

# **RRP Medical Reference Service**

**An RRP Foundation Publication**

**edited by**

**Dave Wunrow and Bill Stern**

**Fall - Winter 2013**

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**Volume 17 • Number 1**

## 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 (2013 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

[Folia Med \(Plovdiv\)](#). 2013 Jan-Mar;55(1):49-54.

*Immunomodulatory effects of BCG in patients with recurrent respiratory papillomatosis.*

[Vetskova EK](#), [Muhtarova MN](#), [Avramov TI](#), [Stefanova TR](#), [Chalakov IJ](#), [Nikolova MH](#).

### Source

BB-NCIPD Ltd, Sofia, Bulgaria.

### Abstract

#### **BACKGROUND:**

Recurrent respiratory papillomatosis (RRP) is a rare manifestation of human papilloma virus (HPV) infection with extremely high relapse frequency, poorly understood immunopathogenesis, and lack of efficient treatment.

Immunotherapy with Calgevax (BCG) in combination with CO<sub>2</sub> surgery significantly improves the outcome of RRP. The present study investigates cellular immunity parameters in RRP patients, and the effects of 20-month Calgevax immunomodulation.

#### **MATERIALS AND METHODS:**

RRP patients (n = 15) subjected to combined therapy were tested before, 6, 12 and 20 months after the start of immunomodulation. Absolute counts and percentage of T, B and NK cells, effector T1 (CD8 + IFN $\gamma$ ); Th1 (CD4+IFN $\gamma$ ), Th17 (CD4+IL-17+) and regulatory (CD4+FoxP3+) T lymphocytes, as well as the in vitro stimulated secretion of IL-2, IL-4, IL-5, IL-10, IFN $\gamma$  and TNF $\alpha$  were determined by flow cytometry (FACSCanto II, BD).

#### **RESULTS:**

While no significant changes were detected in the circulating T, B and NK subsets, RRP patients presented increased proportions of Tc1, Th1 and Th17 cells, and significantly reduced IFN $\gamma$ /IL-4 and IFN $\gamma$ /IL-10 ratios as compared to healthy controls (15% vs. 8%), (58 vs. 139 and 15 vs. 26, respectively), p < 0.05 for all comparisons. Increased Treg (9% vs. 4%), and decreased Th17 effectors share (0.7% vs. 0.4%) were observed at 12 months, while IFN $\gamma$ /IL-4 and IFN $\gamma$ /IL-10 ratios were restored after 20 months of Calgevax application.

**CONCLUSIONS:**

Antiviral response closely depends on cytokine background. Calgevax potentiates Treg differentiation at the expense of proinflammatory Th17, limits hyperactivation and virus-specific T cell clones depletion, and restores a Th1 cytokine background.

PMID: 23905487 [PubMed - in process]

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[Indian J Med Paediatr Oncol](#). 2013 Jan;34(1):34-7. doi: 10.4103/0971-5851.113420.

***Case of childhood laryngeal papillomatosis with metastatic carcinoma esophagus in adulthood.***

[Shetty N](#), [Prabhash K](#), [Joshi A](#), [Sayed SI](#), [Sharma S](#), [Noronha V](#), [Deshmukh A](#), [Chaukar D](#), [Kane S](#), [Gopal](#), [D'cruz AK](#).

**Source**

Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India.

**Abstract**

A young male patient was diagnosed to have laryngeal papillomas at the age of 3 years for which he underwent permanent tracheostomy and also multiple surgical and laser excision procedures. Then, later in life, the patient had progressive breathlessness and dysphagia. On examination, he had supraclavicular lymphadenopathy showing squamous carcinoma pathology. Since laryngeal papillomas have a high propensity to transform into laryngeal squamous cell carcinoma, he was first evaluated for laryngeal carcinoma which was negative. Esophagoscopy showed a growth in the esophagus, the biopsy of which was positive for squamous malignant cells. Patient was then started on palliative chemotherapy with combination of paclitaxel and carboplatin, and at progression with weekly nanoxel with stable disease. This is a rare case of childhood laryngeal papillomatosis progressing to metastatic esophageal carcinoma. This case has been presented to highlight the fact that patients with laryngeal papillomas are not only at high risk of progressing to laryngeal carcinoma but can also have other malignancies of the upper aerodigestive tract and lung. Most of them have been correlated to human papilloma virus (HPV), but in our patient HPV DNA was negative.

**KEYWORDS:**

Larynx, carcinoma esophagus, papillomatosis

PMID: 23878486 [PubMed] PMCID: PMC3715978

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[Otolaryngol Head Neck Surg.](#) 2013 Jul 12. [Epub ahead of print]

***Prevalence of Diabetes Mellitus and Its Impact on Disease Severity in Adult Recurrent Respiratory Papillomatosis.***

[Lee CJ](#), [Allen CT](#), [Merati AL](#).

**Source**

Department of Otolaryngology/Head and Neck Surgery, Shin-Kong Wu-Ho-Su Memorial Hospital, Taipei, Taiwan.

**Abstract**

**Objectives** Following human papilloma virus (HPV) infection, recurrent respiratory papillomatosis (RRP) develops secondary to dysfunction of innate and adaptive immune responses. Diabetes mellitus (DM) is a common medical disorder; these patients are considered to be relatively immunocompromised. It is hypothesized that comorbid DM occurs more frequently than expected in a cohort of adult RRP patients and that RRP patients with DM have more severe disease than those without DM. **Study Design** Retrospective cohort study. **Setting** Tertiary care laryngology practice, 5-year period. **Subjects and Methods** Adult-onset RRP patients from 2007 to 2012 at the University of Washington were reviewed. The gender, age of onset of RRP, number of interventions, pathology, presence or absence of DM, and calculated anatomic Derkay severity score were recorded. **Results** Eighty-four adult RRP patients were characterized; 64 male (76%) and 20 female (24%). Six of 84 patients (7.1%) had DM; this prevalence was not higher than an age-matched general population. The number of interventions required for disease control did not significantly differ ( $P = .13$ ) between adult RRP patients with DM (avg 2.6/yr, median 2.3/year) and those without DM (avg 1.9/yr, median 1.3/yr). There was no significant difference in anatomic Derkay score at the time of intervention ( $P = .26$ ) or presence of dysplasia in biopsy specimens ( $P = .49$ ) between RRP patients with and without DM. **Conclusions** In this large series of adult RRP patients, DM does not appear to have a higher prevalence than that seen in age-matched controls, nor do RRP patients with DM appear to have more severe disease.

**KEYWORDS:**

Derkey severity score, diabetes mellitus, recurrent respiratory papillomatosis

PMID: 23851281 [PubMed - as supplied by publisher]

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[J Matern Fetal Neonatal Med.](#) 2013 Jun 21. [Epub ahead of print]

***Risk factors of the vertical transmission of human papilloma virus in newborns from singleton pregnancy - preliminary report.***

[Skoczyński M](#), [Goździcka-Józefiak A](#), [Kwaśniewska A](#).

**Source**

Department of Obstetrics and Pathology of Pregnancy, Medical University of Lublin , Lublin , Poland and.

**Abstract**

**Abstract Objective:** The aim of this study was to analyze the relationship between the frequency of Human Papilloma Virus (HPV) isolation in pregnant women and their offspring, and to assess the risk of maternal-neonatal transmission. **Study design:** The study included vaginal/buccal smears of 135 pregnant women, as well as the buccal smears and the respiratory discharge samples from their neonates. The material was tested for the presence of HPV DNA by means of PCR. **Results:** Twenty-two HPV 11-positive cases (16.3%) were detected amongst pregnant women, along with 16 neonatal HPV 11-positive cases (11.85%). The concordance rate of maternal and neonatal HPV 11 DNA was 54.5%. **Three maternal variables:** the presence of HPV 11, less than 10 years of education, and common law proved significant risk factors for vertical transmission. **Conclusion:** Asymptomatic HPV infection of a pregnant woman rather than the mode of delivery or other obstetrical characteristics constitutes significant risk factor of vertical transmission.

PMID: 23697795 [PubMed - as supplied by publisher]

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[Hum Immunol.](#) 2013 Aug;74(8):961-4. doi: 10.1016/j.humimm.2013.04.020. Epub 2013 Apr 27.

***Associations of HLA-DRB1 and -DQB1 alleles with severe recurrent respiratory papillomatosis in Korean patients.***

[Song EY](#), [Shin S](#), [Park KU](#), [Park MH](#), [Sung MW](#), [Kim KH](#), [Kwon TK](#).

**Source**

Department of Laboratory Medicine, Seoul National University College of Medicine, Seoul, South Korea.

**Abstract**

Recurrent respiratory papillomatosis (RRP) is characterized by frequent recurrences of papilloma of the larynx with significant morbidity. It is caused by human papillomavirus (HPV) types 6 and 11. Some associations of HLA genes with RRP have been reported, mainly in Caucasians. We performed HLA class II (DRB1 and DQB1) genotyping using Dynal RELI™ HLA-DRB1 SSO kit and PCR-single strand conformation polymorphism on 22 Korean patients with severe RRP and 207 healthy controls. The gene frequencies of HLA-DRB1\*11:01 (18.2% vs 3.6%,  $p=0.0006$ ,  $pc=0.02$ , odds ratio [OR]=5.9) and DQB1\*03:01 (36.4% vs 14.5%,  $p=0.0009$ ,  $pc=0.01$ , OR=3.4) and the haplotype frequency of DRB1\*11:01-DQB1\*03:01 (15.9% vs 3.6%,  $p=0.003$ , OR=5.0) was higher in RRP patients than controls. DRB1\*11:01 and DRB1\*11:01-DQB1\*03:01 haplotype were strongly associated with disease susceptibility to severe RRP in Koreans.

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**KEYWORDS:**

HLA, HPV, OR, PCR, RRP, human leukocyte antigen, human papillomavirus, odds ratio, polymerase chain reaction, recurrent respiratory papillomatosis

PMID: 23628399 [PubMed - in process]

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[Clin Nucl Med](#). 2013 May;38(5):387-9. doi: 10.1097/RLU.0b013e3182868af9.

***Heterogeneous 18F-FDG uptake in recurrent respiratory papillomatosis.***

[Yu JP](#), [Barajas RF Jr](#), [Olorunsola D](#), [Sugrue LP](#), [Hernandez-Pampaloni M](#).

