

RRP Medical Reference Service

An RRP Foundation Publication

edited by

Dave Wunrow and Bill Stern

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Preface

The *RRP Medical Reference Service* is intended to be of potential interest to RRP patients/families seeking treatment, practitioners providing care, micro biological researchers as well as others interested in developing a comprehensive understanding of recurrent respiratory papillomatosis.

This issue focuses on a selection of references with abstracts from recent (2007 and later) RRP related publications. These listings are sorted in approximate reverse chronological order as indicated by the "PMID" numbers. Each listing is formatted as follows:

Journal or reference
Title
Language (if it is not specified assume article is in English)
Author(s)
Primary affiliation (when specified)
Abstract
PMID (PubMed ID)

If copies of complete articles are desired, we suggest that you request a reprint from one of the authors. If you need assistance in this regard or if you have any other questions or comments please feel free to contact:

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RRPF Selected Articles and Abstracts

[Acta Otolaryngol.](#) 2007 Sep;127(9):900-6.

Exploring the relation between human papilloma virus and larynx cancer.

[Torrente MC](#), [Ojeda JM](#).

Servicio de Otorrinolaringología Hospital San Juan de Dios, Universidad de Chile, Santiago, Chile.

Human papilloma virus (HPV) has a role in benign and malignant pathology of the larynx. In this review we present the biological and epidemiological aspects related to these issues.

PMID: 17712666 [PubMed - in process]

[Arch Otolaryngol Head Neck Surg.](#) 2007 Jul;133(7):684-92.

An epigenetically derived monoclonal origin for recurrent respiratory papillomatosis.

[Stephen JK](#), [Vaught LE](#), [Chen KM](#), [Shah V](#), [Schweitzer VG](#), [Gardner G](#), [Benninger MS](#), [Worsham MJ](#).

Department of Otolaryngology-Head and Neck Surgery, Henry Ford Hospital, 1 Ford Pl, 1D, Detroit, MI 48202, USA.

OBJECTIVE: To investigate the contribution of promoter methylation-mediated epigenetic events in recurrent respiratory papillomatosis tumorigenesis. **DESIGN:** Archival tissue DNA, extracted from microdissected papilloma lesions, was interrogated for methylation status by means of the novel, multigene methylation-specific multiplex ligation-dependent probe amplification assay. **SUBJECTS:** Fifteen subjects with recurrent respiratory papillomatosis, 3 females and 12 males, all with adult onset of illness (age range, 23-73 years) except for 1 female patient with juvenile onset (1 year old). **RESULTS:** Promoter hypermethylation was recorded in 14 of 15 cases, and 19 of 22 unique methylation-prone cancer genes in the multigene panel had altered DNA methylation in at least 1 laryngeal papilloma biopsy specimen. Identical abnormally methylated genes were found in 5 of 15 recurrent cases, of which the CDKN2B gene was hypermethylated in all 5 cases. Dissimilar epigenetic events were noted in the remaining cases. **CONCLUSIONS:** A clonal origin was derived for 5 of 15 recurrent respiratory papillomatosis biopsy specimens based on identical epigenetic events. The high frequency of epigenetic events, characterized by consistent promoter

hypermethylation of multiple tumor suppressor genes, points to the use of gene silencing mechanisms in the pathogenesis of recurrent respiratory papillomatosis.

Publication Types:

- [Research Support, N.I.H., Extramural](#)

PMID: 17638782 [PubMed - in process]

[Curr Opin Pediatr.](#) 2007 Aug;19(4):387-8.

Human papilloma virus vaccine: a new frontier or political controversy?

[Forman SF](#), [Woods ER](#).

Publication Types:

- [Comment](#)
- [Editorial](#)

PMID: 17630600 [PubMed - in process]

[Otolaryngol Head Neck Surg.](#) 2007 Jul;137(1):146-51.

Office-based laryngeal laser surgery: a review of 443 cases using three wavelengths.

[Koufman JA](#), [Rees CJ](#), [Frazier WD](#), [Kilpatrick LA](#), [Wright SC](#), [Halum SL](#), [Postma GN](#).

Voice Institute of New York, New York, NY 10023, USA. Jamie.koufman@nyogmd.com

BACKGROUND: Unsedated office-based laser surgery (UOLS) of the larynx and trachea has significantly improved the treatment options for patients with laryngotracheal pathology including recurrent respiratory papillomas, granulomas, leukoplakia, and polypoid degeneration. UOLS delivered by flexible endoscopes has dramatically impacted office-based surgery by reducing the time, costs, and morbidity of surgery. **OBJECTIVES:** To review our experience with 443 laryngotracheal cases treated by UOLS. **METHODS:** The

laser logbooks at the Center for Voice and Swallowing Disorders were reviewed for UOLS, and the medical and laryngological histories were detailed, as were the treatment modalities, frequencies, and complications. RESULTS: Of the 443 cases, 406 were performed with the pulsed-dye laser, 10 with the carbon-dioxide laser, and 27 with the thulium: yttrium-aluminum-garnet laser. There were no significant complications in this series. A review of indications and wavelength selection criteria is presented. CONCLUSION: Unsedated, office-based, upper aerodigestive tract laser surgery appears to be a safe and effective treatment option for many patients with laryngotracheal pathology.

PMID: 17599582 [PubMed - indexed for MEDLINE]

[Mol Med.](#) 2007 Mar-Apr;13(3-4):143-50.

Up-regulation of Rac1 by epidermal growth factor mediates COX-2 expression in recurrent respiratory papillomas.

[Wu R](#), [Coniglio SJ](#), [Chan A](#), [Symons MH](#), [Steinberg BM](#).

The Feinstein Institute for Medical Research, North Shore-LIJ Health System, New Hyde Park, and Department of Otorhinolaryngology-Head and Neck Surgery, Albert Einstein College of Medicine, Bronx, New York, USA.

Recurrent respiratory papillomas are epithelial tumors of the airway caused by human papillomaviruses. We previously reported that the epidermal growth factor receptor (EGFR) is overexpressed in papilloma cells, that cyclooxygenase-2 (COX-2) is induced, and that COX-2 expression in primary papilloma cells requires activation of the EGFR but not Erk. Rac1, a member of the Rho family of GTPases, is a key signaling element that is known to control multiple pathways downstream of the EGFR. Here we report that Rac1 is overexpressed in papilloma cells compared with normal laryngeal epithelial cells and that the increased levels of Rac1 are mediated by EGFR activation. Transfecting cells with Rac1-specific siRNA suppressed COX-2 expression. Surprisingly, Rac1 mediated phosphorylation of p38 mitogen-activated kinase in papilloma cells but not normal cells, and inhibition of p38 with the specific inhibitor SB202190 suppressed COX-2 expression in papilloma cells but had no effect on low-level COX-2 expression in normal cells. Thus, the signaling cascades that regulate COX-2 expression are different in HPV-infected papilloma cells, with a significant contribution by the EGFR-- Rac1-->p38 pathway.

Publication Types:

- [Research Support, N.I.H., Extramural](#)
- [Research Support, Non-U.S. Gov't](#)

PMID: 17592548 [PubMed - indexed for MEDLINE]

[Prescrire Int.](#) 2007 Jun;16(89):91-4.

Human papillomavirus vaccine for genotypes 6, 11, 16 and 18: new drug. Cervical cancer prevention: high hopes....

[No authors listed]

(1) Most cases of high-grade anogenital dysplasia and malignancy are caused by human papillomavirus (HPV) genotypes 16 and 18. Anogenital papilloma and condyloma acuminata are mainly caused by HPV6 and HPV11. (2) A recombinant vaccine covering these four genotypes is now marketed in the European Union for the prevention of condyloma, precancerous lesions, and cancers of the female lower genital tract. (3) A three-dose vaccination schedule (0, 2 and 6 months) elicits an immune response in almost all women, but the minimum antibody titre required for clinical protection is not known. Immune protection lasts at least 5 years, but no one knows what happens after that time. (4) Three double-blind randomised placebo-controlled trials involving a total of about 18 000 women aged 16 to 23 had sufficiently similar designs to pool results for analysis. Nearly all (around 98%) of women not yet infected with papillomavirus of a genotype covered by the vaccine were protected from dysplasia caused by one of these genotypes. The vaccine did not affect dysplasia caused by other genotypes, nor was it effective in women who were already infected. In total, among women not yet infected with a papillomavirus genotype covered by the vaccine, the vaccine prevented about 38% of high-grade dysplasias of all types (0.5 versus 0.8 cases per 100 woman-years). (5) The vaccine also markedly reduced the incidence of genital warts and high-grade vulvar and vaginal dysplasia. There are no data on efficacy beyond 4.5 years. (6) These results are somewhat undermined by methodological problems, such as follow-up lasting only a maximum of 4.5 years whereas cervical cancer takes much longer to develop. In addition, there were very few cases of dysplasia in each trial, and results were largely based on post hoc subgroup analyses. (7) Apart from local reactions, which occurred in more than 80% of vaccinated women, the only adverse effect of papillomavirus vaccination was fever (12.9% of those on the vaccine versus 11% on placebo). (8) There is no evidence thus far that prenatal exposure due to HPV vaccination during the month preceding conception is harmful. (9) The clinical results are promising but further follow-up is needed to answer ongoing questions, such as the incidence of cervical cancer after vaccination and the duration of protection. Cervical cancer screening remains necessary, even for vaccinated women, and a continued need exists for measures designed to prevent all sexually transmitted diseases.

