Available online at www.sciencedirect.com
SCIENCE DIRECT®
Antiviral Research 63 (2004) 141–151
Antiviral Research
www.elsevier.com/locate/antiviral

Review

# Current status of antiviral therapy for juvenile-onset recurrent respiratory papillomatosis

David W. Kimberlin*

*Division of Pediatric Infectious Diseases, The University of Alabama, 1600 Seventh Avenue South CHB 303, Birmingham, AL 35233, USA*

Received 9 June 2002; accepted 22 June 2004

**Abstract**

Human papillomavirus (HPV) infections are among the most prevalent of the sexually transmitted diseases, with up to 75% of women in the United States acquiring genital HPV infection at some point in their lives. HPV infections of the genital tract are of medical and public health concern due to their propensity to lead to the development of cervical cancer, and because they can be transmitted to the respiratory tract of a newborn child, resulting in juvenile-onset recurrent respiratory papillomatosis (JO-RRP). JO-RRP is the second most common cause of hoarseness among pediatric patients, and is the most common benign neoplasm in the larynx. The traditional treatment for JO-RRP is the physical removal of the wart through laryngoscopy and surgical debulking of the airway papillomas. Papillomas frequently recur following surgical resection, however, often necessitating repeated ablative efforts to maintain a patent airway. In a minority of patients, surgical management must be supplemented with adjuvant medical therapy, with interferon being the best studied and most commonly utilized. Recently, a Phase II investigation of a therapeutic vaccine yielded promising results, and a Phase III evaluation of this therapeutic modality is planned. Other adjuvant treatments currently being utilized, but for which controlled data of benefit are lacking, include cidofovir, indole-3-carbinol, ribavirin, mumps vaccine, and photodynamic therapy. As with surgical management, viral persistence occurs following treatment with these adjuvant modalities, further contributing to the challenge of managing patients with this potentially devastating disease.


*Keywords:* Human papillomavirus; Papillomatosis; HPV; Laryngeal papillomatosis; Respiratory papillomatosis; Interferon; Cidofovir; Indole-3-carbinol; Therapeutic vaccine

**Contents**



* Tel.: +1-205-996-6097; fax: +1-205-975-9972.
*E-mail address:* dkimberlin@peds.uab.edu.

0166-3542/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.antiviral.2004.06.013

## 1. Introduction

Although juvenile-onset recurrent respiratory papillomatosis (JO-RRP) is the second most common cause of hoarseness among pediatric patients and the most common benign neoplasm in the larynx, it is still a rare disease (Lindeberg and Elbrond, 1990; Derkay, 1995). As a consequence, virtually no single otolaryngology group in a community, tertiary care, or academic setting has enough patients with JO-RRP to conduct a systematic evaluation of any given adjuvant treatment modality. Adjuvant therapies which are frequently employed in patients whose JO-RRP disease is refractory to surgical ablation alone include interferon α-2a, cidofovir, indole-3-carbinol, ribavirin, mumps vaccine, and photodynamic therapy. With the exception of interferon, none of these has undergone rigorous, controlled evaluation to establish safety and efficacy. Recently, a therapeutic vaccine has completed Phase II testing, with results that are promising enough to warrant a controlled Phase III trial in the JO-RRP population. This review will summarize recent developments in antiviral therapies for JO-RRP, highlighting promising treatment possibilities while also identifying continuing barriers to therapeutic advances. This builds upon earlier summaries of this topic which have already been published (Kimberlin and Malis, 2000; Kimberlin, 2002) (Table 1).

Table 1
Therapeutic modalities employed in the management of juvenile-onset recurrent respiratory papillomatosis

| |
|---|
| Primary treatment |
| Surgical debulking of laryngeal papillomas |
| $CO_2$ laser |
| Microdebrider |
| 585-nm pulsed dye laser |
| Argon plasma coagulation |
| Adjuvant treatments |
| Therapies with efficacy proven in sufficiently large, randomized, controlled trials |
| Interferon α-2a |
| Therapies employed based upon anec dotal case reports and case series |
| Cidofovir |
| Cimetidine |
| *cis*-Retinoic acid |
| Indole-3-carbinol |
| Mumps vaccine |
| Emerging therapies showing promise in controlled trials |
| Photodynamic therapy |
| Therapeutic vaccination with HspE7 |
| Therapies without biologic basis or no longer widely employed |
| Acyclovir |
| Ribavirin |

## 2. Biology of human papillomaviruses

Human papillomaviruses (HPVs) are members of the *Papillomavirus* genus of the *Papovaviridae* family. The HPV genome consists of double-stranded circular DNA contained within an icosahedral capsid composed of 72 capsomeres. The genomes of approximately 76 types of HPVs and 8 putative types of HPVs have been completely sequenced and are available through the HPV Sequence Database at http://hpv-web.lanl.gov/. The viral genome contains eight open reading frames (ORFs). The early ORFs (E1, E2, E4, E5, E6, and E7) code for nonstructural regulatory proteins, and the late ORFs (L1 and L2) code for capsid proteins. The papillomavirus genomes of different viral types all have the same general organization (Fig. 1) (Bonnez, 2002). While papillomaviruses are widespread among vertebrates, each type has a narrow species specificity, and no papillomaviruses are known to cross species barriers in humans. Papillomaviruses also have significant cellular tropism, with specific viral types usually producing disease at distinct body sites (de Villiers, 1989).

The recurrence of localized disease in both the genital and laryngeal regions following periods of clinical inactivity suggests that viral persistence or latency can occur (Shah and Howley, 1996). Perhaps because of these biologic aspects of viral persistence or latency, HPV infections are among the most prevalent of the sexually transmitted diseases, with some reports suggesting that up to 75% of women in the United States acquire genital HPV infection at some point in their lives (Syrjanen et al., 1990; Schneider et al., 1992). An estimated 5,500,000 new cases of genital HPV infections occur each year in the United States, and at least 20 million persons in the U.S. are believed to be actively infected (Cates, 1999; Bonnez, 2002).