**Source**

Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, California 94143-0269, USA. [jp.yu@ucsf.edu](mailto:jp.yu@ucsf.edu)

**Abstract**

Recurrent respiratory papillomatosis (RRP) describes an infection of the upper aerodigestive tract by the human papilloma virus most commonly

affecting the larynx with rare lung involvement in 1%-2% of affected patients. We describe an unusual case of a 28-year-old male patient with a longstanding history of RRP where a whole-body PET/CT obtained for disease staging revealed multiple cavitary pulmonary nodules in addition to the more typical tracheobronchial papillomas. In the case described herein, we report heterogeneous uptake of 18F-FDG among these RRP lesions, suggesting significant unexpected variability in the underlying metabolic behavior of these lesions.

PMID: 23486321 [PubMed - in process]

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[Med J Islam Repub Iran](#). 2012 May;26(2):90-3.

*The role of Human papilloma virus (HPV) genotyping in recurrent respiratory papillomatosis in Rasoul Akram Hospital.*

[Izadi F](#), [Hamkar R](#), [Ghanbari H](#), [Abdolmotallebi F](#), [Jahandideh H](#).

**Source**

MD, Associated professor of Otolaryngology-Head and Neck Surgery, Department of Otolaryngology, ENT.HNS research center, Tehran University of Medical Sciences, Tehran, Iran.  
izadimd@yahoo.com.

**Abstract**

**BACKGROUND:**

The most common laryngeal mass in children is recurrent respiratory papillomatosis (RRP). Studies have attempted to correlate viral typing and its aggressiveness.

**METHOD:**

29 patients with histologically confirmed RRP enrolled in adjuvant therapies. Patients underwent several surgical interventions.

**RESULTS:**

HPV genotyping demonstrated 45% HPV-6 and 55% HPV-11. The mean age at the first surgical intervention was 52.39 months (SD=102.28) (range from 4 months to 426 months). The mean number of surgical intervention was 10.39 (SD=7.76) (range from 2 to 30). The mean time of surgical intervals was 4.63 months (SD=4.02) (range from 2 to 24 months). In fourteen patients (48%) tracheotomy was done. All patients who had tracheotomy received alpha-

interferon. One of our cases was a male who had pulmonary extension with HPV-6.

**CONCLUSION:**

A review of patients with RRP was regarding to HPV genotyping and need for adjuvant therapy and tracheostomy. Mean number of surgical procedure was 10/40 and nearly fourteen patients (48%) need to tracheotomy. The clinical differences between HPV6 and HPV11 disease may not be accurately predictable. Patients with less age and with HPV-11 seemed to have more severe problems, but these differences were not statistically significant which needs much more investigations for reasonable starting point of evaluation for these differences.

**KEYWORDS:**

Human papillomavirus, Laryngeal neoplasms, Papillomatosis, Respiratory tract diseases

PMID: 23483670 [PubMed] PMID: PMC3587898

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[PLoS One](#). 2013;8(2):e57207. doi: 10.1371/journal.pone.0057207. Epub 2013 Feb 20.

***Integration of HPV6 and downregulation of AKR1C3 expression mark malignant transformation in a patient with juvenile-onset laryngeal papillomatosis.***

[Huebbers CU](#), [Preuss SF](#), [Kolligs J](#), [Vent J](#), [Stenner M](#), [Wieland U](#), [Silling S](#), [Drebber U](#), [Speel EJ](#), [Klussmann JP](#).

**Source**

Jean-Uhrmacher-Institute for Otorhinolaryngological Research, University of Cologne, Cologne, Germany. christian.huebbers@uni-koeln.de

**Abstract**

Juvenile-onset recurrent respiratory papillomatosis (RRP) is associated with low risk human papillomavirus (HPV) types 6 and 11. Malignant transformation has been reported solely for HPV11-associated RRP in 2-4% of all RRP-cases, but not for HPV6. The molecular mechanisms in the carcinogenesis of low risk HPV-associated cancers are to date unknown. We report of a female patient, who presented with a laryngeal carcinoma at the age of 24 years. She had a history of juvenile-onset RRP with an onset at the age of three and subsequently several hundred surgical interventions due to multiple recurrences of RRP. Polymerase chain reaction (PCR) or bead-

based hybridization followed by direct sequencing identified HPV6 in tissue sections of previous papilloma and the carcinoma. P16(INK4A), p53 and pRb immunostainings were negative in all lesions. HPV6 specific fluorescence in situ hybridization (FISH) revealed nuclear staining suggesting episomal virus in the papilloma and a single integration site in the carcinoma. Integration-specific amplification of papillomavirus oncogene transcripts PCR (APOT-PCR) showed integration in the aldoketoreductase 1C3 gene (AKR1C3) on chromosome 10p15.1. ArrayCGH detected loss of the other gene copy as part of a deletion at 10p14-p15.2. Western blot analysis and immunohistochemistry of the protein AKR1C3 showed a marked reduction of its expression in the carcinoma. In conclusion, we identified a novel molecular mechanism underlying a first case of HPV6-associated laryngeal carcinoma in juvenile-onset RRP, i.e. that HPV6 integration in the AKR1C3 gene resulted in loss of its expression. Alterations of AKR1C gene expression have previously been implicated in the tumorigenesis of other (HPV-related) malignancies.

PMID: 23437342 [PubMed - indexed for MEDLINE] PMID: PMC3577740

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[Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi](#). 2012 Dec;47(12):974-7.

*[Detection of human papillomavirus in the upper respiratory tract in children without recurrent respiratory papillomatosis].*

[Article in Chinese]

[Sun YF](#), [Wu YD](#), [Wu L](#), [Jiang JJ](#), [Gao R](#), [Xu B](#), [Chen XW](#), [Zhao ZY](#).

### Source

Department of Otorhinolaryngology Head and Neck Surgery, The Children Hospital, Zhejiang University School of Medicine, Key Laboratory of Reproductive Genetics (Zhejiang University), Ministry of Education, Zhejiang Key Laboratory for Diagnosis and Therapy of Neonatal Diseases, Hangzhou 310003, China.

### Abstract

#### **OBJECTIVE:**

The purpose of this prospective study was to investigate the presence of human papillomavirus (HPV) in tonsillectomy and adenoidectomy specimens from pediatric patients without juvenile-onset recurrent respiratory papillomatosis (JORRP), so as to understand the effect of HPV infection in the upper respiratory tract in children.

**METHODS:**

Two hundred and forty-one pediatric patients without known JORRP or other HPV-related diseases undergoing tonsillectomy and/or adenoidectomy for hypertrophy or chronic tonsillitis were enrolled in this prospective study. One hundred and seventy-seven fresh samples of tonsillar tissues and 195 samples of adenoid tissues were collected and then examined for the presence of HPV DNA with the polymerase chain reaction (PCR) technique and typing. Laryngeal papilloma specimens from 17 patients obtained during routine debulking procedures were also analyzed and served as positive controls.

**RESULTS:**

All 17 papilloma specimens were positive for HPV DNA and the type was 6 or 11. This result confirmed that the methods used were valid for detecting HPV infection. HPV DNA was detected in 2 of the 177 tonsillar specimens and zero of the 195 adenoid specimens. The two positive samples were confirmed with typing. One was positive for HPV6 and the other for HPV11. Review of the medical records of these two cases confirmed that there were no history of HPV-related diseases. Histologic analysis of their specimens showed lymphoid hyperplasia, no specific changes suggesting HPV infection and no signs of malignancy. The HPV infection rate in upper respiratory tract was 0.8% (2/241).

**CONCLUSION:**

There is HPV infection in upper respiratory tract in Chinese children without JORRP, but maybe is not sufficient for the formation of JORRP.

PMID: 23328034 [PubMed - in process]

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[Cochrane Database Syst Rev.](#) 2012 Dec 12;12:CD005053. doi: 10.1002/14651858.CD005053.pub4.

***Adjuvant antiviral therapy for recurrent respiratory papillomatosis.***

[Chadha NK, James A.](#)

**Source**

Division of Pediatric Otolaryngology - Head and Neck Surgery, University of British Columbia, Vancouver, Canada. nchadha@cw.bc.ca.

## **Abstract**

### **BACKGROUND:**

This is an update of a Cochrane Review originally published in Issue 4, 2005 of The Cochrane Library and previously updated in 2010. Recurrent respiratory papillomatosis is a condition characterised by benign papillomatous (wart-like) growths in the upper airway. It can affect both adults and children causing airway obstruction and voice change. Treatment usually involves repeated surgical debulking of the papillomata. Several agents have been proposed as adjuvants to surgical debulking, including antivirals, administered systemically or injected into the lesions.

### **OBJECTIVES:**

To assess the effectiveness of antiviral agents as adjuvant therapy in the management of recurrent respiratory papillomatosis in children and adults.

### **SEARCH METHODS:**

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the most recent search was 24 February 2012.

### **SELECTION CRITERIA:**

Randomised controlled trials.

### **DATA COLLECTION AND ANALYSIS:**

We identified 143 references from the searches. Forty-three were appropriate for retrieval and assessed for eligibility by the authors. One randomised controlled trial met the inclusion criteria, involving 19 participants. We contacted the authors to obtain additional data to facilitate the review.

### **MAIN RESULTS:**

The included study was a single-institution, randomised, double-blind, placebo-controlled trial of intralesional cidofovir administered at the time of surgical debulking. Adults (n = 15) and children (n = 4) were included. We judged the study to have a reasonably low risk of bias. After a 12-month trial period, no difference was found between the cidofovir and placebo groups. Both groups showed a significant reduction in disease extent (as assessed at the time of surgery using the Derkey Scoring System), but no significant change in health-related quality of life.

**AUTHORS' CONCLUSIONS:**

There is insufficient evidence to support the efficacy of antiviral agents as adjuvant therapy in the management of recurrent respiratory papillomatosis in children or adults. The included randomised controlled trial showed no advantage of intralesional cidofovir over placebo at 12 months. The study was limited by a small sample size and a change in the cidofovir concentration midway through the trial, from 0.3 mg/ml in children and 0.75 mg/ml in adults, to 5 mg/ml in both adults and children. An adequately powered randomised controlled trial of intra-lesional cidofovir, consistently using higher concentrations of cidofovir in comparison with injected placebo, would be required to determine effectiveness convincingly. Future studies must include health-related quality of life and symptom-based outcome measures.

**Update of**

[Cochrane Database Syst Rev. 2010;\(1\):CD005053.](#)

PMID: 23235619 [PubMed - indexed for MEDLINE]

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[J Infect Dis.](#) 2013 Feb 15;207(4):583-7. doi: 10.1093/infdis/jis733. Epub 2012 Nov 29.

