 mg PO BID. Children 10mg/kg PO daily.
Acyclovir	This appears to slow regrowth in some patients if started at the time of surgery. It reduces rebound regrowth in those treated with interferon.
Interferon	(Generally replaced by cidofovir). Usually reserved for those requiring surgical removal 3 or 4 times

	yearly. Requires at least 6 months of treatment, and a rebound effect may occur after discontinuation of therapy.

Follow-up (initially every 2-4 weeks) is critical to identify evidence of regrowth.

HPV-related cancers

Cervical cancer

While HPV is usually a self-limiting infection, destroyed by the immune system within 2 years, in some cases the infection persists, causing precancerous cell changes (dysplasia or cervical intraepithelial neoplasia--CIN) of the cervix. Both high-risk and low-risk HPV can result in dysplasia, but only the high-risk progress to cancer, usually slowly over 15 or 20 years. Most cases of cervical cancer result from infection with HPV types 16 and 18 although there are 13 different HPVs that can cause cervical cancer. About 10% of women infected with high-risk HPV go on to develop cervical cancer [**See CE course: Cervical Cancer].** Cervical cancer is usually asymptomatic until advanced, and then it is difficult to treat. Regular screenings with Pap smears can help to detect cervical cancer in early stages when it can be surgically removed.

Vulva, vagina, and penis cancer

One type of HPV can cause cancer of the vulva, vagina, anus, head, and neck. Over time, persistent infection can result in precancerous cell changes that can progress to cancer if they are not identified and removed. While there are other causes of these types of cancers, CDC statistics show that HPV is overwhelmingly the cause for most concern:

- Vulvar cancer: About 40% are linked to HPV.
- Vaginal cancer: About 70% are linked to HPV.
- Penile cancer: About 40% are linked to HPV.
- Anal cancer: About 85% are linked to HPV.

Head and neck cancer

While the most common causes of cancers of the head and neck/thrat are alcohol and tobacco, about 25% of mouth cancer and 35% of neck The same type of HPV that causes vulva, vagina, penis, and anus cancer can cause cancers of the head and neck. Incidence appears to be increasing as the numbers of those engaging in oral sex have increased. As rates of smoking and drinking have fallen, the overall numbers of cancers of the head and neck have decreased, but cancers of the tonsils and base of the tongue have increased, as these cancers

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are related to HPV infections. Currently in the United States, about 60% to 70% of tonsil cancers are HPV-related. People having ≥6 oral sex partners over their lifetime triple their risk of developing oropharyngeal cancer.

Summary

Over 100 types of papillomavirus can infect humans, with about 40 spread by sexual contact. HPV is classified as low-risk if it usually does not cause cancer and high risk if it does. Low risk HPVs, primarily types 6 and 11, cause most cases of condylomata acuminata, usually known as genital warts. Genital warts may occur externally anywhere in the perineal area (vulva, anus, penis) as well as internally in the urethra, vagina, cervix, and anus. Lesions may also occur on the lips, mouth, tongue, palate, or throat. The same types of papillomaviruses that cause genital warts can also cause recurrent respiratory papillomatosis (RRP), in which condylomata grow in the throat, resulting in hoarseness and/or dyspnea. A wide range of treatments are available, depending on the site and extent of lesions, but no treatment is 100% effective, and even those in remission can still spread the infection. Treatments for genital warts include surgical excision, cryosurgery, cauterization, and numerous topical treatments, such as podophyllin, podofilox, TCA, 5-FUO, kunecatechins, and imiquimod, and interferon alpha-n3. Two vaccines are now available and advised for those ages 9 to 26 (usually given at 11 to 12): Gardasil®, which provides protection against HPV types 6, 11, 16, and 18 (both cancer-causing and genital-wart causing HPV), and Cervarix®, which provides protection against HPV 16 and 18 (cancer-causing HPV) only.

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