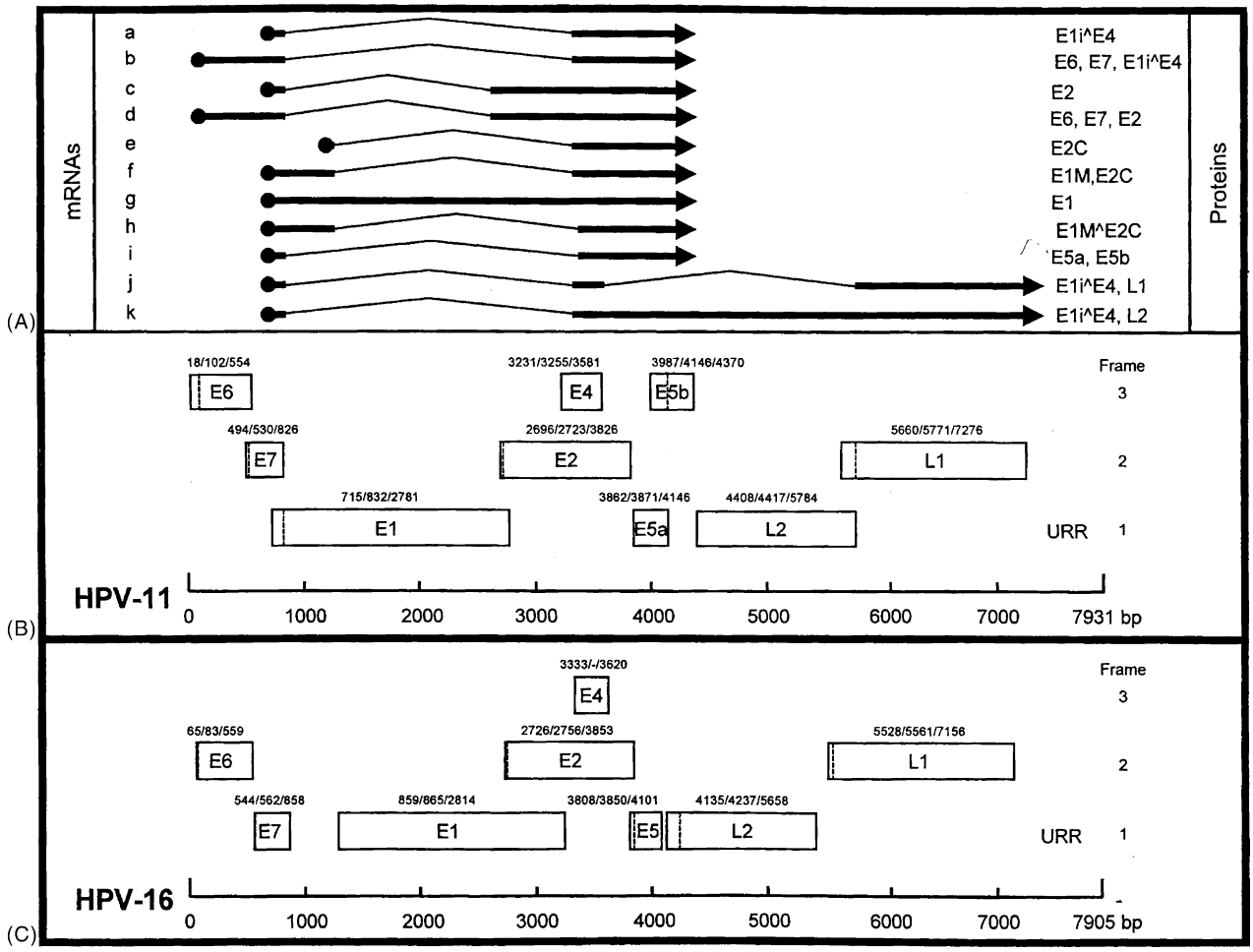


Fig. 1. HPV genetic maps. (A) HPV-11 transcription map. (B) Linearized HPV-11 DNA map. (C) Linearized HPV-16 DNA map. By convention, the map origin of papillomaviruses is defined as the position homologous to the *Hpa*I single restriction site of HPV-1. The open boxes correspond to the ORF in the respective translation frames. The numbers above each ORF indicate the nucleotide position of the preceding stop codon (left solid vertical line)/start codon (dashed vertical line)/stop codon (right vertical line). Each HPV-11 mRNA is depicted with its cap site (solid circle), exons (thick line), introns (thin angled line), and poly(A) site (arrow). The putative corresponding proteins are denoted on the right of the messages. From Bonnez (2002).

## 3. Clinical manifestations

### *3.1. Genital HPV infection*

The majority of patients with anogenital warts present to their physician with asymptomatic growths on their genitalia (Chuang et al., 1984), although occasionally patients will complain of pruritis, burning, pain, or bleeding. The warts are slightly hyperkeratotic, firm, exophytic papules that are flesh to dark gray in color. They can be either sessile or attached by a broad short peduncle, and are typically from 1 mm to 2 cm in size. In circumcised men, the papillomas typically are found on the shaft of the penis, whereas in uncircumcised men they are most frequently located at the preputial cavity (Oriel, 1971; Chuang et al., 1984; Bonnez, 2002). Less commonly involved sites include the urethra, scrotum, perineum, groin, and pubic area. In women, the vast majority of clinically apparent lesions are located over the posterior introitus, including the fourchette, spreading toward the labia minora, labia majora, and clitoris. Less common sites of involvement include the perineum, vagina, anus, cervix, and urethra (Oriel, 1971; Bonnez, 2002). During pregnancy, genital papillomas can increase in both size and number (Osborne and Adelson, 1990). Regardless of anatomic location, most genital warts are caused by HPV-6, HPV-11, or HPV-16, and to a lesser extent other HPV types (Bauer et al., 1991; Sugase et al., 1991; Ho et al., 1998; Woodman et al., 2001; Winer et al., 2003).

Epidemiologic and clinical investigations strongly suggest a role for HPVs in the development of cervical cancer (zur Hausen, 1985; Campion et al., 1986; Stoler and Broker, 1986; Tsunokawa et al., 1986; Shirasawa et al., 1987; Anderson et al., 1991; Koutsky et al., 1992; Lorincz et al., 1992; Stoler et al., 1992). The viral genome is transcriptionally active in all HPV-associated cervical cancers (Tsunokawa et al., 1986; Shirasawa et al., 1987; Stoler et al., 1992; Shah and Howley, 1996) and is found in both primary and metastatic tumors (Lancaster et al., 1986). The HPV ORFs which convey transforming capabilities are the E6 and E7 ORFs. The E6 and E7

ORFs are consistently expressed in HPV-transformed cells and in HPV-associated tumors, with the degree of transcription correlating directly with the grade of the tumor (Durst et al., 1992; Stoler et al., 1992; Shah and Howley, 1996). Human papillomaviruses may also be involved in the pathogenesis of other malignancies, both within the genital tract (Daling and Sherman, 1992; Demeter and Reichman, 1994) and in areas such as the larynx (Chang et al., 1992) and the oropharynx (Mork et al., 2001).

### 3.2. Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis is characterized by the growth of papillomas at sites in the respiratory tract. Two distinct groups of patients with RRP exist: those whose disease presents during childhood (JO-RRP) and those whose disease becomes apparent during adulthood (adult onset recurrent respiratory papillomatosis, or AO-RRP). Approximately one-half to two-thirds of patients with RRP have onset of illness during childhood (Shah and Howley, 1996).

The highest incidence of JO-RRP occurs in patients under 5 years of age (Strong et al., 1979), with the mean age at diagnosis being 4 years (Reeves et al., 2003). Most patients with JO-RRP come to medical attention due to hoarseness or voice changes. Recurrent respiratory papillomatosis is the second most common cause of hoarseness in this age group, and is the most common benign neoplasm in the larynx (Jones and Myers, 1985; Morgan and Zitsch, 1986).

There is extensive evidence to support the theory that viral transmission in JO-RRP occurs at birth as the neonate passes through an infected birth canal (Hajek, 1956; Shah and Howley, 1996): (1) 30–60% of mothers of JO-RRP patients have a known history of genital warts, compared with <5% of mothers whose children do not have JO-RRP (Cook et al., 1973; Quick et al., 1980; Abramson et al., 1987); (2) the vast majority of children with JO-RRP are born vaginally and thus have a potential exposure to an infected birth canal, although cases of JO-RRP have been reported among children delivered by cesarean section (Shah et al., 1986); and (3) HPVs can be detected for several weeks in the oropharynx of infants born to mothers with genital warts (Fredericks et al., 1993). Risk factors associated with JO-RRP include maternal age <20 years, first order births, and vaginal delivery (Shah et al., 1998). Of those children who develop JO-RRP, however, not all have mothers with evidence of vaginal HPV disease, and clinicians should consider the possibility of sexual abuse in children who acquire RRP outside the peripartum period (Yoshpe, 1995).

While papillomas can be found from the nasal vestibule to the peripheral lung, the larynx is the most common site of involvement, with 96% of JO-RRP patients having laryngeal involvement (Reeves et al., 2003). The vocal folds are most commonly involved, with subsequent interference with normal vocal cord closure during phonation resulting in hoarseness. Other sites commonly involved in JO-RRP include the limen vestibule, the nasopharyngeal surface of the soft palate, the midline of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricle, the under surface of the true vocal folds, the carina, and the bronchial spurs (Kashima et al., 1993). Papillomas may also occur throughout the respiratory tract, with or without laryngeal involvement, including the trachea, lungs, nose, and oral cavity. While the prevalence of latent HPV DNA is similar between the larynx and the trachea, the frequency of tracheal disease is lower, suggesting that local cellular factors (e.g., stratified squamous epithelium of the larynx versus ciliated pseudo-stratified columnar epithelium of the trachea) may be contributing to the likelihood of disease (Abramson et al., 2004).

Human papilloma viral Types 6 and 11 are primarily responsible for JO-RRP, with HPV-6 being the most common (Terry et al., 1987; Kashima et al., 1991). HPV-16 and -18 have been implicated as well (Chang et al., 1992). Infection by HPV-11 has been correlated with the most severe form of RRP disease (Mounts and Kashima, 1984; Hartley et al., 1994; Rimell et al., 1997; Rabah et al., 2001; Pou et al., 2004). Recent data suggest that younger children are more likely to have persistence of disease than are older children (Ruparelia et al., 2003), and children with disease progression are more likely to have been diagnosed at a significantly younger age than children with stable disease (Reeves et al., 2003). Children with very aggressive HPV disease may develop distal airway spread of the papillomas into the tracheobronchial tree and/or the pulmonary parenchyma (Silver et al., 2003; Zawadzka-Glos et al., 2003); in these latter patients, the disease is fatal (Kramer et al., 1985; Cole et al., 1989). Although controversy remains over whether the performance of a tracheotomy in those patients with life-threatening proximal airway disease potentiates distal (i.e., tracheobronchial and/or pulmonary parenchymal) airway seeding, there is some evidence that tracheotomy is an independent risk factor in the development of subsequent distal airway spread (Cole et al., 1989).