*Identical human papillomavirus (HPV) genomic variants persist in recurrent respiratory papillomatosis for up to 22 years.*

[Kocjan BJ](#), [Gale N](#), [Hočevar Boltežar I](#), [Seme K](#), [Fujs Komloš K](#), [Hošnjak L](#), [Maver PJ](#), [Jelen MM](#), [Zupanič Pajnič I](#), [Balažic J](#), [Poljak M](#).

**Source**

Institute of Microbiology and Immunology, University of Ljubljana, Ljubljana, Slovenia.

**Abstract**

Seventy initial and 125 follow-up tissue specimens of laryngeal papillomas, obtained from 70 patients who had had recurrent respiratory papillomatosis for from 1-22 years, were investigated for the presence of human papillomavirus (HPV) DNA and HPV E5a, LCR and/or full-length genomic variants. HPV-6 was found in 130/195, HPV-11 in 63/195, and HPV-6/HPV-11 in 2/195 samples. Within 67/70 (95.7%) patients, all follow-up HPV isolates genetically matched completely initial HPV isolate over the highly variable parts of the genome or over the entire genome. Frequent recurrence of

laryngeal papillomas is a consequence of long-term persistence of the identical initial HPV genomic variant.

PMID: 23204170 [PubMed - indexed for MEDLINE]

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[PLoS One](#). 2012;7(11):e49699. doi: 10.1371/journal.pone.0049699. Epub 2012 Nov 21.

### *Economic burden of human papillomavirus-related diseases in Italy.*

[Baio G](#), [Capone A](#), [Marcellusi A](#), [Mennini FS](#), [Favato G](#).

#### **Source**

Department of Statistical Science, University College London, London, United Kingdom.

#### **Abstract**

##### **INTRODUCTION:**

Human papilloma virus (HPV) genotypes 6, 11, 16, and 18 impose a substantial burden of direct costs on the Italian National Health Service that has never been quantified fully. The main objective of the present study was to address this gap: (1) by estimating the total direct medical costs associated with nine major HPV-related diseases, namely invasive cervical cancer, cervical dysplasia, cancer of the vulva, vagina, anus, penis, and head and neck, anogenital warts, and recurrent respiratory papillomatosis, and (2) by providing an aggregate measure of the total economic burden attributable to HPV 6, 11, 16, and 18 infection.

##### **METHODS:**

For each of the nine conditions, we used available Italian secondary data to estimate the lifetime cost per case, the number of incident cases of each disease, the total economic burden, and the relative prevalence of HPV types 6, 11, 16, and 18, in order to estimate the aggregate fraction of the total economic burden attributable to HPV infection.

##### **RESULTS:**

The total direct costs (expressed in 2011 Euro) associated with the annual incident cases of the nine HPV-related conditions included in the analysis were estimated to be €528.6 million, with a plausible range of €480.1-686.2 million. The fraction attributable to HPV 6, 11, 16, and 18 was €291.0 (range €274.5-315.7 million), accounting for approximately 55% of the total annual burden of HPV-related disease in Italy.

**CONCLUSIONS:**

The results provided a plausible estimate of the significant economic burden imposed by the most prevalent HPV-related diseases on the Italian welfare system. The fraction of the total direct lifetime costs attributable to HPV 6, 11, 16, and 18 infections, and the economic burden of noncervical HPV-related diseases carried by men, were found to be cost drivers relevant to the making of informed decisions about future investments in programmes of HPV prevention.

PMID: 23185412 [PubMed - indexed for MEDLINE] PMCID: PMC3504125

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[World J Surg.](#) 2013 Feb;37(2):339-43. doi: 10.1007/s00268-012-1839-y.

***Experience with recurrent respiratory papillomatosis in a developing country: impact of tracheostomy.***

[Orji FT](#), [Okorafor IA](#), [Akpeh JO](#).

**Source**

Department of Otolaryngology, University of Nigeria Teaching Hospital, Enugu, Nigeria.  
tochiorji@yahoo.com

**Abstract****BACKGROUND:**

The frequent relapses of recurrent respiratory papillomatosis (RRP) sometimes demand repeated surgical excision with tracheostomy. This situation plays a vital role in the management of RRP in developing countries such as ours because of late presentation. This study was conducted to evaluate our experience with RRP and to determine the incidence and impact of tracheostomy in the overall management and outcomes of our patients.

**METHODS:**

The records of 59 patients with histologically confirmed RRP treated between 1994 and 2008 at our tertiary institution were reviewed. We collected data such as age at onset, tracheostomy frequency and duration, number of required surgical excisions, papilloma spread to the lower airways. Patients' characteristics and the course of the disease were compared between a juvenile-onset papillomatosis (JoRRP) group and an adult-onset group (AdRRP).

**RESULTS:**

Overall, 68 % of our patients were in the JoRRP group (ages 2-11 years, mean 6 years). The other 32 % were 22-58 years of age (AdRRP group). Two cases of JoRRP continued into adult life. Multiple RRP dominated in the JoRRP group (93 %), whereas solitary papillomas predominated in the AdRRP group (63 %). Tracheostomy was performed because of upper airway obstruction in 42 % of our patients, with children accounting for 72 %. The mean duration of tracheostomy was 3.5 months, with 80 % lasting <4 months. Significantly more JoRRP patients had severe upper airway obstruction, required tracheostomy, and underwent multiple surgical excisions ( $p = 0.04$ ,  $0.02$ , and  $0.009$ , respectively). Tracheobronchial spread occurred in a patient with prolonged tracheostomy.

**CONCLUSIONS:**

Multiple laryngeal papillomatosis clearly followed a more severe and less predictable course than the solitary type in both groups. Although there was a high incidence of tracheostomy in this study, short-duration tracheostomies accounted for the low incidence of extralaryngeal spread.

PMID: 23135424 [PubMed - indexed for MEDLINE]

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[Otolaryngol Head Neck Surg.](#) 2013 Feb;148(2):253-60. doi: 10.1177/0194599812466226. Epub 2012 Nov 2.

***Adult recurrent respirator papillomatosis: a new therapeutic approach with pegylated interferon alpha 2a (Peg-IFN $\alpha$ -2a) and GM-CSF.***

[Suter-Montano T](#), [Montaño E](#), [Martínez C](#), [Plascencia T](#), [Sepulveda MT](#), [Rodríguez M](#).

**Source**

Medical Practice of Dr R. Engler ENT (Buchs SG), Daenikon-Zürich, Switzerland.  
teresumo@bluewin.ch

**Abstract****OBJECTIVE:**

To determine a new therapeutic approach using granulocyte monocyte-colony-stimulating factor (GM-CSF) and pegylated interferon alpha 2a (Peg-IFN $\alpha$ -2a) as adjuvant therapy in patients with adult recurrent respiratory papillomatosis.

**STUDY DESIGN:**

Descriptive observational clinical trial.

**SETTING:**

Departments of Otolaryngology and Immunology.

**METHODS:**

Fourteen patients with adult recurrent respiratory papillomatosis were examined regarding medical history and number of operations before and after treatment. Voice disorder and glottal stop were evaluated using the Voice-Related Quality-of-Life instrument. Papilloma staging was determined using the Coltera/Derkay diagram. The patients received Peg-IFN $\alpha$ -2a at 180 mcg weekly for 6 months. In the third month, the patients began GM-CSF treatment at 400 mcg weekly for 2 months. The patients were observed for 12 months after treatment ended.

**RESULTS:**

Eleven patients met the study criteria; 3 patients had tracheotomies before treatment, and they were decannulated after treatment. Before treatment, the scale of voice quality ranged from 34 to 45 points (mean, 38.31). After treatment, the range was 12 to 35 points (mean, 21.09;  $P < .001$ ). Prior to therapy, the glottal stop ranged from 50% to 90% (average, 62.27%). After therapy, the range decreased to 0% to 15% (mean, 4.63%;  $P < .001$ ). The number of surgical interventions decreased. Two patients each had 1 surgical intervention after treatment began.

**CONCLUSION:**

A new adjuvant treatment based on immunogenetic mechanisms against human laryngeal papilloma virus, with expectations of reducing disease aggressiveness and the number of operations, avoids the risks of surgery.

**IMPLICATION FOR PRACTICE:**

Peg-IFN $\alpha$ -2a and GM-CSF is an adjuvant therapy for treating adult recurrent respiratory papillomatosis.

PMID: 23124924 [PubMed - indexed for MEDLINE]

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[B-ENT](#). 2012;8(3):197-202.

*Intralesional cidofovir in severe juvenile respiratory papillomatosis.*

[Ablanedo-Terrazas Y](#), [Soda-Merhy A](#), [Hernández-Palestina M](#), [Ormsby CE](#), [Reyes-Terán G](#).

**Source**

Centro de Investigación en Enfermedades Infecciosas, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico.

**Abstract**

Recurrent respiratory papillomatosis causes significant morbidity among affected children and usually requires frequent surgeries. We present a prospective case series including nine children at a Mexican tertiary referral center. All enrolled patients had severe disease that had required at least four surgical procedures, with a median of 6. Two children had tracheobronchial involvement, one had lung parenchymal disease, and one had a tracheostomy performed during his first surgery.

**OBJECTIVE:**

To assess the efficacy of intralesional cidofovir in lowering the surgery rate.

**STUDY DESIGN:**

Prospective case series.

**SETTING:**

Tertiary referral center in Mexico City.

**METHODS:**

Nine Mexican children with severe disease were enrolled. Intralesional cidofovir was applied after surgical debulking at a concentration of 5 mg/mL with a four to six week interval.

**RESULTS:**

Six of the nine patients had a notable decrease in the rate of surgeries, with three patients remaining disease-free with follow up ranging from 1.8 to 3.3 years. No patient demonstrated laboratory abnormalities. Two patients showed moderate and mild dysplasia on papilloma biopsy distinguished by a lack of epithelial maturation with no mitoses or cellular atypia. Two patients died several months after the last injection.

**CONCLUSIONS:**

Intralesional cidofovir appears to be effective in the treatment of recurrent respiratory papillomatosis, although further studies are required to determine its safety.

PMID: 23113383 [PubMed - indexed for MEDLINE]

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[Jpn J Clin Oncol.](#) 2013 Jan;43(1):78-82. doi: 10.1093/jjco/hys179. Epub 2012 Oct 30.