PMID: 17582921 [PubMed - indexed for MEDLINE]

[Braz J Infect Dis.](#) 2006 Jun;10(3):165-8.

Detection of human papilloma virus in the tonsils of children undergoing tonsillectomy.

[Ribeiro KM](#), [Alvez JM](#), [Pignatari SS](#), [Weckx LL](#).

Federal University of São Paulo, Paulista School of Medicine, Division of Pediatric Otolaryngology.

Human papilloma virus (HPV) is related to respiratory mucosal diseases, such as recurrent respiratory papillomatosis, as well as to upper-respiratory-tract malignancies. There are few reports concerning the prevalence of HPV in the upper respiratory tract of non-affected individuals. We examined the prevalence of HPV in the tonsils of children of the general population scheduled for tonsillectomy. Samples were taken from the tonsils of 100 children undergoing tonsillectomy and were then tested for HPV with the polymerase chain reaction (PCR) technique, utilizing the generic primers MY09 and MY 11. The study excluded children known to have HPV and HIV-related diseases. Parents and legal guardians completed a standardized socio-demographic questionnaire. The questionnaire revealed that 84% of the mothers had at least one risk factor for genital HPV. None of the tonsil samples were positive for HPV. Apparently HPV does not commonly colonize the tonsils of children undergoing routine tonsillectomy.

PMID: 17568846 [PubMed - in process]

[Otolaryngol Head Neck Surg.](#) 2007 Jun;136(6):863-9.

Antiviral agents for the treatment of recurrent respiratory papillomatosis: a systematic review of the English-language literature.

[Chadha NK](#), [James AL](#).

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OBJECTIVE: To determine the efficacy of antiviral agents for recurrent respiratory papillomatosis (RRP) in children and adults. STUDY DESIGN: Systematic review to include randomized controlled trials (RCTs), comparative studies (historical and/or nonrandomized), case series, and case reports. RESULTS: Twenty-six original studies were included (one case-control series, 21 noncomparative trials, four case reports, and no RCTs). Meta-analysis was not possible. The antiviral modalities included acyclovir, ribavirin, intravenous

cidofovir, and intralesional cidofovir injections. The strongest evidence was for intralesional cidofovir, with 17 studies including 158 patients. Of these, 90 patients (57%) demonstrated complete resolution, 55 patients (35%) a partial response, and 13 patients (8%) showed no improvement. CONCLUSIONS: Insufficient evidence from controlled trials exists for reliable conclusions, but several series indicate intralesional cidofovir may have some efficacy. A well-designed placebo-controlled, double-blinded, randomized controlled trial is needed. SIGNIFICANCE: This study provides the background for future study design and a comprehensive review of the available evidence.

Publication Types:

- [Review](#)

PMID: 17547971 [PubMed - indexed for MEDLINE]

[Minerva Med.](#) 2007 Apr;98(2):121-30.

Prevention of human papilloma virus-induced preneoplasia and cancer by prophylactic HPV vaccines.

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Persistent infection with human papilloma virus (HPV) is a necessary condition for the development of cervical, most of the vulvar and anal carcinoma and their precursors. HPV is the most common sexually transmitted virus throughout the world. About 70-80% of sexually active people are infected during their lifetime. Most infections are transient and asymptomatic and cleared by the host immune system within 12-18 months. Only persistent infections predispose to the development of genital preneoplasia and cancer. The first vaccine against HPV infection has been available in Italy since March 2006. The vaccine is a prophylactic, quadrivalent vaccine against the two most common oncogenic HPV types 16 and 18, responsible for more than 70% of cervical carcinomas and against the two low-risk types 6 and 11 responsible for 90% of cases of genital warts. A second, bivalent HPV 16/18 vaccine will be launched soon. The immunogenicity (100%) and efficacy of the vaccines is very high (96% against infection, 100% against disease). These vaccines constitute a milestone in the battle against cervical carcinoma, which is the second most common cancer in young women in Europe, with 33,500 new cases diagnosed every year.

PMID: 17519854 [PubMed - indexed for MEDLINE]

[Int J Pediatr Otorhinolaryngol.](#) 2007 Jun;71(6):965-72. Epub 2007 Apr 10.

Severity of juvenile onset recurrent respiratory papillomatosis is not associated with socioeconomic status in a setting of universal health care.

[Leung R](#), [Hawkes M](#), [Campisi P](#).

Hospital for Sick Children and the Department of Otolaryngology-Head and Neck Surgery (Leung, Campisi), 555 University Ave., 6th floor Elm, Toronto, Ontario M5G 1X8, Canada.

BACKGROUND: Juvenile onset recurrent respiratory papillomatosis (JORRP) results from HPV transmission. Cervical cancer, also transmitted via HPV, is known to be correlated with socioeconomic status (SES). This study aims to determine if an association exists between SES and severity of JORRP. **METHODS:** Cross-sectional study of all active JORRP patients at the Hospital for Sick Children in Toronto in 2005. SES information from Hollingshead surveys, Postal walk Census data, and Low Income Cutoff Data were compared with Derkay-Wiatrak disease severity scores, peak annual surgical frequency, and age of diagnosis. Statistical analysis was performed using Spearman, Mann-Whitney, and linear regression analyses. **RESULTS:** Twenty-one patients were surveyed. Hollingshead results were as follows: two patients (10%) were class I (major business and professional); 11 patients (52%) were class II (medium business, minor professional, technical); 4 patients (19%) were class III (skilled craftsmen, clerical, sales workers); 4 patients (19%) were class IV (machine operators, semiskilled workers); 0% were from class V (unskilled laborers, menial service workers). Interestingly, based on postal code data nine patients (45%) were below the low income cutoff as compared to the Toronto (metropolitan) and Ontario (provincial) rates of low income (17% and 14%, respectively). There was significant correlation between each of the SES measures and between disease severity measures. However, analysis of the SES measures versus disease severity measures did not demonstrate any significant relationship. **CONCLUSIONS:** Though almost half the patients lived below the low income cutoff, this study did not demonstrate a significant correlation between socioeconomic status and severity of disease in JORRP. One possible explanation is that universal access to the Canadian health care system is able to provide support despite a large proportion of patients being socioeconomically vulnerable. A national level study is underway to further detect any relationship between SES and JORRP severity in the general population.

Publication Types:

- [Comparative Study](#)

PMID: 17428551 [PubMed - indexed for MEDLINE]

[J Laryngol Otol.](#) 2007 Apr 10;:1-3 [Epub ahead of print]

Microdebrider removal of tracheal papilloma via tracheostomy in the child with an obliterated larynx.

[Ulualp SO](#), [Ryan MW](#), [Wright ST](#).

Department of Otolaryngology, Children's Hospital, University of Texas Medical Branch, Galveston, Texas, USA.

In children, recurrent respiratory papillomatosis is the most common benign neoplasm of the airway. The disease frequently involves the larynx and may spread to extralaryngeal sites. Use of a microdebrider has been suggested as a safe and low-cost technique which reduces operating time, compared with laser removal of laryngeal lesions. We describe a technique for using a microdebrider to remove tracheal papillomas when the larynx is obliterated with the disease.

PMID: 17419899 [PubMed - as supplied by publisher]

[Ann Otol Rhinol Laryngol.](#) 2007 Mar;116(3):211-6.

Endoscopic lysis of anterior glottic webs and silicone keel placement.

[Edwards J](#), [Tanna N](#), [Bielamowicz SA](#).

Division of Otolaryngology, The George Washington University, 2150 Pennsylvania Ave NW, Suite 6-301, Washington, DC 20036, USA.

OBJECTIVES: Acquired anterior glottic webs occur most commonly after endoscopic resection of laryngeal papilloma involving the anterior vocal folds. Treatment of anterior glottic webs has included a tracheotomy with laryngofissure and placement of a laryngeal stent or keel. We have used an endoscopic technique of web lysis and placement of a laryngeal keel without tracheotomy over the past 7 years. **METHODS:** A retrospective chart review was conducted of all cases of endoscopic web lysis and keel placement performed by the senior author (S.A.B.). **RESULTS:** Over the past 7 years, 10 patients underwent the procedure, with a mean follow-up of 18 months. The length of the anterior web was up to two thirds of the membranous vocal fold. Outcomes analysis revealed a recurrence in 1 patient and 2 minor complications necessitating treatment. **CONCLUSIONS:** Endoscopic web lysis and keel placement offers superior results with less morbidity compared to open techniques.