Spontaneous malignant transformation/degeneration of previously benign papillomas to squamous cell carcinoma occurs in 3–5% of RRP patients. Increased expression of p53 and pRb proteins and a reduced expression of p21(WAF1) protein appear to be significant events in malignant transformation of respiratory tract papillomas (Lele et al., 2002). Development of malignancy appears to be independent of the apparent risk factors of tobacco use or exposure to radiation therapy (Solomon et al., 1985; Kashima et al., 1988). It is most commonly associated with HPV types of high-malignant potential (i.e., HPV-16 and HPV-18), occurs in both JO-RRP and AO-RRP, and carries a dismal prognosis.

Clinically, the disease course in JO-RRP exhibits extreme intra- and inter-patient variability, with some patients experiencing periods of relatively accelerated disease activity admixed with periods of relative quiescence. Although controversial, some patients and clinicians have observed that the disease becomes less aggressive (as manifest by less frequent surgical interventions) as a child with JO-RRP enters puberty. Whether this is strictly because the diameter of the airway

has increased as the patient has grown, or whether there are hormonal factors at work, remains to be fully elucidated.

Although accurate data regarding the prevalence and incidence of recurrent respiratory papillomas are not available, a task force on recurrent respiratory papillomas queried 1346 board certified otolaryngologists practicing in the United States as of January 1, 1993 (Derkay, 1995). Based on a questionnaire survey, annualized incidences of 2354 new pediatric cases and 3623 new adult cases were reported. The incidence of the disease was estimated at 4.3 per 100,000 children younger than 14 years of age, which is similar to the Danish incidence rate of 3.6 per 100,000 people (Lindeberg and Elbrond, 1990). The U.S. incidence of disease for persons 15 years of age and older is approximately 1.8 per 100,000 persons (Derkay, 1995). The costs for managing JO-RRP annually in the United States are estimated between $40 million and $123 million (Bishai et al., 2000).

## 4. Treatment of JO-RRP

The ultimate goal of therapy is the eradication of all papillomas from the respiratory tract. Given the current treatment modalities, this is not a goal that can be achieved at this time. Therefore, the practical goal of therapy is to manage RRP as a chronic disease, diminishing the frequency with which laser ablation or microdebridement are needed while maintaining an open airway and the best possible voice. Over time, a better understanding of the predictors of JO-RRP may lead to management strategies which ultimately could prevent infection in a person at risk. The knowledge and interventional tools needed for this approach, however, are beyond the current medical technologies.

### *4.1. Surgical therapies for RRP*

At the present time, the most common treatment for RRP is the physical removal of the wart through laryngoscopy and surgical debulking of the papillomas. The goal of surgical therapy is to completely remove the papillomas while maintaining the surrounding normal structures. In younger pediatric patients, a smaller caliber airway, associated with aggressive disease, occasionally necessitates surgical debridement as frequently as every 2 weeks. Mechanical debulking of the laryngeal papillomas is usually accomplished either with the $CO_2$ laser or with microlaryngeal instruments. Sharp dissection techniques, cauterization, and the application of acetic acid or podophyllum have also been described (Bauman and Smith, 1996), but are utilized less frequently. In patients with very aggressive disease, or who have anterior or posterior commissure disease, subtotal removal with clearing of the airway may be the best achievable result to minimize the development of synechia which would make the airway even more narrow.

Although extremely precise, the $CO_2$ laser is not without problems, including: (1) thermal injury to adjacent normal soft-tissues, resulting in permanent laryngeal scarring; (2) aerosolization of HPV viral particles into the laser plume (Kashima et al., 1991), thereby posing potential risks to the patient and operating room team; and (3) risk of a laser-induced airway fire. Fortunately, the development of a laryngeal microdebrider, a technology adapted from orthopedic arthroscopic equipment, has seemingly overcome some of the shortfalls of the $CO_2$ laser (Myer and Cotton, 1999; El-Bitar and Zalzal, 2002; Pasquale et al., 2003; Patel et al., 2003). Additional advances in the surgical debulking of airway papillomas are continually sought, including use of the 585-nm pulsed dye laser (Bower et al., 1998; McMillan et al., 1998; Valdez et al., 2001) and argon plasma coagulation (Bergler et al., 1997).

Papilloma regrowth occurs at variable rates of time after any of these procedures. Similarly, the average number of operative procedures annually is highly variable from patient to patient. It was recently reported that children in a National Registry had a mean of 5.1 surgeries per year (Reeves et al., 2003). Unfortunately, the aforementioned surgical treatment modalities have not resulted in curing this virally-mediated recurrent disease, and therefore several adjuvant therapies have been evaluated.

### *4.2. Adjuvant therapies for RRP*

Up to 10% of patients with RRP will require adjuvant therapy (Derkay, 2001). The criteria for initiating adjuvant therapy vary somewhat, with the most common requirement being the need for surgical debridement more than four times per year (Derkay, 2001).

#### *4.2.1. Interferon α-2a*

The most commonly accepted adjuvant therapy for RRP remains the systemic administration of interferon α-2a. Interferons are a family of nonspecific regulatory proteins associated with a variety of antiviral, antiproliferative, and immunomodulating activities (Borden and Fall, 1981; Kimberlin and Prober, 2003). There are two major types of interferons. Type 1 (α and β) interferons are secreted by all nucleated cells after viral infection; interferon α is predominantly produced by virus-infected leukocytes and interferon β by fibroblasts. There are about 20 subtypes of interferon α that share a high degree of amino acid sequence homology but have different in vitro antiviral and biologic effects on human cells (Dorr, 1993). Interferons do not have direct antiviral activity, but rather exert their antiviral effects by inducing production of more than two dozen effector proteins in exposed cells. Antiviral effects are mediated by inhibition of viral penetration or uncoating, synthesis or methylation of mRNA, viral protein translation, or viral assembly and release (Gen and Ransohoff, 1993). The main inhibitory effect for specific viruses differs among virus families, and individual viruses can be inhibited at more than one step. Antiviral activity also can be facilitated by the complex interactions between interferons and other

components of the immune system, resulting in modification of host response to infection (Kimberlin and Prober, 2003).

At interferon doses at and above 1 to 2 million IU, most persons develop an influenza-like illness, with fever, chills, headache, myalgia, arthralgia, and gastrointestinal disturbances (Renault and Hoofnagle, 1989). These symptoms typically appear during the first week of therapy and remit with continued therapy, rarely necessitating therapy discontinuation or dosage modification. In contrast, major therapy-limiting toxicities of systemically administered interferon are neuropsychiatric complications and bone marrow suppression (McDonald et al., 1987). About 10 to 20% of interferon recipients develop neuropsychiatric problems. Neutropenia and thrombocytopenia are the most common signs of bone marrow suppression (CASL Hepatitis Consensus Group, 1994).

Multi-institutional trials of interferon α-2a have shown variable efficacy in patients with aggressive RRP (Haglund et al., 1981; Schuurman and Van Den Broek, 1986; Healy et al., 1988; Steinberg et al., 1988; Leventhal et al., 1991). Approximately one-third of patients who initially have a good therapeutic response will experience a significant reboundphenomena, with resurgence of the lesions upon discontinuation of treatment. Anecdotal reports of adjuvant therapy combining interferon with methotrexate in patients with pulmonary parenchymal disease have found some benefit in a few patients (Avidano and Singleton, 1995; Silver et al., 2003).