***Lung squamous cell carcinoma arising in a patient with adult-onset recurrent respiratory papillomatosis.***

[Hasegawa Y](#), [Sato N](#), [Niikawa H](#), [Kamata S](#), [Sannohe S](#), [Kurotaki H](#), [Sasaki T](#), [Ebina A](#).

**Source**

The Department of Respiratory Medicine, Aomori Prefectural Central Hospital, 2-1-1 Higashi Tsukurimichi, Aomori 030-8553, Japan. yukihiro\_hasegawa@med.pref.aomori.jp

**Abstract**

A 75-year-old male was admitted to our hospital in December 2011 with a mass in the right upper pulmonary lobe. He was incidentally diagnosed as having tracheal papillomas 10 years ago. Bronchoscopy revealed multiple polypoid papillomas in the dorsal lesion of the trachea. Polymerase chain reaction amplification detected human papillomavirus type 11 DNA in the papilloma tissues. A computed tomography scan demonstrated the occlusion of the right superior segment bronchus with distal consolidation. Furthermore, F-18 fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography showed intense tracer uptake in the right superior segment of the lung. He underwent a right upper lobectomy. The tumor was seen as a rounded nodule,  $\approx$  2 cm in diameter. Histological examination of the tumor revealed squamous papilloma with papillary and solid architecture surrounded by accumulation of acute inflammatory cells. Furthermore, in a part of the tumor, squamous cell carcinoma was also present. The lymph nodes were free of tumor. After the surgery, he continued to undergo endoscopic microwave resection. Recurrent respiratory papillomatosis is a rare disease that can cause life-threatening airway compromise and malignant transformation. The present case indicates that F-18 fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography is indispensable for early detection of lung cancer arising in a patient with recurrent respiratory papillomatosis.

PMID: 23110763 [PubMed - indexed for MEDLINE]

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[Eur Arch Otorhinolaryngol.](#) 2013 Feb;270(2):641-6. doi: 10.1007/s00405-012-2221-2. Epub 2012 Oct 16.

## ***Experience of 11 years use of cidofovir in recurrent respiratory papillomatosis.***

[Graupp M](#), [Gugatschka M](#), [Kiesler K](#), [Reckenzaun E](#), [Hammer G](#), [Friedrich G](#).

### **Source**

Department of Phoniatics, ENT University Clinic, Speech and Swallowing, Medical University Graz, Auenbruggerplatz 26-28, 8036 Graz, Austria. matthias.graupp@gmx.at

### **Abstract**

Recurrent respiratory papillomatosis (RRP) is a viral induced disease, associated with exophytic epithelial lesions affecting the upper airways. Problem of treatment is the high recurrence of papilloma growth after surgical removal; therefore adjuvant therapy schemes have been established. Cidofovir was one of the agents used off-label in adjuvant therapy in the last years. However, there is ongoing discussion about the effectiveness and possible side effects. Aim of our study was to share our experience in treatment of RRP with cidofovir during the last 11 years. We analyzed all the data of patients treated for RRP at the Department for Phoniatics of the Medical University of Graz between 1999 and 2011. 25 out of the 34 treated patients are at the moment under complete remission, in six patients partial remission could be achieved and two patients showed poor response to therapy, therefore the treatment with cidofovir was stopped. 21 patients received one cycle of monthly cidofovir, 11 patients received two and one patient three cycles of therapy. Number of procedures reached from one to six during each cycle. Average cumulative dose of one cycle was 79.7 mg (15-277.5 mg), in one patient 435 mg were used. One patient developed temporary, borderline neutropenia without symptoms. Despite the retrospective approach of this study with the limitation of several incomplete records, our results show promising long-term effects of adjuvant use of cidofovir. During this period, we did not observe any relevant side effects.

### **Comment in**

- [Use of cidofovir in recurrent respiratory papillomatosis.](#) [Eur Arch Otorhinolaryngol. 2013]

PMID: 23070260 [PubMed - indexed for MEDLINE]

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[Mol Med.](#) 2012 Dec 6;18:1338-45. doi: 10.2119/molmed.2012.00284.

*T(H)2-like chemokine patterns correlate with disease severity in patients with recurrent respiratory papillomatosis.*

[Rosenthal DW](#), [DeVoti JA](#), [Steinberg BM](#), [Abramson AL](#), [Bonagura VR](#).

**Source**

Elmezzi Graduate School of Molecular Medicine, Manhasset, New York, USA.

**Abstract**

Recurrent respiratory papillomatosis (RRP), characterized by the recurrent growth of benign tumors of the respiratory tract, is caused by infection with human papillomavirus (HPV), predominantly types 6 and 11. Surgical removal of these lesions can be required as frequently as every 3 to 4 wks to maintain a patent airway. There is no approved medical treatment for this disease. In this study, we have characterized the T(H)2-like chemokine profile (CCL17, CCL18, CCL20, CCL22) in patients with RRP and asked whether it was modulated in patients who had achieved significant clinical improvement. CCL17, CCL18 and CCL22 messenger RNAs (mRNAs) were increased in papillomas compared with clinically normal laryngeal epithelium of the RRP patients. Overall, CCL20 mRNA expression was not increased, but there was intense, selective CCL20 protein expression in the basal layer of the papillomas. Patients with RRP expressed more CCL17 ( $p = 0.003$ ), CCL18 ( $p = 0.0003$ ), and CCL22 ( $p = 0.007$ ) in their plasma than controls. Plasma CCL18 decreased over time in three patients enrolled in a pilot clinical trial of celecoxib, and the decrease occurred in conjunction with clinical improvement. There was a significant correlation between sustained clinical remission in additional patients with RRP and reduced levels of CCL17 ( $p = 0.01$ ), CCL22 ( $p = 0.002$ ) and CCL18 ( $p = 0.05$ ). Thus, the change in expression of these three plasma T(H)2-like chemokines may, with future studies, prove to serve as a useful biomarker for predicting disease prognosis.

PMID: 23019074 [PubMed - indexed for MEDLINE] PMCID: PMC3521785

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[Ann Otol Rhinol Laryngol.](#) 2012 Sep;121(9):587-93.

## ***Safety and dosing of bevacizumab (avastin) for the treatment of recurrent respiratory papillomatosis.***

[Best SR](#), [Friedman AD](#), [Landau-Zemer T](#), [Barbu AM](#), [Burns JA](#), [Freeman MW](#), [Halvorsen YD](#), [Hillman RE](#), [Zeitels SM](#).

### **Source**

Department of Surgery, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, USA.

### **Abstract**

#### **OBJECTIVES:**

Increasing evidence supports the use of laryngeal injections of the antiangiogenic agent bevacizumab (Avastin) for the adjuvant treatment of recurrent respiratory papillomatosis (RRP). A recent prospective open-label investigation, approved by the US Food and Drug Administration, employing 12.5 mg of sublesional bevacizumab demonstrated single-site efficacy without complications; however, the safety of multiple-site injections and higher dosing has not yet been reported. The primary objective of this study was to report on the safety of increased doses of bevacizumab for the treatment of RRP.

#### **METHODS:**

Two cohorts of adult patients were evaluated. In the first group, a prospective analysis was performed on patients with a diagnosis of laryngeal RRP after their participation in the initial clinical trial with a single-site lowerdose (7.5 to 12.5 mg). They received higher doses of sublesional laryngeal bevacizumab (15 to 50 mg total) with detailed physiologic, hematologic, and serum chemistry measurements performed before and after each bevacizumab injection. A second cohort of patients received sublesional laryngeal injections of bevacizumab (15 to 88 mg total) without physiologic measurements and underwent a retrospective analysis of reported complications.

#### **RESULTS:**

One hundred consecutive laryngeal injection sessions (office, 87; operating room, 13) with bevacizumab were performed in 43 patients, with a mean dose of 30 mg total per treatment (range, 15 to 88 mg). Sixty-three of the 100 sessions were accompanied by KTP laser photoangiolytic of the papilloma prior to bevacizumab injections. Eighteen patients (cohort 1) underwent detailed physiologic assessment, and no dysfunction was observed. There were no local or systemic complications of bevacizumab administration. The

second group of 25 patients (cohort 2) also reported no significant local or systemic complications. Neither patient group was observed to have a local wound problem in the larynx.

### **CONCLUSIONS:**

This investigation provides evidence that higher doses of bevacizumab are relatively safe in adult patients with laryngeal RRP. Further refinements in pharmacologic concentration and drug delivery will determine the optimal treatment regimens in the future.

PMID: 23012897 [PubMed - indexed for MEDLINE]

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[Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi](#). 2012 Jun;47(6):454-7.

### ***[Peri-operative management on juvenile recurrent respiratory papillomatosis].***

[Article in Chinese]

[Nan BY](#), [Chen BB](#), [Zhang CQ](#).

### **Source**

Department of Otorhinolaryngology, Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical College, China.

### **Abstract**

#### **OBJECTIVE:**

To investigate the safety of peri-operative management on children with juvenile recurrent respiratory papilloma (JORRP).

#### **METHODS:**

A retrospective analysis was conducted on preoperative assessment, anesthesia methods and options, operative procedure, and postoperative airway maintenance in 28 JORRP children aged from ten months to seven years old. A total of 148 times of surgery was performed on these 28 children.

#### **RESULTS:**

One hundred and nine JORRP children graded one and two-degree dyspnea underwent surgery within 24 hours and were intubated successfully in the first attempt after intravenous induction. Thirty-nine emergency operations were performed in the children graded three and four-degree dyspnea, 35 of them were intubated successfully in the first attempt after inhalation induction and 4 succeeded in the second attempt. No complications occurred in 129 JORRP

children postoperatively, 17 children suffered from mild dyspnea and relieved after oxygen inhalation, 2 children were intubated and sent to intensive care unit because of postoperative hypoxemia. All JORRP children got through the peri-operative period safely. The quality of pronunciation in 101 children improved markedly and 35 suffered from slight hoarseness on the 1st postoperative day. Three children had the tracheal tube of tracheostomy removed after receiving five, four and three operations respectively. Nineteen children were followed up for 2 - 5 years. Among them, one child did not relapse 3 years after surgical management. One child suffered from laryngostenosis postoperatively. No death occurred.

**CONCLUSION:**

Complete preoperative preparation, rational anesthesia methods, careful operative procedure and airway maintenance after surgery could increase the safety for children with recurrent respiratory papilloma.