PMID: 17419526 [PubMed - indexed for MEDLINE]

[Ann Otol Rhinol Laryngol.](#) 2007 Mar;116(3):169-71.

Immunocompetency in children with recurrent respiratory papillomatosis: prospective study.

[Stern Y](#), [Felipovich A](#), [Cotton RT](#), [Segal K](#).

Dept of Pediatric Otolaryngology, Schneider Children's Medical Center of Israel, Petah Tiqwa 49202, Israel.

OBJECTIVES: We sought to investigate the immunologic status of children with recurrent respiratory papillomatosis and to evaluate possible correlations between the patients' immunocompetency and the clinical course of the disease. **METHODS:** Twenty children with recurrent respiratory papillomatosis underwent immunologic evaluation every 6 months for determination of complete blood count, serum immunoglobulin levels, lymphocyte subpopulations, lymphocyte response to mitogen stimulation, and natural killer cell function. The patients were observed prospectively (42 to 56 months), and their clinical course was recorded. The findings were compared with those in healthy age-matched controls. **RESULTS:** The CD4/CD8 ratio and the lymphocyte response to mitogen stimulation were significantly reduced in the study children compared to normal controls. A reduction in lymphocyte response to mitogen stimulation was significantly correlated to a high number of papilloma sites and more frequent recurrences. Abnormal natural killer cell function was significantly correlated to more frequent recurrences. **CONCLUSIONS:** A compromised cell-mediated immune response may be associated with repeated or persistent human papillomavirus infections, leading to the development of recurrent respiratory papillomatosis. Patients with an aggressive clinical course may have underlying cell-mediated immunodeficiency. Long-term prospective investigations are needed to establish the role of the host immune system in the pathogenesis of recurrent respiratory papillomatosis in children.

PMID: 17419519 [PubMed - indexed for MEDLINE]

[Ear Nose Throat J.](#) 2007 Feb;86(2):68, 71.

Surgical therapy for recurrent respiratory papillomatosis.

[Alexander RE](#), [Fried MP](#).

Publication Types:

- [Editorial](#)

PMID: 17385606 [PubMed - indexed for MEDLINE]

[Asian J Surg](#). 2007 Jan;30(1):88-90.

Tracheal papilloma with exceptionally longer interval of recurrence.

[Komatsu T](#), [Takahashi Y](#).

Department of Thoracic Surgery, Kobe City General Hospital, Kobe, Japan.

A case of recurrent respiratory papilloma of the trachea was reviewed in accordance with other literature. A 66-year-old man with the chief complaint of haemoptysis was referred to our department for meticulous checkup. According to his past medical history of laser ablation for laryngeal and tracheal papilloma, recurrence of the papilloma was first suspected and confirmed by bronchoscopic biopsy. The recurrent papilloma, of about 5 mm in diameter, was located at the same endotracheal lesion, left side of the middle trachea, where the former first and second tracheal papillomas had been detected and treated with Nd-YAG laser. Under general anaesthesia with endotracheal intubation, the patient underwent bronchoscopic resection of the recurrent papilloma with KTP laser. The bronchoscopic resection was uneventful, as was the postoperative course. In this report, the clinical manifestations of and therapeutic approach for tracheal papilloma are reviewed.

Publication Types:

- [Case Reports](#)

PMID: 17337381 [PubMed - indexed for MEDLINE]

[Eur Arch Otorhinolaryngol](#). 2007 Jul;264(7):777-82. Epub 2007 Feb 24.

Longstanding recurrent laryngeal papillomatosis: impact on voice quality.

[Lehto L](#), [Aaltonen LM](#), [Rihkanen H](#).

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Human papilloma virus (HPV) infection in the larynx often requires frequent surgical procedures in order to keep voice quality reasonable. The purpose of this study was to evaluate the speaking voice quality of patients with longstanding recurrent laryngeal papillomatosis (RLP). The patients were seven males with adult-onset RLP whose disease had lasted over 5 years, and who were free of papilloma at the time of examination. Each patient had an age- and gender-matched control with similar smoking habits. Voice samples were recorded and acoustic analysis as well as perceptual listening test were performed. In our series a perceptual test discriminates between normal and pathological voice quality more precisely than acoustical voice analysis. It appears that the voice of the papilloma patient, even after frequent phonosurgical operations, is not deviant from the normal when analyzed acoustically, but perceptual assessment shows that overall quality is less than optimal, and roughness and breathiness are increased.

PMID: 17323089 [PubMed - in process]

[Pharmacol Res.](#) 2007 Mar;55(3):224-36. Epub 2007 Jan 25.

Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis.

[Higdon JV](#), [Delage B](#), [Williams DE](#), [Dashwood RH](#).

Linus Pauling Institute, Oregon State University, Corvallis, OR 97331-6512, USA.

Cruciferous vegetables are a rich source of glucosinolates and their hydrolysis products, including indoles and isothiocyanates, and high intake of cruciferous vegetables has been associated with lower risk of lung and colorectal cancer in some epidemiological studies. Glucosinolate hydrolysis products alter the metabolism or activity of sex hormones in ways that could inhibit the development of hormone-sensitive cancers, but evidence of an inverse association between cruciferous vegetable intake and breast or prostate cancer in humans is limited and inconsistent. Organizations such as the National Cancer Institute recommend the consumption of five to nine servings of fruits and vegetables daily, but separate recommendations for cruciferous vegetables have not been established. Isothiocyanates and indoles derived from the hydrolysis of glucosinolates, such as sulforaphane and indole-3-carbinol (I3C), have been implicated in a variety of anticarcinogenic mechanisms, but deleterious effects also have been reported in some experimental protocols, including tumor promotion over prolonged periods of exposure. Epidemiological studies indicate that human exposure to isothiocyanates and indoles through cruciferous vegetable consumption may

decrease cancer risk, but the protective effects may be influenced by individual genetic variation (polymorphisms) in the metabolism and elimination of isothiocyanates from the body. Cooking procedures also affect the bioavailability and intake of glucosinolates and their derivatives. Supplementation with I3C or the related dimer 3,3'-diindolylmethane (DIM) alters urinary estrogen metabolite profiles in women, but the effects of I3C and DIM on breast cancer risk are not known. Small preliminary trials in humans suggest that I3C supplementation may be beneficial in treating conditions related to human papilloma virus infection, such as cervical intraepithelial neoplasia and recurrent respiratory papillomatosis, but larger randomized controlled trials are needed.

Publication Types:

- [Review](#)

PMID: 17317210 [PubMed - indexed for MEDLINE]

[Arch Otolaryngol Head Neck Surg.](#) 2007 Feb;133(2):127-30.

Efficacy of treating children with anterior commissure and true vocal fold respiratory papilloma with the 585-nm pulsed-dye laser.

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OBJECTIVE: To report preliminary results regarding the safety and efficacy of the 585-nm pulsed-dye laser (PDL) for the treatment of juvenile-onset recurrent respiratory papillomatosis (JORRP) in the pediatric population. **DESIGN:** Prospective longitudinal cohort study. **SETTING:** Two pediatric otolaryngology referral centers. **PATIENTS:** Twenty-three pediatric patients ranging in age from 6 months to 17 years. **INTERVENTIONS:** The 585-nm PDL was used for at least 1 treatment on each of these patients to treat JORRP of the true vocal folds or anterior commissure. **MAIN OUTCOME MEASURES:** Complications from the use of the 585-nm PDL in the treatment of JORRP. **RESULTS:** There was no evidence of anterior commissure webbing or true vocal fold scarring in this group of 23 patients followed up for 3 months to 1 year. **CONCLUSIONS:** The 585-nm PDL seems to be a safe instrument for treatment of JORRP. There is the potential that improved voice outcomes may be apparent when compared with traditional therapies because the vocal fold epithelium seems to be unharmed when treated with this method. Furthermore, the lack of epithelial damage incurred by the 585-nm PDL should enable more aggressive surgical excision of anterior commissure disease. Further prospective longitudinal studies examining voice outcomes are needed.

Publication Types:

- [Evaluation Studies](#)

PMID: 17309979 [PubMed - indexed for MEDLINE]

[Ann Otol Rhinol Laryngol.](#) 2007 Jan;116(1):45-8.

Cost savings of unsedated office-based laser surgery for laryngeal papillomas.

[Rees CJ](#), [Postma GN](#), [Koufman JA](#).

Department of Otolaryngology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.