#### 4.2.2. Photodynamic therapy

Photodynamic therapy is based on the selective uptake of hematoporphyrins by neoplastic cells, including papillomatous tissue (Auborn, 2002). In photodynamic therapy, the photosensitizer Foscan® is administered intravenously. After a 6-day waiting period for the sensitizer to selectively accumulate in the papillomas, activation of the sensitizer is accomplished with a non-burning red-light laser. This creates a singlet oxygen reaction within the affected tissue, theoretically resulting in the destruction of the HPV-infected cells. Photodynamic therapy has been shown to decrease the rate of laryngeal papilloma growth following treatment in some human subjects (Abramson et al., 1992, 1994), but not in others (Borkowski et al., 1999). These effects can be long-lasting with continued treatment (Shikowitz et al., 1998). However, viral persistence following photodynamic therapy has been noted, and photosensitivity can persist for weeks after the therapy has been discontinued. A trial of photodynamic therapy for the treatment of JO-RRP is being conducted by Long Island Jewish Medical Center, with support from the National Institute on Deafness and Other Disorders (http://www.lij.edu/lijh/otolaryngology/clinical_research.html).

#### 4.2.3. Indole-3-carbinol

Indol-3-carbinol/diindolylmethane (I3C/DIM) compound is derived from eating cruciferous vegetables, including broccoli, cabbage, and cauliflower. Upon exposure of I3C/DIM to the acidic environment of the stomach, the compound is broken down to estrogen metabolites, which have been shown to have potential anti-papilloma effects (Wiatrak, 2003). Estrogen binds to membranes derived from laryngeal tissue, and this binding is enhanced in papilloma tissue (Essman and Abramson, 1984). Topical estrogen therapy was used in the past as a potential treatment for RRP, and the current rationale for I3C/DIM therapy is that these specific phytochemicals may induce a better estrogen metabolite balance, leading to a cellular environment that discourages pathologic conditions caused by HPV (Auborn et al., 1998; Wiatrak, 2003). Case series reporting the effects of indole-3-carbinol for the treatment of RRP have been published (Coll et al., 1997; Rosen et al., 1998). However, no controlled data are currently available to definitively quantify degree of benefit, if any. A large, multi-institutional study has recently been completed, although results are not yet published (Wiatrak, 2003).

#### 4.2.4. *cis*-Retinoic acid

*cis*-Retinoic acid has been considered to be potentially beneficial in RRP due to its effects on epithelial maturation. Despite case reports of improvement temporally associated with administration of *cis*-retinoic acid (Eicher et al., 1994), this therapy has proven ineffective in the management of HPV infection in humans when evaluated in small controlled trials (Bell et al., 1988; Avidano and Singleton, 1995).

#### 4.2.5. Acyclovir

The HPV genome does not encode any enzymes. Since most antiviral agents are activated by or exert antiviral activity upon viral-specific enzymes, the lack of intrinsic HPV enzymes quite possibly severely limits use of agents such as acyclovir in the management of JO-RRP. Despite the lack of a rationale for mechanism of action, investigations of acyclovir have been undertaken, and small non-controlled studies have suggested that acyclovir decreases the extent of respiratory papillomatosis in patients with recalcitrant disease (Endres et al., 1994; Kiroglu et al., 1994). However, the beneficial effect of acyclovir appears to be insufficient to counteract the rebound phenomenon when interferon is stopped abruptly (Endres et al., 1994). However, as is true with cidofovir (below), the lack of controlled studies dramatically limits the ability to truly assess antiviral action.

#### 4.2.6. Ribavirin, cimetidine, and mumps vaccine

Animal studies utilizing the cottontail rabbit papillomavirus model have found that intradermal ribavirin administration reduces the number of lesions, decreases the time of first appearance of lesions, and reduces the overall mass of the lesions when administered prior to infection (Ostrow et al., 1992). Uncontrolled investigation of ribavirin in RRP have been published (McGlennen et al., 1993), although no controlled studies have verified clinical benefit. Similarly, case reports have suggested potential benefit of cimetidine

(Harcourt et al., 1999) and mumps vaccine (Pashley, 2002), again without the benefit of controlled studies to evaluate efficacy and define safety.

#### 4.2.7. Cidofovir

Cidofovir is a cytosine nucleotide analog with potent in vitro and in vivo activity against a broad spectrum of viruses, including cytomegalovirus, herpes simplex virus Types 1 and 2, varicella-zoster virus, Epstein–Barr virus, human herpesvirus-6, human herpesvirus-8, polyomaviruses, adenovirus, and HPV (Kimberlin, 2001). It has been approved by the Food and Drug Administration for the treatment of CMV retinitis. While the mechanism of cidofovir's potential antiviral activity against HPV infection is unclear, a recent report suggests that the drug reduces viral E6 and E7 protein expression in an in vitro model of HPV-associated tumors, with an associated increase in active p53 (Abdulkarim et al., 2002). Whether this drug effect also is involved in HPV infections such as RRP, in which tumor formation has not occurred, is unknown. The major dose-limiting toxicity experienced by recipients of cidofovir is nephrotoxicity. Product labeling by the FDA indicates that cidofovir should be considered a potential carcinogen in humans due to its propensity to cause tumors, primarily mammary adenocarcinomas, in rats.

In several small, uncontrolled case series, intralesional administration of cidofovir to patients with RRP, with or without initial surgical debulking of the lesions, has been reported to produce dramatic improvement in some patients (Snoeck et al., 1996, 1998; Pransky et al., 1999, 2000; Bielamowicz et al., 2002; Akst et al., 2003; Chhetri and Shapiro, 2003; Naiman et al., 2003; Neumann et al., 2003; Pransky et al., 2003). Due to their uncontrolled nature, these studies are unable to assess what role, if any, inter- and intra-patient disease variability played in their promising results. Other recent uncontrolled studies have reported less impressive therapeutic responses to cidofovir therapy (Milczuk, 2003; Shirley and Wiatrak, 2004), raising questions about the enthusiasm with which cidofovir is being embraced within the RRP treatment community.

A poignant example of the need for caution in interpreting the results of uncontrolled case series can be found in the experience of the NIAID Collaborative Antiviral Study Group (CASG) (D. Kimberlin, personal communication). In the late 1990s, the CASG attempted to conduct a large, placebo-controlled investigation of intralesional cidofovir. This effort ultimately was unsuccessful due to constraints placed by the FDA on the concentration of cidofovir being evaluated: the FDA required that the study begin at very low concentrations of cidofovir (0.3 mg/mL), despite the fact that otolaryngologists in practice were employing cidofovir concentrations of 5 to 10 mg/mL in the management of their patients. The study design allowed the blinded treating physician to determine at the time of the fourth injection of blinded study drug (active cidofovir versus saline placebo) whether the clinical response was adequate. If the response was judged to be suboptimal, the investigator was allowed to change to open-label cidofovir for the remaining three intralesional injections. Only one patient enrolled on the trial before it was closed in 2000 due to poor accrual. At the time of the fourth injection, this study subject's treating physician was very pleased with the therapeutic response to the study medication, and therefore elected to continue with blinded study medication for the remaining three injections. It was only after closure of the study and subsequent unblinding of the randomization that it was determined that the patient actually was receiving intralesional injections of saline, and not active cidofovir.

Thus, while initial reports of the efficacy of intralesional cidofovir are encouraging, caution should be maintained in how these limited data are interpreted. The safety and efficacy of intralesional cidofovir administration has yet to be established, and the development of adenocarcinomas in animal models suggests that controlled studies of this compound are warranted.

#### 4.2.8. Therapeutic vaccination

Finally, therapeutic vaccination as a means of directing the body's own immune system to better control an existing HPV infection has gained interest in recent years (Chu, 2003). A candidate therapeutic vaccine which has completed Phase II testing in JO-RRP patients (Derkay et al., 2003, 2004) named HspE7 consists of a recombinant fusion protein expressed in *E. coli* consisting of the heat shock protein Hsp65 of *Mycobacterium bovis* var. BCG, linked by a single histidine residue at its C terminus to the E7 protein of HPV-16. Utilizing an open-label Phase II study design, three subcutaneous injections of HspE7 were injected over 8 weeks to 27 children with JO-RRP, ages 2 to 18 years (14 males and 13 females). The median pre-treatment intersurgical interval was determined using the four surgeries prior to treatment, which was then compared with the length of the first post-treatment intersurgical interval. The mean (±S.D.) intersurgical interval increased 93%, from a median of 55.3 (±23.98) days pre-treatment to a median of 106.4 (±110.85) days following the first treatment ($p < 0.02$) (Derkay et al., 2004). Likewise, the median of all post-treatment intervals increased to 107.6 (±110.42) days ($p < 0.02$) (Derkay et al., 2004), suggesting that the benefit of treatment is sustained beyond the first post-treatment intersurgical interval. Forty-eight percent of patients doubled their pre-treatment intervals, and two patients required no post-treatment surgeries during the 14 months of follow-up to date (Derkay et al., 2004). Annualized surgical rates were reduced from a mean (±S.D.) of 8.68 (±4.22) surgeries per year pre-treatment to 6.45 (±5.96) surgeries per year post-treatment ($p < 0.003$), for a reduction of 2.23 surgeries per patient per year or 60 surgeries for the entire cohort (Derkay et al., 2004). Other than transient, mild to moderate injection-site reactions, the candidate therapeutic vaccine was well-tolerated. A confirmatory Phase III study of HspE7 is under development at this time.