PMID: 22932135 [PubMed - indexed for MEDLINE]

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[Laryngoscope](#). 2012 Dec;122(12):2844-9. doi: 10.1002/lary.23534. Epub 2012 Jul 30.

***Juvenile recurrent respiratory papilloma: variable intersurgical intervals.***

[Ongkasuwan J](#), [Friedman EM](#).

**Source**

Department of Otolaryngology-Head and Neck Surgery, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, USA. [julinao@bcm.edu](mailto:julinao@bcm.edu)

**Abstract****OBJECTIVES/HYPOTHESIS:**

To analyze the patterns of surgical frequency in pediatric patients undergoing surgery with CO(2) laser ablation for juvenile onset recurrent respiratory papillomatosis (JORRP). The hypothesis is that over time there is a high variability in surgical frequency independent of the use of an adjuvant therapy.

**STUDY DESIGN:**

Retrospective case review.

**METHODS:**

All pediatric patients treated surgically with the CO(2) laser for JORRP by two senior surgeons at a tertiary pediatric hospital over an 11-year period were evaluated. Regression analysis was performed. An online survey was conducted of the American Academy of Pediatric Otolaryngology membership on their practice patterns regarding JORRP.

**RESULTS:**

Twenty-nine patients were identified, and of those, 20 were included in regression analysis. Several distinct patterns were noted. Only five of the 20 patients (25%) had a constant rate of procedures throughout the observation period. Three (15%) of the patients had continual decrease and one (5%) of the patients had a continual increase in the surgical rate throughout the study period. Eleven (55%) had a fluctuation in the pattern of their recurrences. When queried on how they approach when to repeat intervention for JORRP patients, more than 16 responses were given, and the most common determinants included standard set interval, previous operative findings, and previous interval.

**CONCLUSIONS:**

The natural fluctuation in intersurgical intervals without the use of any adjuvant therapy confounds the use of intersurgical interval as an outcome measure for the success of adjuvant therapy. Accelerations and decelerations were noted but cannot be explained.

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PMID: 22847877 [PubMed - indexed for MEDLINE]

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[Pediatrics](#). 2012 Aug;130(2):e249-56. doi: 10.1542/peds.2011-3587. Epub 2012 Jul 9.

***Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction.***

[Kahn JA](#), [Brown DR](#), [Ding L](#), [Widdice LE](#), [Shew ML](#), [Glynn S](#), [Bernstein DI](#).

**Source**

Division of Adolescent Medicine, MLC 4000, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229, USA. [jessica.kahn@cchmc.org](mailto:jessica.kahn@cchmc.org)

**Abstract****OBJECTIVES:**

The aims of this study were to compare prevalence rates of human papillomavirus (HPV) in young women before and after HPV vaccine introduction to determine the following: (1) whether vaccine-type HPV infection decreased, (2) whether there was evidence of herd protection, and (3) whether there was evidence for type-replacement (increased prevalence of nonvaccine-type HPV).

**METHODS:**

Young women 13 to 26 years of age who had had sexual contact were recruited from 2 primary care clinics in 2006-2007 for a prevaccination surveillance study (N = 368, none were vaccinated) and 2009-2010 for a postvaccination surveillance study (N = 409, 59% were vaccinated). Participants completed a questionnaire and were tested for cervicovaginal HPV DNA. HPV prevalence rates were compared in the pre- versus postsurveillance studies by using  $\chi^2$  tests. Propensity score weighting was used to balance differences in covariates between the 2 surveillance studies.

**RESULTS:**

The mean age was ~19 years for both groups of participants and most were African American and non-Hispanic. After propensity score weighting, the prevalence rate for vaccine-type HPV decreased substantially (31.7%-13.4%,  $P < .0001$ ). The decrease in vaccine-type HPV not only occurred among vaccinated (31.8%-9.9%,  $P < .0001$ ) but also among unvaccinated (30.2%-15.4%,  $P < .0001$ ) postsurveillance study participants. Nonvaccine-type HPV increased (60.7%-75.9%,  $P < .0001$ ) for vaccinated postsurveillance study participants.

**CONCLUSIONS:**

Four years after licensing of the quadrivalent HPV vaccine, there was a substantial decrease in vaccine-type HPV prevalence and evidence of herd protection in this community. The increase in nonvaccine-type HPV in vaccinated participants should be interpreted with caution but warrants further study.

PMID: 22778297 [PubMed - indexed for MEDLINE] PMCID: PMC3408690

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[Ear Nose Throat J.](#) 2012 May;91(5):E21-2.

### *Laryngeal papilloma.*

[DeFatta RA](#), [Sataloff JB](#), [Klaris GE](#), [Sataloff RT](#).

No abstract available.

#### **Source**

Department of Otolaryngology-Head and Neck Surgery, Drexel University College of Medicine, Philadelphia, USA.

PMID: 22614564 [PubMed - indexed for MEDLINE]

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[Ghana Med J.](#) 2012 Mar;46(1):43-5.

### *Recurrent respiratory papillomatosis: the Korle-Bu experience.*

[Baidoo KK](#), [Kitcher E](#).

#### **Source**

E.N.T Unit, Korle-Bu Teaching Hospital, P.O. Box 77, Korle Bu, Accra. dr3kbaidoo@yahoo.com

#### **Abstract**

##### **BACKGROUND:**

Recurrent respiratory papillomatosis is a benign disease of the aero digestive tract which is caused by the human papilloma virus type 6 and 11 and mainly affects children.

##### **OBJECTIVE:**

The aim of this study is to describe the pattern of recurrent respiratory papillomatosis at the E.N.T Unit Korle Bu Teaching Hospital, Accra.

##### **METHOD:**

This is a retrospective study of theatre records of patients managed for respiratory papillomata from January 1995 to December 2004 at the E.N.T Unit of Korle Bu Teaching Hospital, Accra which is a tertiary facility. These records were studied and we obtained information on gender, age, number of surgeries and the presence of tracheotomy.

##### **RESULTS:**

Sixty-nine patients were identified over the period. Thirty-three males and 36 females with a M:F ratio 1:1.1, and ages ranging from 2 to 54 years. The mean age was 12.3 years and a median age of 8.5 years. Children less than

10 years accounted for 69% and 46.4% had repeated surgery with overall tracheotomy rate of 14.5%.

**CONCLUSIONS:**

Recurrent Respiratory Papillomatosis is primarily a paediatric disease. Locally, its distribution is comparable to others in the sub region and worldwide and surgery is the mainstay of treatment.

**KEYWORDS:**

ENT, Paediatrics, Recurrent respiratory papillomatosis, Tracheotomy

PMID: 22605888 [PubMed - indexed for MEDLINE] PMCID: PMC3353504

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[Otolaryngol Head Neck Surg.](#) 2012 Sep;147(3):522-4. doi: 10.1177/0194599812448162. Epub 2012 May 17.

***Surgical treatment of laryngeal papillomatosis using narrow band imaging.***

[Imaizumi M](#), [Okano W](#), [Tada Y](#), [Omori K](#).

**Source**

Department of Otolaryngology, School of Medicine, Fukushima Medical University, Fukushima City, Japan.

**Abstract**

Laryngeal papillomatosis has a high rate of recurrence after surgery. Narrow band imaging (NBI) is a novel optical enhancement technology used for the diagnosis. This is the first report to date to indicate the availability of the combination of laryngomicro surgery and videoendoscopic surgery for laryngeal papillomatosis using NBI technology. The patients were a 34-year-old man and a 30-year-old man. Both patients underwent surgery in another hospital. However, due to recurrence, they were subsequently referred to the authors' department for further evaluation. The presence of papillomas was confirmed by NBI, and the papillomas were removed using an XPS Micro Debrider and a CO2 laser. Using the NBI system, the border between the normal mucosa and the papillomas could be clearly identified, allowing precise resection. Further treatment on the lesions has been carried out several times to date using NBI. The lesions have now been eradicated without further recurrence.

PMID: 22597574 [PubMed - indexed for MEDLINE]

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[Eur Arch Otorhinolaryngol.](#) 2012 Nov;269(11):2367-71. doi: 10.1007/s00405-012-2049-9. Epub 2012 May 16.

*Transmission of human papillomavirus DNA from patient to surgical masks, gloves and oral mucosa of medical personnel during treatment of laryngeal papillomas and genital warts.*

[Ilmarinen T](#), [Auvinen E](#), [Hiltunen-Back E](#), [Ranki A](#), [Aaltonen LM](#), [Pitkäranta A](#).

**Source**

Department of Otorhinolaryngology, Head and Neck Surgery, Helsinki University Hospital, P.O. Box 220, 00029, Helsinki, Finland. taru.ilmarinen@helsinki.fi

**Abstract**

The risk of occupational human papillomavirus (HPV) transmission from patient to medical personnel during laser vaporization procedures remains controversial. The purpose of this study was to determine the risk of HPV transmission from the patient to the protective surgical masks, gloves and oral mucosa of medical personnel during the treatment of laryngeal papillomas and genital warts. The study involved five male patients scheduled for the surgical treatment of laryngeal papillomas, and five male patients undergoing carbon dioxide (CO<sub>2</sub>) laser treatment for urethral warts. Oral mucosa specimens were obtained from the study patients and the employees pre- and postoperatively. Samples were collected from the HPV-infected patient tissue, and from the surgical masks and gloves used by the employees. A total of 120 samples were analyzed for the presence of HPV DNA by PCR, using the degenerated MY09/11/HMB01 primers. After the papilloma procedures, the surgeons' gloves tested HPV positive in one of the five cases and those of the surgical nurse in three of the five cases. After the treatment of genital warts, HPV DNA corresponding to the patient tissue specimens was present in all the samples obtained from the surgical gloves of the operators. All oral mucosa samples obtained from 18 different employees tested HPV negative, as did the surgical mask specimens. According to our study, HPV may contaminate protective equipment, most of all surgical gloves, but transmission of HPV DNA to medical personnel is unlikely to occur provided that protective surgical gloves and masks are applied and disposed of properly.

PMID: 22588197 [PubMed - indexed for MEDLINE]

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[Otolaryngol Clin North Am.](#) 2012 Jun;45(3):671-94, viii-ix. doi: 10.1016/j.otc.2012.03.006.

### ***Recurrent respiratory papillomatosis.***

[Venkatesan NN](#), [Pine HS](#), [Underbrink MP](#).

