

RRP Medical Reference Service

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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 (2005 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

[Virology](#). 2006 Jan 5;344(1):240-9.

New viral vaccines.

[Arvin AM](#), [Greenberg HB](#).

Vaccination is the most effective medical intervention against diseases caused by human viral pathogens. Viral vaccines prevent or modify the severity of illness in the individual and interrupt or reduce the transmission of the pathogens to other susceptible people. Through these mechanisms, vaccines against smallpox, polio, measles and hepatitis B have had an enormous impact on world health over the last 50 years. Advances in basic virology and understanding of human immunity promise more progress in the control of human viral diseases as the 21st century begins. Some important targets, including human immunodeficiency virus, respiratory syncytial virus and hepatitis C virus present challenges that require more basic research. The purpose of this review is to highlight four new viral vaccines that have recently, or will soon demonstrate the effective translation of basic investigations into clinical benefits for disease control in healthy and high-risk populations. These vaccines include the live attenuated vaccines against the RNA viruses, rotavirus and influenza A and B, and vaccines against human papilloma virus and varicella-zoster virus, which are DNA viruses that cause morbidity and mortality through their capacity to establish persistent infection. Although only the influenza vaccine has been licensed in the United States, these other new tools for disease prevention are likely to be introduced within the next few years, with profound effects on the diseases that they cause. Hence, as *Virology* celebrates its 50th anniversary, it is appropriate to examine these examples of recent advances in viral vaccines.

PMID: 16364754

[Ann Otol Rhinol Laryngol](#). 2005 Nov;114(11):836-9.

Case of progressive dysplasia concomitant with intralesional cidofovir administration for recurrent respiratory papillomatosis.

[Wemer RD](#), [Lee JH](#), [Hoffman HT](#), [Robinson RA](#), [Smith RJ](#).

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Recurrent respiratory papillomatosis (RRP) is characterized by benign wartlike growths in the larynx with occasional spread to the lungs. A broad range of therapeutic measures have been used to treat RRP; the primary treatment is laser vaporization of the lesions.

Recurrences of the disease are common, and alternate methods of treatment are being used to prevent recurrence, including cidofovir. Cidofovir is a cytosine nucleotide analog with antiviral properties that is approved by the US Food and Drug Administration for treatment of cytomegalovirus retinitis and is currently being used off-label for RRP. Cidofovir has gained initial success in slowing the rate of disease recurrence when used at the time of surgery. However, the use of cidofovir lends concern to several adverse side effects, including the potential for carcinogenesis. We report here a 28-year-old woman who was treated with intralesional cidofovir at the time of surgery over the span of 27 months. The initial pathology results demonstrated benign disease with progression to severe dysplasia during the treatment time. Cidofovir's potential for carcinogenicity remains largely undefined, and thus, we are currently undertaking a project involving the evaluation of sequential paraffin-embedded samples of resections from a large cohort of patients with RRP treated at the University of Iowa Hospitals and Clinics.

PMID: 16358603

[Vestn Otorinolaringol. 2005;\(6\):62-3.](#)

[A complicated course of juvenile respiratory papillomatosis]

[Article in Russian]

[Sidorenko SI.](#)

No abstract available.

PMID: 16353015

[Saudi Med J. 2005 Nov;26\(11\):1737-45.](#)

The use of mitomycin-C for respiratory papillomas: clinical, histologic and biochemical correlation.

[Hamza AH](#), [Nasr MM](#), [Deghady AA](#).

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OBJECTIVE: To assess the clinical effects of mitomycin-C (MMC) on human papilloma virus (HPV)-infected tissues of the airway. **METHODS:** We included 10 patients with previous histologic diagnosis of recurrent respiratory papillomas (RRP) in this prospective study, conducted at the Department of Otolaryngology-Head and Neck Surgery, University

of Alexandria, Egypt, between January 2000 and December 2002. Under general anesthesia, each patient underwent laser excision of all visible papillomas, followed by topical application of 1 cc of 0.5 mg/ml MMC. The procedure was repeated weekly until no visible papillomas could be microscopically detected. We histopathologically studied the obtained specimens and tested for the presence of HPV DNA using polymerase chain reaction (PCR) technique. We collected blood samples from all patients and from another 10 healthy volunteers for determination of serum interleukin-2 (IL-2) level using enzyme-linked immunosorbent assay technique. RESULTS: We achieved clinical remission in 8 of the patients (80%), a fact that was confirmed histopathologically and by PCR data. The mean serum IL-2 levels \pm SD was significantly lower in papilloma patients (83.6 \pm 28.83 pg/ml) than in control subjects (196.3 \pm 42.46 pg/ml) ($p < 0.01$). Among patients with RRP, serum IL-2 levels \pm SD was lower in initial samples (83.6 \pm 28.83) than follow-up (95.7 \pm 27.98 and 112.3 \pm 33.8 and 129.4 \pm 34.04) and remission samples (154 \pm 37.84 pg/ml) CONCLUSION: Our result suggests that topical application of MMC may act adjunctively to laser surgery for RRP.