OBJECTIVES: Unsedated office-based laryngeal laser surgery (UOLS) is now an effective alternative to traditional operating room-based suspension microdirect laryngoscopy under general anesthesia. This procedure includes pulsed dye laser (PDL) treatment of recurrent respiratory papillomas, granulomas, leukoplakia, and polypoid degeneration. The objective of this study was to determine the magnitude of the cost savings derived by moving these types of procedures from the operating room to the office setting. **METHODS:** Retrospective cost-identification analysis was performed by comparing the billing records of patients who underwent surgical laser treatment for recurrent respiratory papillomatosis in the operating room to the costs and charges for patients who underwent similar procedures with the in-office PDL. **RESULTS:** In performing surgery with the PDL in the office, the average cost savings was more than \$5,000 per case. Current reimbursement rates do not cover the cost of performing UOLS. **CONCLUSIONS:** The potential cost savings of UOLS are tremendous; however, at present significant financial disincentives prevent proliferation of this technology.

Publication Types:

- [Comparative Study](#)

PMID: 17305277 [PubMed - indexed for MEDLINE]

[Transpl Int.](#) 2007 Mar;20(3):238-46.

Local administration of cidofovir for human papilloma virus associated skin lesions in transplant recipients.

[Bonatti H](#), [Aigner F](#), [De Clercq E](#), [Boesmueller C](#), [Widschwendner A](#), [Larcher C](#), [Margreiter R](#), [Schneeberger S](#).

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Human papilloma virus (HPV)-associated diseases are increasingly diagnosed in solid organ recipients. Cidofovir (CDV) is a broad-spectrum antiviral agent with activity against all human herpes viruses and HPV. From 2000-2004, a total of 1303 solid organ transplants (SOT) were performed at our center. Six transplant recipients were treated with topical CDV for HPV-associated lesions. One cardiac recipient responded to a single injection of CDV into his recurrent anal condylomata. In a renal recipient with recurrent penile condylomata CDV was injected into the lesions four times (2 week interval) until lesions regressed. One renal recipient developed multiple vaginal and anal intradermal neoplasias, which relapsed after laser ablation. The lesions were repeatedly injected with CDV and completely disappeared. Two renal recipients with widespread verrucae vulgares were treated with CDV gel, which resulted in regression of the lesions. One patient developed donor derived verrucae vulgares on both transplanted hands, which responded to CDV gel. Four of the six patients were switched from calcineurin inhibitors (CNIs) to Sirolimus (SIR). CDV was found effective in the treatment of HPV-associated skin lesions in SOT recipients. It needs to be determined whether switch from CNIs to SIR might have contributed to the beneficial effect of CDV.

Publication Types:

- [Case Reports](#)
- [Clinical Trial](#)

PMID: 17291217 [PubMed - indexed for MEDLINE]

[Laryngoscope](#). 2007 Feb;117(2):253-7.

Protein expression of the tumor suppressors p16INK4A and p53 and disease progression in recurrent respiratory papillomatosis.

[Pham TT](#), [Ongkeko WM](#), [An Y](#), [Yi ES](#).

Department of Pathology, University of California - San Diego, San Diego, California, USA.

BACKGROUND: Recurrent respiratory papillomatosis (RRP) is a benign condition that rarely metastasizes as invasive squamous cell carcinoma. Although this disease is associated with human papillomavirus, the role of this virus in tumorigenesis is unclear. **OBJECTIVES:** The aim of this study is to assess the involvement of the tumor suppressors P16INK4A and p53 in RRP tumor progression. **DESIGN:** Immunohistochemistry of p16INK4A and p53 was performed on biopsies of recurrent squamous papillomas and invasive lesions in nine patients. **RESULTS:** Twenty biopsies were graded as papillomas (RP), three as papillomas with high-grade dysplasia/carcinoma in situ (HGD/CIS), and two as invasive squamous cell carcinoma (SCCA). Forty-five percent of RP and 60% of HGD/CIS/SCCA expressed p16INK4A. Fifty percent of RP and 100% of HGD/CIS/SCCA expressed p53. The difference in the frequency of p53-positive staining between HGD/CIS and SCCA (100% of tissues examined) and RP (50% of tissues examined) approached statistical significance. Neither p16INK4A nor p53 was predictive of invasive transformation. **CONCLUSIONS:** Expression of p16INK4A, which is a surrogate for the tumor suppressor retinoblastoma (Rb), did not immediately lead to invasive disease. There is no correlation between disease severity of RRP and level of p16INK4A.

PMID: 17277618 [PubMed - indexed for MEDLINE]

[Otolaryngol Head Neck Surg.](#) 2007 Feb;136(2):321-3.

Unusual malignant transformation of juvenile recurrent respiratory papillomatosis.

[Sidhu TS](#), [Sharma AK](#), [Sharma N](#), [Sen AK](#), [Das BC](#).

Department of Otolaryngology, Dr. RML Hospital, New Delhi, India.

Publication Types:

- [Case Reports](#)

PMID: 17275567 [PubMed - indexed for MEDLINE]

[Int J Pediatr Otorhinolaryngol.](#) 2007 Apr;71(4):671-2; authore reply 673. Epub 2007 Jan 18.

Comment on:

- [Int J Pediatr Otorhinolaryngol.](#) 2006 Oct;70(10):1799-803.

Advocating for the quadravalent HPV vaccination, Gardasil, by Merck.

[Rothengass BE](#).

Publication Types:

- [Comment](#)
- [Letter](#)

PMID: 17239965 [PubMed - indexed for MEDLINE]

[Pediatr Infect Dis J](#). 2006 Dec;25(12):1158-62.

Human papilloma virus in hyperplastic tonsillar and adenoid tissues in children.

[Mammas IN](#), [Sourvinos G](#), [Michael C](#), [Spandidos DA](#).

Laboratory of Virology, School of Medicine, University of Crete, Heraklion, Greece.

BACKGROUND: Human papillomavirus (HPV) in childhood causes skin and anogenital warts as well as the recurrent respiratory papillomatosis, a life-threatening cause of upper airway obstruction in children. To date, the information on HPV infection in tonsillar and adenoid hyperplasia in children is limited. **PURPOSE:** The purpose of this study was to investigate the presence of HPV DNA in children with benign tonsillar and/or adenoid hyperplasia. **METHODS:** One hundred six samples of paraffin-embedded adenoid and/or tonsillar tissues from 102 children, 57 girls and 45 boys (age range, 2-14 years), were tested for the presence of HPV DNA using polymerase chain reaction (PCR) with general primers GP5+/GP6+. HPV typing was performed by PCR with specific primers for HPV-16, -18, -33 and -11. **RESULTS:** HPV DNA was detected in 9 (8.5%) of the 106 collected specimens. The frequencies of HPV typing were 6 of 9 (66.7%) for HPV-16, 2 of 9 (22.2%) for HPV-11, zero of 9 (0%) for HPV-33 and HPV-18, whereas one HPV-positive sample remained untyped. No multiple HPV infection was detected. HPV was detected in 6 (9.4%) children with tonsillar hyperplasia and in 3 (7.1%) with adenoid hyperplasia. The mean age of children with HPV-positive specimens was lower than that of HPV-negative children ($P = 0.006$). No statistical correlation in the prevalence of HPV infection was observed according to children's sex, origin or residence (urban or rural). **CONCLUSION:** Although the significance of the presence of HPV DNA in tonsillar and adenoid hyperplasias remains obscure, the PCR detection of high-risk HPV DNA should be evaluated cautiously.

PMID: 17133162 [PubMed - indexed for MEDLINE]

[Pediatrics](#). 2006 Nov;118(5):1925-31.

Recurrent respiratory papillomatosis in children: masquerader of common respiratory diseases.

[Zacharisen MC](#), [Conley SF](#).

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BACKGROUND: Recurrent respiratory papillomatosis in children is an uncommon but potentially life-threatening benign tumor of the respiratory tract with laryngeal predilection. The diagnosis of recurrent respiratory papillomatosis may be challenging unless there is a high index of suspicion and awareness of the variable presentations. **METHODS:** We reviewed the medical charts of children with recurrent respiratory papillomatosis treated at a tertiary children's hospital. The presentation of recurrent respiratory papillomatosis is illustrated by a series of case reports. We provide a paradigm to assist in the early diagnosis of children with recurrent respiratory papillomatosis. **RESULTS:** Five patients, aged 2 to 6 years, were erroneously diagnosed with recurrent croup, asthma, laryngeal hemangioma, and tracheomalacia after presenting with variable degrees of chronic dyspnea, cough, stridor, dysphonia, weak cry, and syncope. Once the diagnosis of recurrent respiratory papillomatosis was made, recurring surgical ablation of papillomata was initiated. **CONCLUSIONS:** Any child presenting with a voice disturbance with or without stridor is recommended to have diagnostic flexible fiber-optic laryngoscopy. Recurrent respiratory papillomatosis should be considered in children when other common pediatric airway diseases either do not follow the natural history or do not respond to treatment of the common disorder.