## 5. Commentary

The rare nature of JO-RRP and the geographically diverse locations of the JO-RRP patients has had an unfortunate impact on the systematic evaluation of treatment modalities by otolaryngologists in community, tertiary care, and academic institutions. With the exception of interferon and the therapeutic vaccine described above, the antiviral trials for the treatment of RRP have been dramatically limited by their uncontrolled nature and/or small sample sizes. There simply is no way to know at the current time if most of the adjuvant therapies with purported efficacy truly provide any benefit, and equally importantly what their true degree of toxicities are. The experience of the CASG trial of cidofovir is a vivid example of why, in a disease with as much inter- and intra-patient variability as JO-RRP, controls are needed in the evaluation of any potential therapeutic agent. Faced with a dearth of scientific evidence of the efficacies of different treatments, families of patients have established patient groups such as the RRP Foundation (www.rrpf.org) to, among other things, disseminate information on the disease and its treatment options. While these groups do a very good job at this, one unforeseen consequence can be that the anecdotal research information that is shared can actually impede researchers' abilities to conduct large, multicentered, controlled studies of promising therapeutic agents. It is only through the conduct of such studies, in which uniform scoring systems and outcome measures are employed, that the potential efficacy of any given treatment modality can be established. Diligence, therefore, must be maintained, both by investigators and by patients and their families, in order for any treatment modality to be proven effective and of benefit to future patients with this devastating disease.

Given the challenges in treating JO-RRP, perhaps the most hopeful intervention which can be developed, is to prevent its occurrence in the first place. As noted above, vaginal delivery is a risk factor associated with JO-RRP (Shah et al., 1998). This raises the possibility that cesarean delivery might one day be employed to prevent perinatal transmission in the first place. However, cases of JO-RRP have been reported among children delivered by cesarean section (Shah et al., 1986), and substantial research is needed to prove this hypothesis before recommendations for cesarean delivery could be devised. Furthermore, it would be imperative to know which women were shedding HPV at delivery in order to implement such a program, necessitating development of rapid bedside diagnostic assays as well. Perhaps the ultimate solution to the significant problem of JO-RRP lies in prevention of genital HPV infections in the first place. Recent advances in developing vaccines based upon virus-like particle (VLP) technology have brought this possibility within reach for the first time (Kirnbauer et al., 1992; Breitburd et al., 1995; Suzich et al., 1995). Large-scale efficacy trials of VLP vaccines are being conducted by Merck, GlaxoSmithKline, and the National Cancer Institute (Koutsky et al., 2002; Schiller and Davies, 2004). Licensure applications for one or more of these vaccines may come as early as 2005.

## 6. Summary

Recurrent respiratory papillomatosis remains an orphan disease with a relatively low prevalence. For persons suffering from this malady, however, the impact upon their daily living can be profound. Therapeutic interventions remain focused on the surgical removal of the papillomas where possible, and additional adjuvant therapy is available for the minority of patients for whom surgical management fails to adequately control their disease. Of particular promise is a therapeutic vaccine which has recently completed Phase II evaluation and for which a controlled Phase III study is planned.

## Acknowledgments

Supported under contract with the Virology Branch, Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases (NIAID), NO1-AI-15113 and NO1-AI-62554, and by grants from the General Clinical Research Center Program (RR-032) and the State of Alabama.

## References

Abdulkarim, B., Sabri, S., Deutsch, E., Chagraoui, H., Maggiorella, L., Thierry, J., Eschwege, F., Vainchenker, W., Chouaib, S., Bourhis, J., 2002. Antiviral agent cidofivir restores p53 function and enhances the radiosensitivity in HPV-associated cancers. Oncogene 21, 2334–2346.

Abramson, A.L., Nouri, M., Mullooly, V., Fisch, G., Steinberg, B.M., 2004. Latent Human Papillomavirus infection is comparable in the larynx and trachea. J. Med. Virol. 72, 473–477.

Abramson, A.L., Shikowitz, M.J., Mullooly, V.M., Steinberg, B.M., Amella, C.A., Rothstein, H.R., 1992. Clinical effects of photodynamic therapy on recurrent laryngeal papillomas. Arch. Otolaryngol. Head Neck Surg. 118, 25–29.

Abramson, A.L., Shikowitz, M.J., Mullooly, V.M., Steinberg, B.M., Hyman, R.B., 1994. Variable light-dose effect on photodynamic therapy for laryngeal papillomas. Arch. Otolaryngol. Head Neck Surg. 120, 852–855.

Abramson, A.L., Steinberg, B.M., Winkler, B., 1987. Laryngeal papillomatosis: clinical, histopathologic and molecular studies. Laryngoscope 97, 678–685.

Akst, L.M., Lee, W., Discolo, C., Knott, D., Younes, A., Koltai, P.J., 2003. Stepped-dose protocol of cidofovir therapy in recurrent respiratory papillomatosis in children. Arch. Otolaryngol. Head Neck Surg. 129, 841–846.

Anderson, M.C., Brown, C.L., Buckley, C.H., Fox, H., Jenkins, D., Lowe, D.G., Manners, B.T., Melcher, D.H., Robertson, A.J., Wells, M., 1991. Current views on cervical intraepithelial neoplasia. J. Clin. Pathol. 44, 969–978.

Auborn, K., Abramson, A., Bradlow, H.L., Sepkovic, D., Mullooly, V., 1998. Estrogen metabolism and laryngeal papillomatosis: a pilot study on dietary prevention. Anticancer Res. 18, 4569–4573.

Auborn, K.J., 2002. Therapy for recurrent respiratory papillomatosis. Antiviral Ther. 7, 1–9.

Avidano, M.A., Singleton, G.T., 1995. Adjuvant drug strategies in the treatment of recurrent respiratory papillomatosis. Otolaryngol. Head Neck Surg. 112, 197–202.

Bauer, H.M., Ting, Y., Greer, C.E., Chambers, J.C., Tashiro, C.J., Chimera, J., Reingold, A., Manos, M.M., 1991. Genital human papillomavirus infection in female university students as determined by a PCR-based method. JAMA 265, 472–477.

Bauman, N.M., Smith, R.J., 1996. Recurrent respiratory papillomatosis. Pediatr. Clin. North Am. 43, 1385–1401.

Bell, R., Hong, W.K., Itri, L.M., McDonald, G., Strong, M.S., 1988. The use of *cis*-retinoic acid in recurrent respiratory papillomatosis of the larynx: a randomized pilot study. Am. J. Otolaryngol. 9, 161–164.

Bergler, W., Honig, M., Gotte, K., Petroianu, G., Hormann, K., 1997. Treatment of recurrent respiratory papillomatosis with argon plasma coagulation. J. Laryngol. Otol. 111, 381–384.

Bielamowicz, S., Villagomez, V., Stager, S.V., Wilson, W.R., 2002. Intralesional cidofovir therapy for laryngeal papilloma in an adult cohort. Laryngoscope 112, 696–699.

Bishai, D., Kashima, H., Shah, K., 2000. The cost of juvenile-onset recurrent respiratory papillomatosis. Arch. Otolaryngol. Head Neck Surg. 126, 935–939.

Bonnez, W., 2002. Papillomavirus. In: Richman, D.D., Whitley, R.J., Hayden, F.G. (Eds.), Clinical Virology, 2nd ed. ASM Press, Washington, DC, pp. 557–596.

Borden, E.C., Fall, L.A., 1981. Interferons: biochemical, cell growth, inhibitory, and immunological effects. Prog. Hematol. 350, 1–64.

Borkowski, G., Sommer, P., Stark, T., Sudhoff, H., Luckhaupt, H., 1999. Recurrent respiratory papillomatosis associated with gastroesophageal reflux disease in children. Eur. Arch. Otorhinolaryngol. 256, 370–372.