PMID: 16311658

[Curr Opin Otolaryngol Head Neck Surg.](#) 2005 Dec;13(6):354-9.

Recurrent respiratory papillomatosis: pathogenesis to treatment.

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PURPOSE OF REVIEW: Recurrent respiratory papillomatosis remains a serious disease and is commonly treated by otolaryngologists. The goals of this review are to update physicians on current understandings regarding viral pathogenesis, patient risks, and current trends in treatment strategies. RECENT FINDINGS: Surgical debulking still remains the foundation of treatment; however, newer surgical approaches utilizing microdebriders are replacing laser ablation. Genetic studies have identified individuals with specific immune cell alleles to be at greater risk for persistent infection. Our understanding of the viral pathogenesis has increased by the identification of a viral mechanism to downregulate antigen expression in cells infected with human papillomavirus, thus possibly allowing decreased immune detection. Although the viral types responsible for recurrent respiratory papillomatosis have been identified, the mechanism by which they alter cellular growth has not been identified. Research studies investigating adjuvant medical therapies aimed at reducing required surgical therapy intervals and possibly helping cure the infection are being completed. A safe, effective adjuvant therapy is still currently not available. SUMMARY: Improved surgical approaches have slightly enhanced patient care; however, more research is needed to understand how human papillomavirus causes disease so that these therapies can be developed.

PMID: 16282764

[Chron Respir Dis. 2004;1\(4\):229-31.](#)

'Papillomatization' and 'malignant transformation' of an abscess cavity in a 25-year old man with recurrent respiratory papillomatosis who may have had Lemierre syndrome.

[Veale A, Jurisevic C, Pieterse S, Psaltis A.](#)

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We report here an unusual case of a 25-year old male with juvenile onset recurrent respiratory papillomatosis who developed an infestation of papillomata 'papillomatization' of an old abscess cavity that, when removed, was coincidentally found to contain a 2 cm well differentiated squamous cell carcinoma. The abscess cavity had been caused by a previous *Fusobacterium necrophorum* infection that probably developed as a result of septic emboli from his internal jugular veins. This once common but now rare occurrence was first reported by Dr Lemierre in 1936 (Lemierre syndrome).

PMID: 16281650

[ORL J Otorhinolaryngol Relat Spec. 2005;67\(4\):237-41. Epub 2005 Nov 4.](#)

Investigation of a broad-spectrum PCR assay for human papillomaviruses in screening benign lesions of the upper aerodigestive tract.

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BACKGROUND: A variety of different human papillomavirus (HPV) types can be found in benign and malignant lesions of the upper aerodigestive tract. Therefore a broad-spectrum assay is needed for screening reasons. **METHODS:** A PCR system with degenerate consensus primers originating from a very conserved region (e.g. L1) of the HPV genome was applied. The sensitivity level was improved by combining PCR and nested PCR. **RESULTS:** A total of 27 biopsies from laryngeal papillomas (9), exophytic (3) and inverted (6) papillomas of the nasal cavity or paranasal sinuses, papillomas of the uvula or soft palate (5), leukoplakias of the larynx (2), seborrheic keratosis (1) and granulation tumor of the tongue (1) were analyzed by the broad-spectrum PCR system. Sixteen cases showed a positive result in either PCR or nested PCR or both. **CONCLUSIONS:** It was shown that the applied broad-spectrum PCR system is a reliable tool in the detection of HPV DNA in benign

lesions of the upper aerodigestive tract.

PMID: 16276120

[Ann Emerg Med.](#) 2005 Nov;46(5):405, 419. Epub 2005 Jul 14.

Images in emergency medicine. Laryngeal papilloma.

[Hess EP, Colletti JE.](#)

Department of Emergency Medicine, Mayo Clinic, Rochester, MN, USA.

No abstract available.

PMID: 16271666

[Lin Chuang Er Bi Yan Hou Ke Za Zhi.](#) 2005 Aug;19(15):694-6.

[The detection of human papilloma virus in juvenile-onset respiratory papillomatosis]

[Article in Chinese]

[Yang L, Wei Y, Wang Y, Wang J, Zhao Y.](#)

Center Lab, Beijing Tongren Hospital, Affiliated Capital University of Medical Sciences, Beijing, 100730, China.