#### **Source**

Department of Otolaryngology, University of Texas Medical Branch, 7.104 John Sealy Annex, 301 University Boulevard, Galveston, TX 77555-0521, USA.

#### **Abstract**

Recurrent respiratory papillomatosis (RRP) is a rare, benign disease with no known cure. RRP is caused by infection of the upper aerodigestive tract with the human papillomavirus (HPV). Passage through the birth canal is thought to be the initial transmission event, but infection may occur in utero. HPV vaccines have helped to provide protection from cervical cancer; however, their role in the prevention of RRP is undetermined. Clinical presentation of initial symptoms of RRP may be subtle. RRP course varies, and current management focuses on surgical debulking of papillomatous lesions with or without concurrent adjuvant therapy.

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PMID: 22588043 [PubMed - indexed for MEDLINE] PMCID: PMC3682415

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[Rev Assoc Med Bras.](#) 2012 Mar-Apr;58(2):204-8.

### ***Laryngeal sequelae of recurrent respiratory papillomatosis surgery in children.***

[Hermann JS](#), [Pontes P](#), [Weckx LL](#), [Fujita R](#), [Avelino M](#), [Pignatari SS](#).

#### **Source**

Department of Otorhinolaryngology and Head and Neck Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil. juli64@ig.com.br

**Abstract****OBJECTIVE:**

To evaluate laryngeal sequelae from surgical treatment of recurrent respiratory papillomatosis in children, as well as associated risk factors.

**METHODS:**

Case-control study. Medical record data analysis of 50 children with recurrent respiratory papillomatosis, divided into two groups: with and without laryngeal sequelae. The group of patients with laryngeal sequelae was compared to those without sequelae in regard to the onset of disease, age at first surgery, number and frequency of surgeries, disease stage, and type of surgery (CO2 laser, cold forceps).

**RESULTS:**

23 patients (46%) sustained laryngeal sequelae. The most frequent sequela was anterior commissure synechia (17 patients [34%]), followed by glottic stenosis (six patients [12%]). There was no statistically significant difference between groups with and without laryngeal sequelae regarding the disease onset ( $p = 0.93$ ), age at first surgery ( $p = 0.68$ ), number of surgeries ( $p = 0.22$ ), annual frequency of surgery ( $p = 0.93$ ), presence of papilloma in anterior ( $p = 0.430$ ) or posterior commissure ( $p = 0.39$ ), and type of surgery ( $p = 0.27$ ). The Derkay anatomical score (a staging system that assesses the extent of the disease in the aerodigestive tract) was significantly higher in the laryngeal sequelae group ( $p = 0.04$ ).

**CONCLUSION:**

Laryngeal sequelae are a frequent complication of recurrent respiratory papillomatosis surgical treatment in children, particularly anterior commissure synechiae and glottic stenosis. Advanced stages are associated with increased risk of laryngeal sequelae after surgery.

PMID: 22569615 [PubMed - indexed for MEDLINE]

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[Expert Rev Vaccines](#). 2012 Apr;11(4):395-406. doi: 10.1586/erv.12.20.

*A prophylactic quadrivalent vaccine for the prevention of infection and disease related to HPV-6, -11, -16 and -18.*

[Goldstone SE](#), [Vuocolo S](#).

**Source**

Mount Sinai School of Medicine, 420 West 23rd Street, New York, NY, USA. segmd@prodigy.net

**Abstract**

Human papillomavirus infection causes cervical cancer, a significant portion of anal, genital and oropharyngeal cancers, genital warts and recurrent respiratory papillomatosis. In June 2006, a quadrivalent human papillomavirus-6/11/16/18 vaccine (GARDASIL/SILGARD®; Merck, NJ, USA) was licensed in the USA; subsequent approval has been granted in the EU (September 2006). It has since been approved in 121 countries with over 74 million doses distributed globally as of March 2011.

PMID: 22551023 [PubMed - indexed for MEDLINE]

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[Adv Otorhinolaryngol.](#) 2012;73:105-8. doi: 10.1159/000334457. Epub 2012 Mar 29.

***Juvenile-onset recurrent respiratory papillomatosis.***

[Maturó SC](#), [Hartnick CJ](#).

**Source**

Department of Otolaryngology, San Antonio Military Medical Center, Fort Sam Houston, TX, USA.

**Abstract**

Juvenile-onset recurrent respiratory papillomatosis, caused by the human papilloma virus, is the most common benign neoplasm of the larynx in children. Recurrent respiratory papillomatosis is relatively rare, but it can have a significant impact on afflicted children and their family's quality of life as dysphonia and multiple surgical procedures are hallmarks of this disease. The current standard of care is surgical therapy with a goal of complete papilloma removal and preservation of normal structures. The technique in this atlas combines both the microdebrider and the pulse KTP laser. The microdebrider allows for rapid removal of bulky lesions without the risk of thermal injury, yet it cannot provide precise removal in areas such as the anterior commissure and ventricle. The pulse KTP laser allows for removal of sessile lesions and in sensitive areas such as the vocal folds. The authors describe this technique as well as discuss adjuvant therapies and pearls for success.

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PMID: 22472239 [PubMed - indexed for MEDLINE]

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[Clin Cancer Res.](#) 2012 Apr 1;18(7):1925-35. doi: 10.1158/1078-0432.CCR-11-2941. Epub 2012 Feb 9.

*Immune suppression in premalignant respiratory papillomas: enriched functional CD4<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells and PD-1/PD-L1/L2 expression.*

[Hatam LJ](#), [Devoti JA](#), [Rosenthal DW](#), [Lam F](#), [Abramson AL](#), [Steinberg BM](#), [Bonagura VR](#).

### Source

The Feinstein Institute for Medical Research, 350 Community Drive, Room 1239, Manhasset, NY 11030, USA.

### Abstract

#### **PURPOSE:**

Respiratory papillomas, caused by human papillomaviruses types 6 and 11 (HPV6/11), are premalignant lesions with potential for malignant conversion. The cytokine and chemokine microenvironment of papillomas is T(H)2-like with a marked absence of IFN- $\gamma$  expression. To illuminate why patients with recurrent respiratory papillomatosis (RRP) fail to effectively control their disease, we further investigated the suppressive cellular microenvironment in papillomas.

#### **EXPERIMENTAL DESIGN:**

CD4(+)CD25(+)CD127(low/-)Foxp3(+) regulatory T cells (Treg) and CD4(+)CD25(-)CD127(low/-)Foxp3(-) T cells within papillomas were characterized and isolated. Their suppressor function was measured by inhibition of peripheral blood mononuclear cell (PBMC) proliferation. Expression of PD-1, CD69, and Helios was identified on these T cells. PD-L1, PD-L2, CCL17, and CCL22 mRNA was also identified in papillomas by quantitative PCR.

#### **RESULTS:**

Functional Tregs were markedly enriched in papillomas and strongly inhibited anti-CD3 and anti-CD28 antibody activated PBMC proliferation. The natural Treg marker Helios was reduced on Tregs from papillomas, indicating that the majority of Tregs in papillomas are adaptive. The majority of the papilloma-derived CD4(+) T cells expressed the CD4(+)CD25(-)CD127(low/-)Foxp3(-)PD1(+)-CD69(+) phenotype and failed to suppress PBMC proliferation,

suggesting that they are chronically activated and exhausted. The Treg-attracting chemokine CCL22 was equally expressed by all laryngeal tissues examined. However, CCL17 was robustly expressed by papillomas compared with unaffected laryngeal tissues from RRP patients and individuals without RRP. PD-L1 was elevated in papillomas compared with control laryngeal tissues.

### **CONCLUSIONS:**

Papilloma CD4(+) T cells are enriched with functional Tregs, and the adaptive Helios(-) Treg fraction was increased within the T(H)2-like papilloma micromilieu. CD4(+)CD25(-)CD127(low/-)Foxp3(-) T-cells failed to suppress PBMC proliferation and may be exhausted. The PD-1/PDL-1 pathway may represent an additional immunosuppressive mechanism that contributes to defective HPV6/11 clearance in RRP.

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PMID: 22322668 [PubMed - indexed for MEDLINE] PMCID: PMC3319851

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[Eur Arch Otorhinolaryngol.](#) 2012 Oct;269(10):2271-6. doi: 10.1007/s00405-011-1908-0. Epub 2012 Jan 4.

***Pharyngeal squamous cell papilloma in adult Japanese: comparison with laryngeal papilloma in clinical manifestations and HPV infection.***

[Hirai R](#), [Makiyama K](#), [Higuti Y](#), [Ikeda A](#), [Miura M](#), [Hasegawa H](#), [Kinukawa N](#), [Ikeda M](#).

### **Source**

Department of Otolaryngology-Head and Neck Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan. hirai.ryoji@nihon-u.ac.jp

### **Abstract**

A number of reports have investigated the relationship between laryngeal papilloma and human papilloma virus (HPV) infection. On the other hand, it is unclear whether the HPV infection is involved in the occurrence of pharyngeal papilloma. We hypothesized that HPV infection was involved in the occurrence of pharyngeal papilloma similarly to laryngeal papilloma. To verify this hypothesis, we investigated the presence of HPV infection. Furthermore, clinical manifestations of pharyngeal papilloma, which had rarely been

reported, were discussed. A male-to-female ratio, solitary or multiple occurrences, and koilocytosis were examined in cases with pharyngeal papilloma. HPV DNA was examined with unfixed surgically resected specimens of pharyngeal papilloma. A screening test by the liquid-phase hybridization method was carried out for the HPV high-risk group (16, 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, and 68) and HPV low-risk group (6, 11, 42, 43, 44). As a control, 15 cases with laryngeal papilloma for which the same screening test was carried out were employed. Pharyngeal papilloma occurred as a solitary lesion more often, whereas laryngeal papilloma occurred as multiple tumors more frequently. The HPV infection rate was 0% in pharyngeal papilloma cases, which was in stark contrast with 66.7% in the HPV low-risk group in laryngeal papilloma cases. Pharyngeal papilloma occurred as a solitary lesion in females more frequently. Contrary to our hypothesis, the involvement of HPV infection was unlikely in the occurrence of pharyngeal papilloma.

PMID: 22215212 [PubMed - indexed for MEDLINE]

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[Acta Dermatovenerol Alp Panonica Adriat.](#) 2011 Sep;20(3):175-80.

### *Adjuvant therapy for laryngeal papillomatosis.*

[Boltežar IH](#), [Bahar MS](#), [Zargi M](#), [Gale N](#), [Matičič M](#), [Poljak M](#).