Bower, C.M., Waner, M., Flock, S., Schaeffer, R., 1998. Flash pump dye laser treatment of laryngeal papillomas. Ann. Otol. Rhinol. Laryngol. 107, 1001–1005.

Breitburd, F., Kirnbauer, R., Hubbert, N.L., Nonnenmacher, B., Trin-Dinh-Desmarquet, C., Orth, G., Schiller, J.T., Lowy, D.R., 1995. Immunization with viruslike particles from cottontail rabbit papillomavirus (CRPV) can protect against experimental CRPV infection. J. Virol. 69, 3959–3963.

Campion, M.J., McCance, D.J., Cuzick, J., Singer, A., 1986. Progressive potential of mild cervical atypia: prospective cytological, colposcopic, and virological study. Lancet 2, 237–240.

CASL Hepatitis Consensus Group, 1994. Treatment of chronic viral hepatitis with alpha interferon: a consensus conference report. Can. J. Infect. Dis. 5, 107–112.

Cates Jr., W., 1999. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. Sex Transm. Dis. 26, S2–S7.

Chang, F., Wang, L., Syrjanen, S., Syrjanen, K., 1992. Human papillomavirus infections in the respiratory tract. Am. J. Otolaryngol. 13, 210–225.

Chhetri, D.K., Shapiro, N.L., 2003. A scheduled protocol for the treatment of juvenile recurrent respiratory papillomatosis with intralesional cidofovir. Arch. Otolaryngol. Head Neck Surg. 129, 1081–1085.

Chu, N.R., 2003. Therapeutic vaccination for the treatment of mucosotropic human papillomavirus-associated disease. Expert. Opin. Biol. Ther. 3, 477–486.

Chuang, T.Y., Perry, H.O., Kurland, L.T., Ilstrup, D.M., 1984. Condyloma acuminatum in Rochester, Minn., 1950–1978. I. Epidemiology and clinical features. Arch. Dermatol. 120, 469–475.

Cole, R.R., Myer III, C.M., Cotton, R.T., 1989. Tracheotomy in children with recurrent respiratory papillomatosis. Head Neck 11, 226–230.

Coll, D.A., Rosen, C.A., Auborn, K., Potsic, W.P., Bradlow, H.L., 1997. Treatment of recurrent respiratory papillomatosis with indole-3-carbinol. Am. J. Otolaryngol. 18, 283–285.

Cook, T.A., Brunschwig, J.P., Butel, J.S., Cohn, A.M., Goepfert, H., Rawls, W.E., 1973. Laryngeal papilloma: etiologic and therapeutic considerations. Ann. Otol. Rhinol. Laryngol. 82, 649–655.

Daling, J.R., Sherman, K.J., 1992. Relationship between human papillomavirus infection and tumors of anogenital sites other than the cervix. In: Muñoz, N., Bosch, F.X., Shah, K.V. (Eds.), The Epidemiology of Cervical Cancer and Human Papillomavirus. IARC Scientific Publications, International Agency for Research on Cancer, Lyon, France, pp. 223–241.

de Villiers, E.M., 1989. Heterogeneity of the human papillomavirus group. J. Virol. 63, 4898–4903.

Demeter, L.M., Reichman, R.C., 1994. Association of human papillomaviruses (HPV) with other female genital tract tumors. In: Mindel A. (Ed.), Human Papillomavirus Infection. Sydney, Australia.

Derkay, C.S., 1995. Task force on recurrent respiratory papillomas. A preliminary report. Arch. Otolaryngol. Head Neck Surg. 121, 1386–1391.

Derkay, C.S., 2001. Recurrent respiratory papillomatosis. Laryngoscope 111, 57–69.

Derkay, C.S., Arnold, J., Bower, C., McClay, J., Smith, R., van Burik, J., Wiatrak, B., Wohl, D., Berger, B., Neefe, J., 2003. HspE7 treatment of pediatric recurrent respiratory papillomatosis (RRP): interim results of an open-label trial. In: 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, Abstract G-1655, 2003, p. 295 (http://www.rrpf.org/rrpf/therapies/HspE297_ICAAC.pdf).

Derkay, C.S., Arnold, J., Bower, C., McClay, J., Smith, R., van Burik, J., Wiatrak, B., Wohl, D., Berger, B., Neefe, J., 2004. HspE7 treatment of pediatric recurrent respiratory papillomatosis (RRP): final results of an open-label trial. In: 21st International Papillomavirus Conference, Mexico City, Mexico (http://www.rrpf.org/rrpf/therapies/HPV2004RRP.pdf).

Dorr, R.T., 1993. Interferon alpha in malignant and viral diseases: a review. Drugs 45, 177–211.

Durst, M., Glitz, D., Schneider, A., zur Hausen, H., 1992. Human papillomavirus type 16 (HPV 16) gene expression and DNA replication in cervical neoplasia: analysis by in situ hybridization. Virology 189, 132–140.

Eicher, S.A., Taylor-Cooley, L.D., Donovan, D.T., 1994. Isotretinoin therapy for recurrent respiratory papillomatosis. Arch. Otolaryngol. Head Neck Surg. 120, 405–409.

El-Bitar, M.A., Zalzal, G.H., 2002. Powered instrumentation in the treatment of recurrent respiratory papillomatosis: an alternative to the carbon dioxide laser. Arch. Otolaryngol. Head Neck Surg. 128, 425–428.

Endres, D.R., Bauman, N.M., Burke, D., Smith, R.J., 1994. Acyclovir in the treatment of recurrent respiratory papillomatosis. A pilot study. Ann. Otol. Rhinol. Laryngol. 103, 301–305.

Essman, E.J., Abramson, A., 1984. Estrogen binding sites on membranes from human laryngeal papilloma. Int. J. Cancer 33, 33–36.

Fredericks, B.D., Balkin, A., Daniel, H.W., Schonrock, J., Ward, B., Frazer, I.H., 1993. Transmission of human papillomaviruses from mother to child. Aust. N. Z. J. Obstet. Gynaecol. 33, 30–32.

Gen, G.C., Ransohoff, R.M., 1993. Interferon induced antiviral actions and their regulation. Adv. Virus Res. 42, 57–102.

Haglund, S., Lundquist, P.G., Cantell, K., Strander, H., 1981. Interferon therapy in juvenile laryngeal papillomatosis. Arch. Otolaryngol. 107, 327–332.

Hajek, E., 1956. Contribution to the etiology of laryngeal papilloma in children. J. Laryngol. Otol. 70, 166–168.

Harcourt, J.P., Worley, G., Leighton, S.E., 1999. Cimetidine treatment for recurrent respiratory papillomatosis. Int. J. Pediatr. Otorhinolaryngol. 51, 109–113.

Hartley, C., Hamilton, J., Birzgalis, A.R., Farrington, W.T., 1994. Recurrent respiratory papillomatosis—the Manchester experience, 1974–1992. J. Laryngol. Otol. 108, 226–229.

Healy, G.B., Gelber, R.D., Trowbridge, A.L., Grundfast, K.M., Ruben, R.J., Price, K.N., 1988. Treatment of recurrent respiratory papillomatosis with human leukocyte interferon. Results of a multicenter randomized clinical trial. N. Engl. J. Med. 319, 401–407.

Ho, G.Y., Bierman, R., Beardsley, L., Chang, C.J., Burk, R.D., 1998. Natural history of cervicovaginal papillomavirus infection in young women. N. Engl. J. Med. 338, 423–428.

Jones, S., Myers, G., 1985. Benign neoplasms of the larynx. Otolaryngol. Clin. North Am. 17, 151–178.

Kashima, H., Mounts, P., Leventhal, B., Hruban, R.H., 1993. Sites of predilection in recurrent respiratory papillomatosis. Ann. Otol. Rhinol. Laryngol. 102, 580–583.

Kashima, H., Wu, T.C., Mounts, P., Heffner, D., Cachay, A., Hyams, V., 1988. Carcinoma ex-papilloma: histologic and virologic studies in whole-organ sections of the larynx. Laryngoscope 98, 619–624.

Kashima, H.K., Kessis, T., Mounts, P., Shah, K., 1991. Polymerase chain reaction identification of human papillomavirus DNA in $CO_2$ laser plume from recurrent respiratory papillomatosis. Otolaryngol. Head Neck Surg. 104, 191–195.