Publication Types:

- [Case Reports](#)

PMID: 17079563 [PubMed - indexed for MEDLINE]

[Eur Arch Otorhinolaryngol](#). 2007 Jan;264(1):63-70. Epub 2006 Oct 13.

Intralesional Cidofovir application in recurrent laryngeal papillomatosis.

[Pudszuhn A](#), [Welzel C](#), [Bloching M](#), [Neumann K](#).

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Recurrent laryngeal papillomatosis is a benign disease of the larynx often leading to organic and functional restrictions. The therapeutic treatment of choice in larynx-obstructing papillomatosis is at present surgical laser ablation. The effectiveness of adjuvant intralesional injection of the virustaticum Cidofovir has been investigated recently in a variety of therapeutic models. The present case study deals with the treatment of recurrent laryngeal papillomatosis by means of surgical laser ablation of the laryngeal papillomas with adjuvant local injection of the virustaticum Cidofovir (dose of 5 mg/1 ml). Within the period from October 2001 to August 2004, ten patients aged between 5- and 70 years were treated with intralesional injections of Cidofovir. Papillomatosis was confirmed histologically in all cases, and the virus types were defined in part. Each of the patients underwent clinical-phoniatric examinations and was photographed for documentation. After 2-7 treatments with surgical laser papilloma ablation and intralesional Cidofovir injections, all patients showed a definite papilloma reduction, while in six cases complete remission was achieved. During the follow-up period of 8-30 months, not a single recurrence of the laryngeal papillomatosis occurred. In the majority of patients, a clear improvement in the voice was achieved. There were no local or systemic side effects caused by the virustaticum. Intralesional injection of Cidofovir is an adjuvant, but not a curative therapeutic option in recurrent laryngeal papillomatosis. Remission of previously frequently recurrent laryngeal papillomas can be achieved, but recurrence after longer treatment-free intervals is also possible.

PMID: 17058091 [PubMed - in process]

[Ann Otol Rhinol Laryngol](#). 2006 Sep;115(9):679-85.

Comment in:

- [Ann Otol Rhinol Laryngol](#). 2007 Apr;116(4):317.

Office-based 532-nm pulsed KTP laser treatment of glottal papillomatosis and dysplasia.

[Zeitels SM](#), [Akst LM](#), [Burns JA](#), [Hillman RE](#), [Broadhurst MS](#), [Anderson RR](#).

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OBJECTIVES: Treatment of glottal papillomatosis and dysplasia was mirror-guided and done in surgeons' offices in the 19th century. It migrated to the operating room in the 20th century to accommodate direct laryngoscopic surgery, which required assistants to administer anesthesia and procedural support. The primary treatment goals, which are disease regression and voice restoration and/or maintenance, are tempered by the morbidity of general anesthesia and potential treatment-induced vocal deterioration. To obviate general anesthesia, office-based laser laryngeal surgery was first done in 2001 with the 585-nm pulsed dye laser (PDL), because it employs a fiber delivery system and its energy is selectively absorbed by oxyhemoglobin. Since then, this new angiolytic laser treatment paradigm has become a mainstay of management for many surgeons; however, there are a number of shortcomings of the PDL. To further develop this concept and address the limitations of the PDL, we used a 532-nm pulsed potassium titanyl phosphate (KTP) laser.

METHODS: A prospective assessment was performed on 48 patients in 72 cases of recurrent glottal dysplasia (36) or papillomatosis (36). All individuals had previously undergone microlaryngoscopic management with histopathologic evaluation.

RESULTS: Two dysplasia patients did not tolerate the procedure. Of the treatable dysplasia cases, there was follow-up in 29 of 34. Disease regression was at least 75% in 18 of 29 cases (62%), 50% to 75% in 7 of 29 (24%), and 25% to 50% in the remaining 4 of 29 (14%). Papilloma patients returned for treatment when symptoms recurred, so disease regression could not be assessed accurately. Similar to data obtained with the PDL, these data confirmed that dysplastic mucosa could normalize without resection.

CONCLUSIONS: Our observations revealed that the 532-nm pulsed KTP laser provided enhanced performance over the PDL laser in a number of ways. The ability to use smaller glass fibers precluded mechanical trauma to the channels of the flexible laryngoscopes and allowed for improved suctioning of secretions. Oxyhemoglobin absorbs energy better at 532 nm than at 585 nm, and the KTP laser can be delivered through a longer pulse width. These factors provide enhanced hemostasis and improved intralesional energy absorbance. Finally, unlike the PDL, the KTP laser is a solid-state laser and is not prone to mechanical failure.

Publication Types:

- [Clinical Trial](#)

PMID: 17044539 [PubMed - indexed for MEDLINE]

[Ann Otol Rhinol Laryngol](#). 2006 Sep;115(9):667-72.

Intermediate-term and long-term results after treatment by cidofovir and excision in juvenile laryngeal papillomatosis.

[Naiman AN](#), [Avari S](#), [Nicollas R](#), [Landry G](#), [Colombeau B](#), [Froehlich P](#).

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OBJECTIVES: We assessed the intermediate-term and long-term efficacy of intralesional injection of cidofovir used with surgical excision in juvenile-onset recurrent respiratory papillomatosis. **METHODS:** The protocol was revised during the study, from endoscopy at 4-week intervals with intralesional injection of cidofovir at 5 mg/mL, to a 2-week interval and a 7.5-mg/mL dosage. Partial surgical excision of hypertrophic papillomas was performed before the initiation of injection. Further injections at 4-week (or 2-week) intervals were performed until complete remission. **RESULTS:** Sixteen patients received a mean 8.9 injections. Complete remission was obtained in 12 patients (75%) after a mean 7.2 endoscopic treatments. Remission was stable at a mean 33.6 months' follow-up. Five of these 12 patients received 5.2 injections and remained disease-free at a mean 39.3 months' follow-up. Seven of the 12 had 1 relapse; they needed complementary treatment to become disease-free, and remained so thereafter over a mean 27.3 months' follow-up. The other 4 of the 16 patients (25%) continued to present active disease. **CONCLUSIONS:** Active endoscopic treatment until complete remission led to a higher-than-expected complete remission rate on intermediate-term to long-term follow-up, with or without relapse. Transient relapse was associated with a long delay in initiating cidofovir treatment.

Publication Types:

- [Clinical Trial](#)

PMID: 17044537 [PubMed - indexed for MEDLINE]

[Lin Chuang Er Bi Yan Hou Ke Za Zhi](#). 2006 Aug;20(15):704-6.

[Clinical study of tracheotomied children with juvenile onset recurrent respiratory papillomatosis]

[Article in Chinese]

[Ma L](#), [Wang J](#), [Han D](#), [Ye J](#), [Xu W](#).

Department of Otorhinolaryngology-Head and Neck Surgery, Affiliated Beijing Tongren Hospital, Capital University of Medical Sciences, Beijing, 100730, China.

OBJECTIVE: To analysis the clinical characteristics of tracheotomied children with Juvenile-onset recurrent respiratory papillomatosis (JORRP) and to discuss the time of decannulation. **METHOD:** Thirty-one children with JORRP, who underwent tracheotomy and treated with CO2 laser in Otorhinolaryngololgy department of Tongren Hospital between 1993 and 2005, were reviewed in this essay. We analysis the age, the site of intratracheal papilloma, invasion fashion of lesion, et al. **RESULT:** Thirty-one tracheotomied children

underwent 32 tracheotomy, 20 cases was decannulated. Among the 32 tracheotomied cases, three cases were decannulated in 1 month post operation and the intratracheal lesions were not found. There were presented intratracheal lesions in 29 cases. Intratracheal lesions were not presented in 20 cases after three months of decannulation. CONCLUSION: The tracheotomy should strive to be avoided to JORRP patients. If a JORRP patient was underwent tracheotomy, he should be decannulated as early as possible. The time of decannulation was performed in the operation or post operation when the intratracheal lesions was less.

Publication Types:

- [English Abstract](#)

PMID: 17037021 [PubMed - in process]

[Paediatr Respir Rev.](#) 2006;7 Suppl 1:S330.

CR12/339--Nebulized cidofovir for recurrent respiratory papillomatosis: a case report.

[Giles BL](#), [Seifert B](#).

University of Manitoba, Pediatrics and Child Health, Winnipeg, Canada.

Publication Types:

- [Case Reports](#)

PMID: 17036412 [PubMed - indexed for MEDLINE]

[Can Respir J.](#) 2006 Oct;13(7):381-3.

Recurrent respiratory papillomatosis causing chronic stridor and delayed speech in an 18-month-old boy.

[Alharbi A](#), [Drummond D](#), [Pinto A](#), [Kirk V](#).