#### **Source**

Department of Otorhinolaryngology and Cervicofacial Surgery, Ljubljana University Medical Center, Slovenia.

#### **Abstract**

Respiratory papillomatosis affects the larynx in most cases. It is a relatively rare disease, with potentially devastating consequences for the patient. Many studies have proven the viral etiology of the disease. Surgery is the most successful mode of treatment. Adjuvant therapy is used in cases of aggressive disease. The most successful adjuvant drugs are interferon, various virostatics (e.g., acyclovir, valacyclovir, and cidofovir) and indole-3-carbinol. Vaccination with a quadrivalent vaccine against HPV will probably decrease the incidence of respiratory papillomatosis or help in the treatment of the disease in the future. The results of adjuvant therapy of laryngeal papillomatosis at the University Department of ORL & HNS in Ljubljana are comparable to the results in other centers around the world.

PMID: 22131118 [PubMed - indexed for MEDLINE]

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[Mol Med.](#) 2012 Mar 30;18:244-9. doi: 10.2119/molmed.2011.00447.

***Constitutive overexpression of the oncogene Rac1 in the airway of recurrent respiratory papillomatosis patients is a targetable host-susceptibility factor.***

[Lucs AV](#), [Wu R](#), [Mullooly V](#), [Abramson AL](#), [Steinberg BM](#).

### Source

Feinstein Institute for Medical Research, North Shore-Long Island Jewish-LIJ Health System, Manhasset, New York, United States of America.

### Abstract

Recurrent respiratory papillomatosis (RRP) is caused by human papillomaviruses (HPVs), primarily types 6 and 11. The disease is characterized by multiple recurrences of airway papillomas, resulting in high levels of morbidity and significant mortality. The prevalence of latent HPV in the larynx of the general population is much greater than the prevalence of RRP, suggesting a host-susceptibility factor for disease. We report that the oncogene Rac1 and its downstream product cyclooxygenase-2 (COX-2) are both constitutively expressed at high levels throughout the airway of these patients, independent of active HPV infection. Use of the COX-2 inhibitor celecoxib in primary papilloma cell culture resulted in the downregulation of HPV transcription. Furthermore, a proof-of-principle study treating three patients with severe RRP with celecoxib resulted in remission of disease in all cases. Therefore, we have identified the first pharmacologically targetable host-susceptibility pathway that contributes to RRP recurrence.

PMID: 22113496 [PubMed - indexed for MEDLINE] PMCID: PMC3324949

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[Ann Otol Rhinol Laryngol.](#) 2011 Oct;120(10):627-34.

***Local injection of bevacizumab (Avastin) and angiolytic KTP laser treatment of recurrent respiratory papillomatosis of the vocal folds: a prospective study.***

[Zeitels SM](#), [Barbu AM](#), [Landau-Zemer T](#), [Lopez-Guerra G](#), [Burns JA](#), [Friedman AD](#), [Freeman MW](#), [Halvorsen YD](#), [Hillman RE](#).

**Source**

Department of Surgery, Harvard Medical School, and the Center for Laryngeal Surgery and Voice Rehabilitation the Massachusetts General Hospital Institute of Health Professions, Massachusetts General Hospital, Boston, MA 02114, USA.

**Abstract**

**OBJECTIVES:**

Photoangiolytic laser treatment of recurrent respiratory papillomatosis (RRP) is effective, but does not reliably prevent recurrence. Therefore, sublesional injections of the antiangiogenic agent bevacizumab (Avastin) were given to assess the adjunctive effect on disease recurrence. Since bevacizumab is a new therapeutic modality for RRP, there were also primary safety objectives to determine whether there was a negative impact on the voice and whether there were local or systemic complications.

**METHODS:**

A prospective open-label investigation was conducted in 20 adult patients with bilateral vocal fold RRP. The patients underwent planned 532-nm pulsed KTP laser photoangiolytic of bilateral glottal disease 4 times with an approximately 6-week interval between procedures. At each planned laser procedure, the vocal fold that on initial presentation had a greater volume of disease also underwent 4 serial sublesional bevacizumab injections (7.5 to 12.5 mg in 0.3 to 0.5 mL). A sham injection with saline solution was administered to the other vocal fold as a control. Disease resolution was compared between subjects' vocal folds, and objective measures of vocal function (acoustic, aerodynamic), as well as patients' self-assessments of vocal function (Voice-Related Quality of Life survey), were obtained.

**RESULTS:**

All 20 patients completed the study, and there were no local or systemic complications. After 4 injections, 3 of the 20 patients had no discernible disease in either vocal fold. Of the remaining 17 subjects, 16 had less disease in the bevacizumab-treated vocal fold despite starting with more disease. Only 1 of the 17 had more disease in the bevacizumab-treated vocal fold after 4 injections. Moreover, 7 of the 20 patients (35%) did not require a laser

procedure in the vocal fold that had received 4 bevacizumab injections, as compared with 3 of the 20 vocal folds (15%) that were treated with laser alone. All of the vocal function measures displayed statistically significant posttreatment improvements, except for average fundamental frequency in the 3 female patients, in whom it fell below the normal range.

### **CONCLUSIONS:**

This prospective investigation provided evidence that bevacizumab injections enhanced KTP laser treatment of glottal papillomatosis without systemic or local complications. Coupling the antiangiogenesis agent bevacizumab with KTP laser photoangiolytic is conceptually synergistic and scientifically promising since the mechanisms of action are complementary.

PMID: 22097147 [PubMed - indexed for MEDLINE]

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[Nihon Kokyuki Gakkai Zasshi](#). 2011 Sep;49(9):667-73.

### ***[Two cases of juvenile-onset and adult-onset recurrent respiratory papillomatosis].***

[Article in Japanese]

[Shiobara Y](#), [Goto H](#), [Hoshino M](#), [Tsukahara T](#), [Yamaguchi N](#), [Ito M](#), [Nozawa A](#), [Tsukiji J](#), [Ishigatsubo Y](#), [Kaneko T](#).

### **Source**

Respiratory Disease Center, Yokohama City University Medical Center.

### **Abstract**

We recently experienced one each of 2 types of recurrent respiratory papillomatosis (RRP). Case 1 (juvenile-onset type): A 30-year-old woman presenting with bloody sputum and large tumors with cavities on her chest Xray film, was referred to our hospital. She had been diagnosed with laryngeal papillomatosis when she was three years old. According to our bronchoscopic examination biopsy, she was diagnosed with squamous cell carcinoma of the lung in addition to papillomatosis of the trachea and bronchus. Although chemotherapy was performed, she died 2 years after the diagnosis of lung cancer without any distinct treatment efficacy. Case 2 (adult-onset type): A 43 year-old woman presenting with fever and dry cough visited our hospital. Chest CT revealed that there was narrowing of bilateral main bronchi and hilar lymphadenopathy. Bronchoscopic examination revealed

diffuse papilloma distributed extensively from the trachea to bilateral main bronchi. However, she recovered spontaneously in 6 months and has remained stable without recurrence. Both cases were diagnosed with RRP based on the separation of HPV in case 1 and pathological findings of koilocytosis in case 2. Case 1 was complicated with squamous cell carcinoma of the lung in the clinical course, presumably due to occurrence of malignant conversion of papillomatosis. Since RRP is a rare but refractory disease, novel effective treatment is necessary.

PMID: 22073613 [PubMed - indexed for MEDLINE]

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[Eur Arch Otorhinolaryngol.](#) 2012 Feb;269(2):361-2. doi: 10.1007/s00405-011-1804-7. Epub 2011 Oct 22.

***Treatment of recurrent respiratory papillomatosis and adverse reactions following off-label use of cidofovir (Vistide®).***

[Tjon Pian Gi RE](#), [Dietz A](#), [Djukic V](#), [Eckel HE](#), [Friedrich G](#), [Golusinski W](#), [Hantzakos A](#), [Lawson G](#), [Remacle M](#), [Rihkanen H](#), [Dikkers FG](#).

Noabstract available.

PMID: 22020697 [PubMed - indexed for MEDLINE] PMID: PMC3259328

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[Chron Respir Dis.](#) 2011;8(4):233-5. doi: 10.1177/1479972311416381. Epub 2011 Oct 4.

***Tracheal papillomatosis: what do we know so far?***

[Harris K](#), [Chalhoub M](#).

**Source**

Staten Island University Hospital, Staten Island, NY 10305, USA. kassemharris@gmail.com

**Abstract**

Tracheal papillomatosis (TP) is a benign condition characterized by papillomatous growth of the bronchial epithelium that involves the trachea. This abnormal growth is a result of infection with human papilloma virus (HPV). Two subtypes of HPV were found in most cases of TP, HPV-6 and HPV-11. TP, presents in two forms, the juvenile onset (JO) or adult onset (AO). The clinical presentation is typically nonspecific and it ranges from mild

symptoms like cough to life-threatening conditions like upper airway obstruction. Treatment depends on the location of the papillomas and age of the patient and the plan of therapy is usually made on an individual basis. Treatment can range from observation with symptomatic control to specific medical therapy and multiple surgeries in case of recurrence or progressively worsening disease. The recent invention of HPV vaccine is expected to be the first step in eradicating respiratory papillomatosis.

PMID: 21971565 [PubMed - indexed for MEDLINE]

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[Am J Otolaryngol.](#) 2010 Jul-Aug;31(4):291-6. doi: 10.1016/j.amjoto.2009.02.019. Epub 2009 Jul 10.

***Malignant transformation of a highly aggressive human papillomavirus type 11-associated recurrent respiratory papillomatosis.***

[Lin HW](#), [Richmon JD](#), [Emerick KS](#), [de Venecia RK](#), [Zeitels SM](#), [Faquin WC](#), [Lin DT](#).

**Source**

Department of Otolaryngology-Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, Boston, MA 02114, USA. [harrison\\_lin@meei.harvard.edu](mailto:harrison_lin@meei.harvard.edu)

**Abstract**

**OBJECTIVE:**

The objective is to present an uncommon case of squamous cell carcinoma (SCC) arising from extensive recurrent respiratory papillomatosis (RRP) involving the upper and lower airway and temporal bone.

**STUDY DESIGN:**

This is a case report and a review of the literature.