Kimberlin, D.W., 2001. Acyclovir derivatives and other new antiviral agents. Semin. Pediatr. Infect. Dis. 12, 224–234.

Kimberlin, D.W., 2002. Pharmacotherapy of recurrent respiratory papillomatosis. Expert. Opin. Pharmacother. 3, 1091–1099.

Kimberlin, D.W., Malis, D.J., 2000. Juvenile onset recurrent respiratory papillomatosis: possibilities for successful antiviral therapy. Antiviral Res. 45, 83–93.

Kimberlin, D.W., Prober, C.G., 2003. Antiviral agents and interferons. In: Long, S.S., Pickering, L.K., Prober, C.G. (Eds.), Principles and Practice of Pediatric Infectious Diseases, 2nd ed. W.B. Saunders Company, US, pp. 1527–1547.

Kirnbauer, R., Booy, F., Cheng, N., Lowy, D.R., Schiller, J.T., 1992. Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic. Proc. Natl. Acad. Sci. U.S.A. 89, 12180–12184.

Kiroglu, M., Cetik, F., Soylu, L., Abedi, A., Aydogan, B., Akcali, C., Kiroglu, F., Ozsahinoglu, C., 1994. Acyclovir in the treatment of recurrent respiratory papillomatosis: a preliminary report. Am. J. Otolaryngol. 15, 212–214.

Koutsky, L.A., Ault, K.A., Wheeler, C.M., Brown, D.R., Barr, E., Alvarez, F.B., Chiacchierini, L.M., Jansen, K.U., for investigators of the Proof of Principle Study, 2002. A controlled trial of a human papillomavirus type 16 vaccine. N. Engl. J. Med. 347, 1645–1651.

Koutsky, L.A., Holmes, K.K., Critchlow, C.W., Stevens, C.E., Paavonen, J., Beckmann, A.M., DeRouen, T.A., Galloway, D.A., Vernon, D., Kiviat, N.B., 1992. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. N. Engl. J. Med. 327, 1272–1278.

Kramer, S.S., Wehunt, W.D., Stocker, J.T., Kashima, H., 1985. Pulmonary manifestations of juvenile laryngotracheal papillomatosis. Am. J. Roentgenol. 144, 687–694.

Lancaster, W.D., Castellano, C., Santos, C., Delgado, G., Kurman, R.J., Jenson, A.B., 1986. Human papillomavirus deoxyribonucleic acid in cervical carcinoma from primary and metastatic sites. Am. J. Obstet. Gynecol. 154, 115–119.

Lele, S.M., Pou, A.M., Ventura, K., Gatalica, Z., Payne, D., 2002. Molecular events in the progression of recurrent respiratory papillomatosis to carcinoma. Arch. Pathol. Lab. Med. 126, 1184–1188.

Leventhal, B.G., Kashima, H.K., Mounts, P., Thurmond, L., Chapman, S., Buckley, S., Wold, D., The Papilloma Study Group, 1991. Long-term response of recurrent respiratory papillomatosis to treatment with lymphoblastoid interferon alfa-N1. N. Engl. J. Med. 325, 613–617.

Lindeberg, H., Elbrond, O., 1990. Laryngeal papillomas: the epidemiology in a Danish subpopulation 1965–1984. Clin. Otolaryngol. All. Sci. 15, 125–131.

Lorincz, A.T., Reid, R., Jenson, A.B., Greenberg, M.D., Lancaster, W., Kurman, R.J., 1992. Human papillomavirus infection of the cervix: relative risk associations of 15 common anogenital types. Obstet. Gynecol. 79, 328–337.

McDonald, E.M., Mann, A.H., Thomas, H.C., 1987. Interferons as mediators of psychiatric morbidity. Lancet 2, 1175–1178.

McGlennen, R.C., Adams, G.L., Lewis, C.M., Faras, A.J., Ostrow, R.S., 1993. Pilot trial of ribavirin for the treatment of laryngeal papillomatosis. Head Neck 15, 504–512.

McMillan, K., Shapshay, S.M., McGilligan, J.A., Wang, Z., Rebeiz, E.E., 1998. A 585-nanometer pulsed dye laser treatment of laryngeal papillomas: preliminary report. Laryngoscope 108, 968–972.

Milczuk, H.A., 2003. Intralesional cidofovir for the treatment of severe juvenile recurrent respiratory papillomatosis: long-term results in 4 children. Otolaryngol. Head Neck Surg. 128, 788–794.

Morgan, A.H., Zitsch, R.P., 1986. Recurrent respiratory papillomatosis in children: a retrospective study of management and complications. Ear Nose Throat J. 65, 19–28.

Mork, J., Lie, A.K., Glattre, E., Hallmans, G., Jellum, E., Koskela, P., Moller, B., Pukkala, E., Schiller, J.T., Youngman, L., Lehtinen, M., Dillner, J., 2001. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N. Engl. J. Med. 344, 1125–1131.

Mounts, P., Kashima, H., 1984. Association of human papillomavirus subtype and clinical course in respiratory papillomatosis. Laryngoscope 94, 28–33.

Myer, C.M., Wiliging., P., Cotton, R., 1999. Use of a laryngeal microresector system. Laryngoscope 109, 1165–1166.

Naiman, A.N., Ceruse, P., Coulombeau, B., Froehlich, P., 2003. Intralesional cidofovir and surgical excision for laryngeal papillomatosis. Laryngoscope 113, 2174–2181.

Neumann, K., Pudszuhn, A., Welzel, C., Bartel-Friedrich, S., Passmann, M., 2003. Intralesional cidofovir injections for recurrent laryngeal papillomatosis: first results. Laryngorhinootologie 82, 700–706.

Oriel, J.D., 1971. Natural history of genital warts. Br. J. Vener. Dis. 47, 1–13.

Osborne, N.G., Adelson, M.D., 1990. Herpes simplex and human papillomavirus genital infections: controversy over obstetric management. Clin. Obstet. Gynecol. 33, 801–811.

Ostrow, R.S., Forslund, K.M., McGlennen, R.C., Shaw, D.P., Schlievert, P.M., Ussery, M.A., Huggins, J.W., Faras, A.J., 1992. Ribavirin mitigates wart growth in rabbits at early stages of infection with cottontail rabbit papillomavirus. Antiviral Res. 17, 99–113.

Pashley, N.R., 2002. Can mumps vaccine induce remission in recurrent respiratory papilloma? Arch. Otolaryngol. Head Neck Surg. 128, 783–786.

Pasquale, K., Wiatrak, B., Woolley, A., Lewis, L., 2003. Microdebrider versus $CO_2$ laser removal of recurrent respiratory papillomas: a prospective analysis. Laryngoscope 113, 139–143.

Patel, N., Rowe, M., Tunkel, D., 2003. Treatment of recurrent respiratory papillomatosis in children with the microdebrider. Ann. Otol. Rhinol. Laryngol. 112, 7–10.

Pou, A.M., Weems, J., Deskin, R.W., Nason, R., Payne, D.A., 2004. Molecular characterization of mutations in patients with benign and aggressive recurrent respiratory papillomatosis: a preliminary study. Ann. Otol. Rhinol. Laryngol. 113, 180–186.

Pransky, S.M., Albright, J.T., Magit, A.E., 2003. Long-term follow-up of pediatric recurrent respiratory papillomatosis managed with intralesional cidofovir. Laryngoscope 113, 1583–1587.

Pransky, S.M., Brewster, D.F., Magit, A.E., Kearns, D.B., 2000. Clinical update on 10 children treated with intralesional cidofovir injections for severe recurrent respiratory papillomatosis. Arch. Otolaryngol. Head Neck Surg. 126, 1239–1243.

Pransky, S.M., Magit, A.E., Kearns, D.B., Kang, D.R., Duncan, N.O., 1999. Intralesional cidofovir for recurrent respiratory papillomatosis in children. Arch. Otolaryngol. Head Neck Surg. 125, 1143–1148.

Quick, C.A., Watts, S.L., Krzyzek, R.A., Faras, A.J., 1980. Relationship between condylomata and laryngeal papillomata. Clinical and molecular virological evidence. Ann. Otol. Rhinol. Laryngol. 89, 467–471.

Rabah, R., Lancaster, W.D., Thomas, R., Gregoire, L., 2001. Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus-6-associated disease. Pediatr. Dev. Pathol. 4, 68–72.