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Recurrent respiratory papillomatosis is a relatively uncommon disease that presents clinically with symptoms ranging from hoarseness to severe dyspnea. Human papilloma virus types 6 and 11 are important in the etiology of papillomas and are most probably transmitted from mother to child during birth. Although spontaneous remission is frequent, pulmonary spread and/or malignant transformation resulting in death has been reported. CO2 laser evaporation of papillomas and adjuvant drug therapy using lymphoblastoid interferon-alpha are the most common treatments. However, several other treatments have been tried, with varying success. In the present report, a case of laryngeal papillomatosis presenting with chronic stridor and delayed speech is described.

Publication Types:

- [Case Reports](#)

PMID: 17036092 [PubMed - indexed for MEDLINE]

[Curr Opin Infect Dis.](#) 1998 Dec;11(6):733-7.

Specific therapies for human papilloma virus infections.

[Snoeck R](#), [Andrei G](#), [De Clercq E](#).

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Human papillomavirus induces the hyperproliferation of epithelial cells, leading to a broad spectrum of human diseases, ranging from benign warts to malignant neoplasms, depending on the location of the lesion, the immune status of the patient and the type of human papillomavirus. Current therapies for human papillomavirus-associated diseases are based on the excision or ablation of dysplastic or malignant tissue, and are associated with a high frequency of recurrent disease, discomfort and costs. A better understanding of the viral replicative cycle and of the interaction between the virus and the host cell, particularly the cell cycle regulation, has opened new perspectives. Recently, new treatment modalities for human papillomavirus-induced lesions have been identified, including the use of antiviral/immunomodulatory therapies, such as cidofovir, antisense oligonucleotides, imiquimod and human papillomavirus vaccines.

PMID: 17035751 [PubMed]

[Head Neck](#). 2007 Feb;29(2):155-62.

Juvenile recurrent respiratory papillomatosis: still a mystery disease with difficult management.

[Stamataki S](#), [Nikolopoulos TP](#), [Korres S](#), [Felekis D](#), [Tzangaroulakis A](#), [Ferekidis E](#).

ENT Department, Johns Hopkins Hospital, Baltimore, Maryland, USA.

Juvenile recurrent respiratory papillomatosis (RRP) is the most common benign neoplastic disease of the larynx in children and adolescents and has a significant impact on patients and the health care system with a cost ranging from \$60,000 to \$470,000 per patient. The aim of this paper is to review the current literature on RRP and summarize the recent advances. RRP is caused by human papillomavirus (HPV; mainly by types 6 and 11). Patients suffer from wart-like growths in the aerodigestive tract. The course of the disease is unpredictable. Although spontaneous remission is possible, pulmonary spread and malignant transformation have been reported. Surgical excision, including new methods like the microdebrider, aims to secure an adequate airway and improve and maintain an acceptable voice. Repeated recurrences are common and thus overenthusiastic attempts to eradicate the disease may cause serious complications. When papillomas recur, old and new adjuvant methods may be tried. In addition, recent advances in immune system research may allow us to improve our treatment modalities and prevention strategies. A new vaccine is under trial to prevent HPV infection in women; the strongest risk factor for juvenile RRP is a maternal history of genital warts (transmitted from mother to child during delivery). Better understanding of the etiology of the disease and the knowledge of all available therapies is crucial for the best management of the affected patients.

Publication Types:

- [Review](#)

PMID: 17022088 [PubMed - indexed for MEDLINE]

[Virol J](#). 2006 Sep 8;3:75.

High level expression of human epithelial beta-defensins (hBD-1, 2 and 3) in papillomavirus induced lesions.

[Chong KT](#), [Xiang L](#), [Wang X](#), [Jun EL](#), [Xi LF](#), [Schweinfurth JM](#).

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BACKGROUND: Epithelial defensins including human beta-defensins (hBDs) and alpha-defensins (HDs) are antimicrobial peptides that play important roles in the mucosal defense system. However, the role of defensins in papillomavirus induced epithelial lesions is unknown. **RESULTS:** Papilloma tissues were prospectively collected from 15 patients with recurrent respiratory papillomatosis (RRP) and analyzed for defensins and chemokine IL-8 expression by quantitative, reverse-transcriptase polymerase chain reaction (RT-PCR) assays. HBD-1, -2 and -3 mRNAs were detectable in papilloma samples from all RRP patients and the levels were higher than in normal oral mucosal tissues from healthy individuals. Immunohistochemical analysis showed that both hBD-1 and 2 were localized in the upper epithelial layers of papilloma tissues. Expression of hBD-2 and hBD-3 appeared to be correlated as indicated by scatter plot analysis ($r = 0.837$, $p < 0.01$) suggesting that they were co-inducible in papillomavirus induced lesions. Unlike hBDs, only low levels of HD5 and HD6 were detectable in papillomas and in oral mucosa. **CONCLUSION:** Human beta-defensins are upregulated in respiratory papillomas. This novel finding suggests that hBDs might contribute to innate and adaptive immune responses targeted against papillomavirus-induced epithelial lesions.

Publication Types:

- [Research Support, Non-U.S. Gov't](#)

PMID: 16961924 [PubMed - indexed for MEDLINE]

[Radiat Med.](#) 2006 May;24(4):297-301.

Pulmonary spread of laryngeal papillomatosis: radiological findings.

[Abe K](#), [Tanaka Y](#), [Takahashi M](#), [Kosuda S](#), [Hayashi K](#), [Tanabe T](#), [Iwasaki Y](#), [Aida S](#), [Kawauchi T](#), [Yamamoto M](#), [Kita T](#), [Kaji T](#).

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Laryngeal papillomatosis is a rare benign disease seen in children and young adults. The spread of laryngeal papillomas throughout the respiratory tract occurs rarely; and involvement of the distal bronchi, bronchioles, and lung parenchyma is very rare. We report a case of pulmonary spread of laryngeal papillomatosis in a 34-year-old man, focusing on the radiological evidence. Chest radiographs showed pulmonary nodules, but computed tomography scans more clearly demonstrated multiple small nodules showing cavitations and distributed centrilobularly. Pulmonary nodules and cavitations progressed gradually through the 6-year follow-up. The combination of clinical and characteristic radiological features suggests a diagnosis of pulmonary spread of laryngeal papillomatosis.

Publication Types:

- [Case Reports](#)

PMID: 16958405 [PubMed - indexed for MEDLINE]

[Int J Pediatr Otorhinolaryngol.](#) 2006 Dec;70(12):2061-6. Epub 2006 Sep 1.

Children and partners of patients with recurrent respiratory papillomatosis have no evidence of the disease during long-term observation.

[Gerein V](#), [Soldatski IL](#), [Babkina N](#), [Onufrieva EK](#), [Barysik N](#), [Pfister H](#).

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OBJECTIVE: Recurrent respiratory papillomatosis (RRP) is the most common benign neoplasm affecting the larynx and upper respiratory tract. The aim of our study was to investigate whether children and partners of patients with RRP develop the same disease and to determine whether there is an impact of pregnancy on the course of RRP. **PATIENTS AND METHODS:** Thirty-eight of 42 patients with RRP were accepted for a multicenter prospective study in Germany in 21.06.83-12.03.90. Mean follow-up duration was 15.3+/-1.8 years. The data of partners of patients with RRP was collected during the period of observation and then updated via interviews in January 2006. Twenty-nine children and four grandchildren were born to 14 patients with RRP. Fifteen of 448 cases of patients with RRP were treated in Saint Vladimir Moscow Children's Hospital in Russia in 1988-2003 and analyzed retrospectively. Sixteen children and one grandchild were born to 15 patients with RRP from Russia. In both studies, the virus type of patients with RRP was identified by nested PCR or Southern blot hybridization. Statistical analysis was performed using Fisher's exact test (probability value set at $p < 0.05$). **RESULTS:** All children born to patients with RRP were healthy. RRP was not diagnosed in any of them on the basis of clinical or histological examination. Four of 45 children developed dysphonia, two of them had vocal cord nodules. None of the sexual partners of patients has developed RRP during the follow-up period. Pregnancy was accompanied by excessive growth of papillomas in all women (100%) with RRP associated with HPV type 11, and only in 16.7% of women with RRP associated with HPV type 6 ($p = 0.001$). **CONCLUSIONS:** Patients with RRP are able to have healthy children regardless of the stage of the disease. Partners of RRP patients do not develop RRP during an observation period of 15 years. Pregnancy has a negative impact on the course of RRP and local laryngeal status in patients; it is more significant in HPV type 11 associated cases as it is manifested by more rapid papillomas growth and more frequent recurrence.

Publication Types:

- [Multicenter Study](#)

PMID: 16945430 [PubMed - indexed for MEDLINE]

[Int J Pediatr Otorhinolaryngol.](#) 2006 Nov;70(11):1911-7. Epub 2006 Aug 17.

3.5-Year follow-up of intralesional cidofovir protocol for pediatric recurrent respiratory papillomatosis.

[Chung BJ](#), [Akst LM](#), [Koltai PJ](#).