**METHODS:**

We describe a case of a 24-year-old woman with a history of human papillomavirus (HPV) type 11 since childhood originating in the larynx and trachea, then progressing to involve the distal pulmonary alveoli and right middle ear through the eustachian tube. Papillomatous growth was treated with multiple surgeries including laser cytorreduction of laryngotracheal papillomatosis and radical mastoidectomy, followed by a trial of chemotherapy. Despite this aggressive treatment regimen, papillomatous

growth progressed with recurrence in the right eustachian tube, middle ear, and mastoid eventually extending to involve the calvaria and scalp.

**RESULTS:**

The patient underwent a composite resection of involved tissues, including the scalp, auricle, and lateral temporal bone, with reconstruction using a latissimus dorsi free flap. Final pathologic analysis revealed an extensive infiltrative well-differentiated SCC arising from the papilloma. A review of the literature on aggressive respiratory papillomatosis suggests that malignant transformation of juvenile-onset RRP occurs exclusively in cases positive for HPV-11.

**CONCLUSIONS:**

We report an unusual case of SCC originating from extensive RRP involving the airway, temporal bone, and scalp and describe the medical and surgical management. Although the incidence of juvenile-onset RRP transformation to SCC is very low, the presence of HPV-11 as a risk factor for malignant transformation of RRP is becoming evident.

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PMID: 20015762 [PubMed - indexed for MEDLINE]

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[N Engl J Med](#). 2012 Sep 27;367(13):1220-7.

*Use of reprogrammed cells to identify therapy for respiratory papillomatosis.*

[Yuan H](#), [Myers S](#), [Wang J](#), [Zhou D](#), [Woo JA](#), [Kallakury B](#), [Ju A](#), [Bazylewicz M](#), [Carter YM](#), [Albanese C](#), [Grant N](#), [Shad A](#), [Dritschilo A](#), [Liu X](#), [Schlegel R](#).

**Source**

Department of Pathology, Georgetown University Medical Center, Washington, DC 20057, USA.

[\(Link to full article\)](#)

**Abstract**

A patient with a 20-year history of recurrent respiratory papillomatosis had progressive, bilateral tumor invasion of the lung parenchyma. We used conditional reprogramming to generate cell cultures from the patient's

normal and tumorous lung tissue. Analysis revealed that the laryngeal tumor cells contained a wild-type 7.9-kb human papillomavirus virus type 11 (HPV-11) genome, whereas the pulmonary tumor cells contained a 10.4-kb genome. The increased size of the latter viral genome was due to duplication of the promoter and oncogene regions. Chemosensitivity testing identified vorinostat as a potential therapeutic agent. At 3 months after treatment initiation, tumor sizes had stabilized, with durable effects at 15 months.

PMID: 23013073 [PubMed - indexed for MEDLINE]

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[JAMA Otolaryngol Head Neck Surg.](#) 2013 May;139(5):496-501. doi: 10.1001/jamaoto.2013.1810.

Rogers DJ, Ojha S, Maurer R, Hartnick CJ

*Use of adjuvant intralesional bevacizumab for aggressive respiratory papillomatosis in children.*

#### Source

Departments of Pediatric Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA, USA.

#### Abstract

##### **IMPORTANCE:**

Juvenile recurrent respiratory papillomatosis (RRP) can be an aggressive disease process necessitating frequent trips to the operating room with multiple anesthetics for tumor debulking and airway preservation. Adjuvant therapy, such as that which is reported in this article, may help reduce the number of operative procedures affected children need each year and therefore may also affect their overall quality of life (QOL).

**OBJECTIVE:**

To describe our experience with intralesional bevacizumab (Avastin) treatment for children with severe RRP by comparing median number of surgical procedures per year, median duration of time between procedures, Derkay staging, and voice QOL before and after bevacizumab treatment.

**DESIGN:**

Prospective, consecutive case series.

**SETTING:**

Tertiary care aerodigestive center.

**PARTICIPANTS:**

Ten children, aged 18 months to 18 years, with severe RRP necessitating more than 4 operative interventions in 1 year whose parents (or legal guardians) consented to intralesional bevacizumab treatment.

**INTERVENTIONS:**

Intralesional bevacizumab administered at concentration of 2.5 mg/mL for 3 consecutive injections (with 532-nm pulsed KTP [potassium titanyl phosphate] laser when necessary) at intervals of 2 to 3 weeks.

**MAIN OUTCOME MEASURES:**

Time between surgical procedures, number of procedures per year, Derkay staging, total Pediatric Voice-Related Quality of Life (PVRQOL) score, Emotional PVRQOL score, and Physical PVRQOL score defined by comparing the year leading up to first of 3 bevacizumab injections with the year following the third bevacizumab injection.

**RESULTS:**

The median duration of time between surgical procedures increased by 5.9 weeks after bevacizumab ( $P = .002$ ). The median number of procedures per year decreased by 4 ( $P = .002$ ). Derkay staging decreased by 6 ( $P = .03$ ). The median total PVRQOL score increased by 25.5 ( $P = .02$ ), the median Emotional PVRQOL score increased by 11.3 ( $P = .047$ ), and the median Physical PVRQOL score increased by 14.3 ( $P = .047$ ).

**CONCLUSIONS AND RELEVANCE:**

Intralesional bevacizumab treatment may increase duration of time between surgical procedures and decrease number of procedures per year, while improving voice QOL.

PMID: 23681032 [PubMed - indexed for MEDLINE]

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[Int J Pediatr Otorhinolaryngol.](#) 2013 Oct;77(10):1729-33. doi: 10.1016/j.ijporl.2013.08.003. Epub 2013 Aug 14.

*Management of complex glottic stenosis in children with recurrent respiratory papillomatosis.*

[Siegel B, Smith LP.](#)

Source

Albert Einstein College of Medicine, Bronx, NY, United States. Electronic address: gruberb@gmail.com.

**Abstract****OBJECTIVES:**

To describe our management of complex glottic stenosis in tracheotomy dependent children with severe recurrent respiratory papillomatosis.

**METHODS:**

Retrospective chart review at a tertiary care children's hospital.

**RESULTS:**

Three children with complex glottic stenosis secondary to severe recurrent respiratory papillomatosis were treated at our institution since 2011. Two patients had complete stenosis, and the third had near-complete stenosis. Two patients were managed using balloon dilation alone, and the third also underwent laryngotracheal reconstruction with posterior costal cartilage grafting. Two patients have been successfully decannulated and the third

has been tolerating continuous tracheotomy capping for greater than twelve months. All three patients underwent aggressive debridement of papillomatosis and balloon dilation every 4-6 weeks until their burden of disease was controlled. In two patients, the glottic airway was patent, and the third continued to have complete restenosis between procedures and required laryngotracheoplasty with multiple post-operative dilation procedures to establish an adequate glottic airway.

### **CONCLUSIONS:**

Severe laryngeal stenosis is a well-described complication of recurrent respiratory papillomatosis, but its management is not well-defined. Aggressive management of papillomatosis with frequent debridement is critical in successfully managing laryngeal stenosis. Balloon dilation alone may be surprisingly effective in these patients, and laryngotracheoplasty can be used as an adjunct procedure in those patients who fail balloon dilation. Given the quality of life issues and concerns regarding distal spread of disease with tracheotomies in these patients, we feel that aggressive management and early decannulation is in the patient's best interest.

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### **KEYWORDS:**

Decannulation, Glottic, Laryngotracheal, RRP, Reconstruction, Recurrent respiratory papillomatosis, Stenosis, Tracheotomy

PMID: 23972336 [PubMed - in process]

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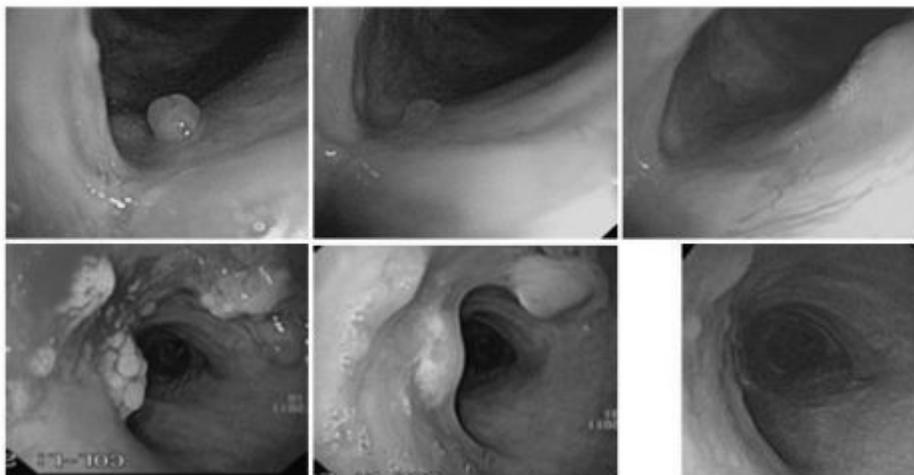
**Presentation at the European Respiratory Society Annual Congress 09 September 2013 – Session 202 : Clinical management of orphan lung diseases**

### *Recurrent respiratory papillomatosis - rapid response to systemic bevacizumab*

C. Schliemann, C. Biermann, A. Hilbis, T. Kessler, J. Schmidt, K. Wiebe, K. M. Müller, T. K. Hoffmann, C. Werner, A. H. Groll, C. Kessler, R. Wiewrodt, C. Rudack, B. Wolfgang, M. Mohr (Muenster, Ulm, Germany)

#### **Abstract**

Recurrent respiratory papillomatosis (RRP) is a potentially devastating, non-curable disease caused by infection with human papilloma virus (HPV), mainly HPV-6 and -11. Manifestations of RRP can occur everywhere in the respiratory tract and may lead to laryngeal, tracheal or bronchial obstructions, pulmonary nodes and cystic lesions due to valve effects. Malignant transformation occurs in 3 to 5% of the cases. Long-term management of patients with recurrent respiratory papillomatosis (RRP) remains challenging. Local debulking is the current treatment of choice and antiviral therapy is a possible adjuvant approach. Here, we report an immediate and sustained therapeutic effect of systemically applied bevacizumab without further local treatment in a series of five consecutive patients (7-56y) with RRP. In all cases, a rapid response to the first infusion of bevacizumab could be documented bronchoscopically within a few days.



prior treatment

3 days after first application

after 4 cycles

Continued anti-VEGF treatment resulted in sustained (very good) partial responses of tracheal or laryngeal papilloma manifestations. Due to limited alternatives

VEGF-targeted therapies represent a promising novel strategy in the treatment of RRP and should be further investigated in clinical trials.

**RRP Foundation**  
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