Reeves, W.C., Ruparelia, S.S., Swanson, K.I., Derkay, C.S., Marcus, A., Unger, E.R., 2003. National registry for juvenile-onset recurrent

respiratory papillomatosis. Arch. Otolaryngol. Head Neck Surg. 129, 976–982.

Renault, P.F., Hoofnagle, J.H., 1989. Side effects of alpha interferon. Semin. Liver Dis. 9, 273–277.

Rimell, F.L., Shoemaker, D.L., Pou, A.M., Jordan, J.A., Post, J.C., Ehrlich, G.D., 1997. Pediatric respiratory papillomatosis: prognostic role of viral typing and cofactors. Laryngoscope 107, 915–918.

Rosen, C.A., Woodson, G.E., Thompson, J.W., Hengesteg, A.P., Bradlow, H.L., 1998. Preliminary results of the use of indole-3-carbinol for recurrent respiratory papillomatosis. Otolaryngol. Head Neck Surg. 118, 810–815.

Ruparelia, S., Unger, E.R., Nisenbaum, R., Derkay, C.S., Reeves, W.C., 2003. Predictors of remission in juvenile-onset recurrent respiratory papillomatosis. Arch. Otolaryngol. Head Neck Surg. 129, 1275–1278.

Schiller, J.T., Davies, P., 2004. Delivering on the promise: HPV vaccines and cervical cancer. Nat. Rev. Microbiol. 2, 343–347.

Schneider, A., Kirchhoff, T., Meinhardt, G., Gissmann, L., 1992. Repeated evaluation of human papillomavirus 16 status in cervical swabs of young women with a history of normal Papanicolaou smears. Obstet. Gynecol. 79, 683–688.

Schuurman, A.M., Van Den Broek, P., 1986. Results of treatment with alpha-interferon in adult-onset laryngeal papillomatosis. Clin. Otolaryngol. All. Sci. 11, 447–453.

Shah, K., Kashima, H., Polk, B.F., Shah, F., Abbey, H., Abramson, A., 1986. Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis. Obstet. Gynecol. 68, 795–799.

Shah, K.V., Howley, P.M., 1996. Papillomaviruses. In: Fields, B.N., Knipe, D.M., Howley, P.M., Chanock, R.M., Melnick, J.L., Monath, T.P., Roizman, B., Straus, S.E. (Eds.), Fields Virology, 3rd ed. W.B. Lippincott-Raven Publishers, Philadelphia, pp. 2077–2109.

Shah, K.V., Stern, W.F., Shah, F.K., Bishai, D., Kashima, H.K., 1998. Risk factors for juvenile onset recurrent respiratory papillomatosis. Pediatr. Infect. Dis. J. 17, 372–376.

Shikowitz, M.J., Abramson, A.L., Freeman, K., Steinberg, B.M., Nouri, M., 1998. Efficacy of DHE photodynamic therapy for respiratory papillomatosis: immediate and long-term results. Laryngoscope 108, 962–967.

Shirasawa, H., Tomita, Y., Sekiya, S., Takamizawa, H., Simizu, B., 1987. Integration and transcription of human papillomavirus type 16 and 18 sequences in cell lines derived from cervical carcinomas. J. Gen. Virol. 68, 583–591.

Shirley, W.P., Wiatrak, B., 2004. Is cidofovir a useful adjunctive therapy for recurrent respiratory papillomatosis in children? Int. J. Pediatr. Otorhinolaryngol. 68, 413–418.

Silver, R.D., Rimell, F.L., Adams, G.L., Derkay, C.S., Hester, R., 2003. Diagnosis and management of pulmonary metastasis from recurrent respiratory papillomatosis. Otolaryngol. Head Neck Surg. 129, 622–629.

Snoeck, R., Wellens, W., Desloovere, C., Van Ranst, M., Naesens, L., De Clercq, E., Feenstra, L., 1998. Treatment of severe laryngeal papillomatosis with intralesional injections of cidofovir [(*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine]. J. Med. Virol. 54, 219–225.

Snoeck, R., Wellens, W., Desloovers, C., Van Ranst, M., de Clercq, E., Feenstra, L., 1996. Treatment of severe recurrent laryngeal papillomatosis by local injections of (*S*)-1-(3)hydroxy-2-(phosphonylmethoxypropyl) cytosine (cidofovir). In: Abstract in the Program for the Ninth International Conference on Antiviral Research, Eurabandi, Fukushima, Japan, May 19–24, 1996, pp. 19–24.

Solomon, D., Smith, R.R., Kashima, H.K., Leventhal, B.G., 1985. Malignant transformation in non-irradiated recurrent respiratory papillomatosis. Laryngoscope 95, 900–904.

Steinberg, B.M., Gallagher, T., Stoler, M., Abramson, A.L., 1988. Persistence and expression of human papillomavirus during interferon therapy. Arch. Otolaryngol. Head Neck Surg. 114, 27–32.

Stoler, M.H., Broker, T.R., 1986. In situ hybridization detection of human papillomavirus DNAs and messenger RNAs in genital condylomas and a cervical carcinoma. Hum. Pathol. 17, 1250–1258.

Stoler, M.H., Rhodes, C.R., Whitbeck, A., Wolinsky, S.M., Chow, L.T., Broker, T.R., 1992. Human papillomavirus type 16 and 18 gene expression in cervical neoplasias. Hum. Pathol. 23, 117–128.

Strong, M., Vaughan, C., Healy, G.B., 1979. Recurrent respiratory papillomatosis. In: Healy, G.B., McGill, T.J.I. (Eds.), Laryngo-Tracheal Problems in the Pediatric Patient. Springfield, IL, USA, pp. 88–98.

Sugase, M., Moriyama, S., Matsukura, T., 1991. Human papillomavirus in exophytic condylomatous lesions on different female genital regions. J. Med. Virol. 34, 1–6.

Suzich, J.A., Ghim, S.J., Palmer-Hill, F.J., White, W.I., Tamura, J.K., Bell, J.A., Newsome, J.A., Jenson, A.B., Schlegel, R., 1995. Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. Proc. Natl. Acad. Sci. U.S.A. 92, 11553–11557.

Syrjanen, K., Hakama, M., Saarikoski, S., Vayrynen, M., Yliskoski, M., Syrjanen, S., Kataja, V., Castren, O., 1990. Prevalence, incidence, and estimated life-time risk of cervical human papillomavirus infections in a nonselected Finnish female population. Sex Transm. Dis. 17, 15–19.

Terry, R.M., Lewis, F.A., Griffiths, S., Wells, M., Bird, C.C., 1987. Demonstration of human papillomavirus types 6 and 11 in juvenile laryngeal papillomatosis by in-situ DNA hybridization. J. Pathol. 153, 245–248.

Tsunokawa, Y., Takebe, N., Nozawa, S., Kasamatsu, T., Gissmann, L., zur Hausen, H., Terada, M., Sugimura, T., 1986. Presence of human papillomavirus type-16 and type-18 DNA sequences and their expression in cervical cancers and cell lines from Japanese patients. Int. J. Cancer 37, 499–503.

Valdez, T.A., McMillan, K., Shapshay, S.M., 2001. A new laser treatment for vocal cord papilloma—585-nm pulsed dye. Otolaryngol. Head Neck Surg. 124, 421–425.

Wiatrak, B.J., 2003. Overview of recurrent respiratory papillomatosis. Curr. Opin. Otolaryngol. Head Neck Surg. 11, 433–441.

Winer, R.L., Lee, S.K., Hughes, J.P., Adam, D.E., Kiviat, N.B., Koutsky, L.A., 2003. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am. J. Epidemiol. 157, 218–226.

Woodman, C.B., Collins, S., Winter, H., Bailey, A., Ellis, J., Prior, P., Yates, M., Rollason, T.P., Young, L.S., 2001. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet 357, 1831–1836.

Yoshpe, N.S., 1995. Oral and laryngeal papilloma: a pediatric manifestation of sexually transmitted disease? Int. J. Pediatr. Otorhinolaryngol. 31, 77–83.

Zawadzka-Glos, L., Jakubowska, A., Chmielik, M., Bielicka, A., Brzewski, M., 2003. Lower airway papillomatosis in children. Int. J. Pediatr. Otorhinolaryngol. 67, 1117–1121.

zur Hausen, H., 1985. Genital papillomavirus infections. Prog. Med. Virol. 32, 15–21.