Head & Neck Institute, Cleveland Clinic Foundation, Desk A71, 9500 Euclid Avenue, Cleveland, OH 44195, United States. chungb@ccf.org

OBJECTIVES: Intralesional injection of cidofovir has been described as an adjunctive treatment for pediatric recurrent respiratory papillomatosis (RRP). However, questions remain regarding the optimal dosing schedule and side-effect profile. The objective of this study was to describe patient outcomes following a standardized cidofovir protocol.

METHODS: Eleven pediatric patients originally treated with a standardized stepped-dose protocol of intralesional cidofovir for RRP were followed for an extended observational period. Additional interventions, disease severity, and adverse outcomes were recorded.

RESULTS: Five of 11 patients have required no further treatments following the original cidofovir protocol. Two patients initially achieved remission but have subsequently required additional treatment for recurrent disease. Four patients never achieved remission and have undergone multiple additional interventions. Mean follow-up time for all patients from the conclusion of the original study was 30.2 months (10-45). No adverse outcomes were noted.

CONCLUSIONS: Intralesional injection of cidofovir may have some potential as an adjunct in the treatment of RRP. Response to cidofovir is unpredictable. Further study of cidofovir is necessary to more clearly define whether the favorable responses observed represent a true treatment effect or simply reflect the natural history of the disease. Perhaps as important is to refine treatment protocols and informed consents that reflect the concern about the carcinogenic potential of cidofovir and to better characterize the drug's side-effect profile.

Publication Types:

- [Clinical Trial](#)

PMID: 16919339 [PubMed - indexed for MEDLINE]

[B-ENT](#). 2006;2(2):51-4.

Papillomatosis of the larynx: treatment with CO2 laser.

[Meselella M](#), [Motta G](#), [Laguardia M](#), [Galli V](#).

ENT Department, University Federico II, Naples, Italy.

OBJECTIVES: We report our experience treating papillomatosis of the larynx using CO2 laser which has a lower risk of post surgical complications. Papillomatosis has a high incidence of recurrence after surgical treatment. **METHODS:** We treated 42 patients (10 adults and 32 children) affected by multiple papillomatosis of the larynx. Smaller papillomas were vaporized with a 7-8 Watt CO2 laser and larger papillomas were resected at the base of their implantation. A strict follow-up during the first 3 years after surgical treatment was necessary to manage recurrences with CO2 laser endoscopy. **RESULTS:** All patients presented with recurrences after the first surgical treatment, but within 18-60 months all patients presented a solution of their pathology. Post-operative complications were observed in patients who did not comply with the strict follow-up protocol and presented with large lesions requiring more invasive surgery. **CONCLUSIONS:** CO2 laser endoscopy, although it did not prevent recurrences of papillomatosis in the larynx, is a valid surgical approach in the management of this pathology.

PMID: 16910287 [PubMed - indexed for MEDLINE]

[B-ENT](#). 2006;2(2):47-9.

Comparative assessment of aluminum and lead concentrations in serum and tissue bioplates in patients with laryngeal papilloma or cancer.

[Olszewski J](#), [Latusiński J](#), [Kita A](#), [Pietkiewicz P](#), [Starostecka B](#), [Majak J](#).

Department of Otolaryngology and Oncology, Medical University Lodz, Poland.

A comparative assessment of toxic element concentrations in serum and tissue bioplates in patients with laryngeal papilloma or cancer was performed. Examinations were conducted in 60 patients (40 men and 20 women) aged 20-88 years (average 59 +/- 05). Patients were divided into 3 groups; 20 patients with laryngeal papilloma were in group I, 20 with laryngeal cancer were in group II, and 20 with deviated nasal septums were included as a control group (III). Diagnosis of laryngeal papilloma (removed by direct microlaryngoscopy-Kleinsasser method) and laryngeal cancer (removed by the Rethi method) was histopathologically confirmed in patients from groups I and II, respectively. Patients in the

control group received functional surgery to repair deviated nasal septums. Serum and tissue samples were obtained from all patients before surgery. Aluminum and lead concentrations were analysed by inductively coupled plasma atomic emission spectrometry (ICP-AES) using a Spectroflame M spectrometer. The considerable rise of aluminum and lead concentration in tissue bioptates and aluminum in serum in groups I and II in comparison to the control group suggests that these elements may play a significant part in the aetiology and development of precancerous lesions and laryngeal cancers. Measuring toxic chemical element concentrations in tissue bioptates can be useful in the diagnosis and estimation of development of precancerous lesions of the larynx as well as laryngeal cancer. Toxic elements concentration may play a significant role in carcinogenesis and may determine trends in cancer aetiology.

Publication Types:

- [Comparative Study](#)

PMID: 16910286 [PubMed - indexed for MEDLINE]

[Otolaryngol Head Neck Surg.](#) 2006 Aug;135(2):189-96.

Unique challenges of obtaining regulatory approval for a multicenter protocol to study the genetics of RRP and suggested remedies.

[Sherwood ML](#), [Buchinsky FJ](#), [Quigley MR](#), [Donfack J](#), [Choi SS](#), [Conley SF](#), [Derkay CS](#), [Myer CM 3rd](#), [Ehrlich GD](#), [Post JC](#).

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OBJECTIVE: Investigations that seek to generalize findings or to understand uncommon diseases must be conducted at multiple centers. This study describes the process of obtaining regulatory approval for a minimal risk genetic study in a multi-center setting as undertaken by the Recurrent Respiratory Papillomatosis (RRP) Task Force. **STUDY DESIGN AND SETTING:** Sequential cohort of American children's hospitals. A single protocol was submitted to each Institutional Review Board (IRB). **RESULTS:** Documentation was prepared for 14 IRBs over 2.5 years. The median time between enlistment and approval at the first 8 sites was 15 months. Institutions varied considerably in their requirements and in the issues that were raised. Protocols were submitted sequentially and accumulated experience was used in the preparation of applications to subsequent IRBs. Nevertheless, there was no correlation between the accumulated experience and the number of issues that were raised. **CONCLUSION:** Despite uniform federal standards, all local IRBs required unique and individualized submissions. For multicenter studies, investigators should

seriously consider the establishment of cooperative authorization agreements. On a simpler level, a standardized format for applications needs to be adopted nationwide. EBM rating: B-3b.

Publication Types:

- [Research Support, N.I.H., Extramural](#)
- [Research Support, Non-U.S. Gov't](#)

PMID: 16890066 [PubMed - indexed for MEDLINE]

[Laryngoscope](#). 2006 Aug;116(8):1372-4.

Presence of human papillomavirus DNA in tonsillectomy specimens.

[Sisk J](#), [Schweinfurth JM](#), [Wang XT](#), [Chong K](#).

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OBJECTIVES: The objectives of this prospective case-control study were to study the prevalence of human papillomavirus (HPV) in tonsillectomy specimens from pediatric patients without recurrent respiratory papillomatosis (RRP), and to study methods of HPV detection. **METHODS:** Fifty pediatric patients without known RRP undergoing tonsillectomy for hypertrophy or recurrent tonsillitis were enrolled in the study. After tonsillectomy, a 20-mg section was subjected to DNA extraction, and DNA content and purity were confirmed with spectrophotometry. Polymerase chain reaction (PCR) was performed using consensus primer pools PGMY 09/11 targeted at the L1 region. Amplification products were detected and analyzed with standard agarose gel electrophoresis. Positive samples were then subjected to reverse line blot assay to determine virus genotype. Laryngeal papilloma specimens of 15 patients obtained during routine debulking procedures were also analyzed and served as positive controls. **RESULTS:** Of 50 tonsil samples tested, two were positive for HPV DNA after PCR and gel electrophoresis. One of these samples was confirmed with typing and tested positive for HPV 11. All 15 papilloma specimens were positive for DNA of HPV types 6 and/or 11. **CONCLUSIONS:** In the current study, the prevalence of HPV DNA in tonsillar tissue of patients without RRP is 2%, whereas the incidence of this disease is 2 to 4 cases per 100,000 (0.004%). These findings are significantly different ($P = .005$ within a 95% confidence interval) suggesting that host factors in addition to infection play a role in pathogenesis of RRP. The molecular methods described in this study are well suited for detection of HPV in tonsillar tissue.

Publication Types:

- [Research Support, Non-U.S. Gov't](#)

PMID: 16885738 [PubMed - indexed for MEDLINE]

[Int J Pediatr Otorhinolaryngol.](#) 2006 Oct;70(10):1799-803. Epub 2006 Aug 1.

Comment in:

- [Int J Pediatr Otorhinolaryngol.](#) 2007 Apr;71(4):671-2; [author reply 673.](#)

Prevention of recurrent respiratory papillomatosis: role of HPV vaccination.

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Recurrent respiratory papillomatosis is a rare, but devastating, cause of airway lesions in children and adults. This disease is caused by human papilloma virus subtypes 6 and 11. At this time there are two vaccines in late stages of development seeking Food and Drug Administration (FDA) approval to prevent cervical cancer, which is also caused by human papilloma virus. One of these vaccines has been developed to stimulate immunity to the most common subtypes that cause cervical cancer but also includes those responsible for recurrent respiratory papillomatosis. With the possibility this could drastically reduce the incidence of RRP, the otolaryngology community should advocate for implementation of a vaccine program that provides effective prevention of HPV infection with subtypes 6 and 11.

Publication Types:

- [Review](#)

PMID: 16884786 [PubMed - indexed for MEDLINE]

[Arch Dis Child.](#) 2006 Aug;91(8):689-91.

Recurrent respiratory papillomatosis.

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Recurrent respiratory papillomatosis (RRP) is a benign, often multi-focal neoplasm. A potentially fatal manifestation of human papilloma virus infection, the condition is characterised by multiple warty excrescences on the mucosal surface of the respiratory tract. RRP is rare--incidence is estimated at 3.5 per million person-years, with a prevalence of 4 in 100,000 children. Affected children usually require multiple interventions; the impact on patients, their families, and the healthcare system is considerable. Treatment of RRP accounts for an estimated dollar 109 million annual expenditure in the USA.

Publication Types:

- [Review](#)

PMID: 16861486 [PubMed - indexed for MEDLINE]

[J Formos Med Assoc.](#) 2006 Jun;105(6):508-11.

Virtual bronchoscopy for diagnosis of recurrent respiratory papillomatosis.

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Virtual bronchoscopy is a new method for viewing helical/spiral computed tomography (CT) images of the tracheobronchial trees. Using commercially available software to process the CT data, the tracheobronchial trees can be inspected through a series of three-dimensional images. Recently, this technique has been increasingly used to detect benign and malignant airway stenosis. We report the findings of virtual bronchoscopy in a 41-year-old man with recurrent respiratory papillomatosis (RRP). Several tiny nodules were evident in the lower trachea. Fiberoptic bronchoscopy was performed 1 month later during a planned surgery for laryngeal papillomas, and the findings were in agreement with virtual bronchoscopy. Detection of intrabronchial spreading in RRP is important since peripheral seeding of RRP can cause complications, including recurrent pneumonia, obstructive atelectasis, hemoptysis, and, rarely, may degenerate to squamous cell carcinoma. Virtual bronchoscopy is an alternative method for inspecting the tracheobronchial trees in patients with RRP when laryngeal papillomas impede fiberoptic bronchoscopy.

Publication Types:

- [Case Reports](#)

PMID: 16801040 [PubMed - indexed for MEDLINE]

[Prim Care Respir J](#). 2006 Apr;15(2):125-7. Epub 2006 Mar 9.

Juvenile laryngeal papillomatosis.

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Always ask about hoarseness and quality of voice in a history of any child presenting with cough or asthma-like symptoms. Children presenting with what appears to be an acute onset of hoarseness, without any physical signs of airways obstruction, should be reviewed after two weeks. If there is chronic hoarseness, referral to an ENT specialist should be considered with a view to laryngoscopy. If the child develops clinical signs of acute airway obstruction such as stridor or respiratory distress, prompt paediatric review is indicated. When referring, it is important to emphasise whether or not there is chronic hoarseness in order to differentiate the diagnosis from croup. Juvenile Laryngeal Papillomatosis may present with cough, pneumonia, dysphagia, or stridor, as well as hoarseness. These patients are often misdiagnosed as having asthma or allergies.

Publication Types:

- [Case Reports](#)

PMID: 16701772 [PubMed - indexed for MEDLINE]

[Int J Pediatr Otorhinolaryngol](#). 2006 Jun;70(6):1097-101. Epub 2006 Jan 6.

Airway reconstruction in children with recurrent respiratory papillomatosis.

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OBJECTIVE: To determine if children with recurrent respiratory papillomatosis were at

increased risk of complications due to their disease following major airway reconstruction. **METHODS:** We retrospectively reviewed our airway surgery database and the medical records of all children diagnosed with recurrent respiratory papillomatosis who were evaluated at Cincinnati Children's Hospital Medical Center between January 1998 and August 2003. All patients with active airway papillomas or a history of recurrent respiratory papillomatosis who underwent open airway reconstruction at our institution were included in the study. **RESULTS:** Seven children with recurrent respiratory papillomatosis underwent major airway reconstruction. Six children had tracheotomies and five are now decannulated following their airway reconstruction. Five children had active papillomas at the time of surgery and none had significant worsening of their papillomas following their procedures. Two patients in remission underwent airway reconstruction without recurrence of their papillomas. **CONCLUSIONS:** Major airway reconstruction can be safely performed in children with recurrent respiratory papillomatosis.

Publication Types:

- [Case Reports](#)
- [Comparative Study](#)

PMID: 16406073 [PubMed - indexed for MEDLINE]
[Vaccine](#). 2003 Jul 4;21(23):3219-27.

Heterologous boosting increases immunogenicity of chimeric papillomavirus virus-like particle vaccines.

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Chimeric human papillomavirus virus-like particles (HPV cVLPs), containing the HPV16 non-structural protein E7, are potent vaccines for inducing antigen-specific protective immunity against HPV-transformed tumors in animal models. Previous data demonstrated that the effectiveness of cytotoxic T lymphocyte (CTL) induction after repetitive vaccination with the same cVLP, and thus vaccine efficacy, is limited by the presence of neutralizing antibodies induced after the first application. Here, we determined if altering the route of vaccine delivery or incorporation of the target antigen into VLPs of a heterologous papillomavirus type could overcome inhibition of MHC class I antigen presentation by neutralizing antibodies, resulting in a boosting of CD8(+) T-cell responses against the incorporated antigen, HPV16 E7. Mucosal delivery of cVLPs resulted in detection of systemic E7-specific CD8(+) T cells, however, these routes were not able to bypass the inhibitory effect of circulating antibodies against homologous VLP types. In contrast, mice immunized and boosted with heterologous cVLPs containing HPV16 E7 showed a higher frequency of E7-specific T cells in vitro and displayed reduced tumor growth in a therapeutic setting compared to mice treated with homologous cVLPs. The data indicate that the use of

different cVLP types for prime/boost regimens is a promising strategy to increase the efficacy and usefulness of cVLP-based vaccines for the treatment of cervical neoplasia.

PMID: 12804851 [PubMed - indexed for MEDLINE]

[Virology](#). 2001 Nov 25;290(2):350-60.

Effect of preexisting neutralizing antibodies on the anti-tumor immune response induced by chimeric human papillomavirus virus-like particle vaccines.

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Chimeric human papillomavirus virus-like particles (HPV cVLPs) carrying HPV16 E7 protein are potent vaccines for inducing cell-mediated immunity (CMI) against HPV-induced tumors in animal models. We tested the hypothesis that virion-neutralizing antibodies generated during an initial vaccination might prevent effective boosting of CMI to the cVLPs. Mice with circulating HPV16-neutralizing antibodies, generated by direct immunization with wild-type VLPs or by passive transfer of hyperimmune anti-HPV16 VLP mouse sera, were subsequently vaccinated with HPV16 E7-containing cVLPs. Mice with preexisting neutralizing antibodies were not protected from HPV16 E7-positive TC-1 tumor challenge, compared to the protection seen in mice lacking these antibodies. Antibody-coated VLPs bound very inefficiently to receptor-positive cell lines, suggesting that one of the mechanisms of antibody interference is blocking of VLP binding to its receptor and thereby uptake of VLPs by antigen-presenting cells. Our results suggest that repetitive vaccination with a cVLP for induction of cellular immune responses to an incorporated antigen may be of limited effectiveness due to the presence of neutralizing antibodies against the capsid proteins induced after the first application. This limitation could potentially be overcome by boosting with cVLPs containing the same target antigen incorporated into other papillomavirus-type VLPs.

PMID: 11883199 [PubMed - indexed for MEDLINE]

[Curr Opin Mol Ther](#). 1999 Feb;1(1):82-8

Papillomavirus virus-like particles as anticancer vaccines.

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Papillomavirus virus-like particles (VLPs) are empty, non-replicative, non-infectious particles that retain conformationally correct epitopes for the generation of antibody responses to the viral capsid proteins. Chimeric human papillomavirus (HPV) virus-like particles incorporating non-structural virus proteins offer an exciting approach for combined prophylactic and therapeutic vaccines against HPV-induced lesions. Both HPV VLPs and chimeric VLPs can induce potent humoral and cellular immune responses when injected into mice, leading to the generation of virus-neutralizing antibodies, priming of CD8⁺ T-cells and activation of cytotoxic T-cell effector functions. This review summarizes recent advances in the production of chimeric VLPs, the immune response elicited by VLPs and chimeric VLPs, and their ability to generate strong protective and therapeutic antitumor immune responses.

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