OBJECTIVE: To investigate the relationship between juvenile-onset respiratory papillomatosis (JOP) and human papilloma virus (HPV6, HPV11), and the immune function of patients. **METHOD:** Fluorescence quantitative PCR (FQ-PCR) which combines PCR and fluorescence probe hybridization was used to detect HPV6, HPV11 DNA in 130 cases. Of these, 68 cases were used Flow Cytometry to measure CD3, CD4, CD8. **RESULT:** One hundred and fifteen of 130 cases were HPV6, HPV11 DNA positive, the average copy was 5.68 +/- 2.65. For 68 cases, the average percent of CD3, CD4, CD8 were 62.73 +/- 8.63, 30.54 +/- 7.05, 26.08 +/- 6.93, respectively. To compare with control group, there was not statistical significance. **CONCLUSION:** FQ-PCR is a convenient, accurate and specific method which can quantify the amount of pathogenic germs from 10(1) to 10(10), and is also a reliable factor to predicate clinical diagnose and cure.

PMID: 16248508

[Vestn Otorinolaringol.](#) 2005;(5):20-5.

[Papillomatosis of the lower respiratory tracts in children]

[Article in Russian]

[Soldatskii IuL](#), [Onufrieva EK](#), [Steklov AM](#), [Strygina IuV](#), [Shchepin NV](#), [Gasparin SF](#), [Pogosova IE](#).

Papillomatosis of the trachea, bronchi and lungs was investigated in 40 children with papillomatosis of the lower airways in comparison with 408 children with laryngeal papillomatosis. All the patients were operated in 1988-2003 with histological verification of the diagnosis. Papillomas involved the lower airways because of tracheotomy (92.5%) or tracheal intubation (7.5%). Papillomatosis of the lower airways runs a more aggressive course than laryngeal papillomatosis, its treatment efficacy is worse. All the patients suffering from laryngeal papillomatosis with a history of tracheotomy need a regular endoscopic and x-ray control as papillomatosis of the trachea and/or lungs may develop in them several years after decanulation. Pulmonary papillomatosis has an invariably poor prognosis.

PMID: 16247363

[Ann Otol Rhinol Laryngol](#). 2005 Sep;114(9):730-7.

HspE7 treatment of pediatric recurrent respiratory papillomatosis: final results of an open-label trial.

[Derkay CS](#), [Smith RJ](#), [McClay J](#), [van Burik JA](#), [Wiatrak BJ](#), [Arnold J](#), [Berger B](#), [Neefe JR](#).

Department of Otolaryngology-Head and Neck Surgery, Eastern Virginia Medical School, Norfolk, Virginia, USA.

OBJECTIVES: We sought to evaluate the effectiveness of HspE7, a recombinant fusion protein of Hsp65 from *Mycobacterium bovis* BCG and E7 protein from human papillomavirus 16, to improve the clinical course of pediatric patients with recurrent respiratory papillomatosis. **METHODS:** An open-label, single-arm intervention study was conducted in 8 university-affiliated medical centers. Twenty-seven male and female patients with recurrent respiratory papillomatosis, ages 2 to 18 years, were enrolled and followed up to 60 weeks. Before enrollment, these patients required surgery on average every 55 days. After a baseline debulking surgery, the patients received HspE7 500 microg subcutaneously monthly, for 3 doses over 60 days. The primary end point was the length of the interval from the last surgery during the treatment period until the first debulking surgery in the posttreatment period, compared with the median intersurgical interval (ISI) of the 4 surgeries before the treatment. **RESULTS:** The mean of the first posttreatment ISI increased 93% (from 55 days to 106 days; $p < .02$). The median ISI for all surgeries after treatment was similarly prolonged (mean, 107 days; $p < .02$), indicating a sustained treatment effect, and was associated with a significant decrease in the number of required surgeries ($p < .003$).

Unexpectedly, the treatment effect was most striking in the 13 female patients, who had statistically significant increases in both the first posttreatment ISI (142%; $p < .03$) and the median ISI (147%; $p < .03$). The most common adverse events were mild-to-moderate injection site reactions. CONCLUSIONS: Treatment with HspE7 appears to significantly improve the clinical course in pediatric patients with RRP insofar as it reduces the frequency of required surgeries. These results warrant a confirmatory phase III trial.

PMID: 16240938

[*Ann Otol Rhinol Laryngol.* 2005 Sep;114\(9\):657-61.](#)

Immune stimulation for the treatment of papilloma.

[Poetker DM](#), [Kerschner JE](#), [Patel NJ](#), [Bauman NM](#), [Sandler AD](#).

Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

OBJECTIVES: There is no curative therapy for recurrent respiratory papillomatosis. Unmethylated dinucleotides of cytosine and guanine (CpG) are potent immune stimulants that have shown efficacy against tumors as monotherapy, as vaccine adjuvants, and in combination with chemotherapies. We examined the therapeutic effect of CpG oligodeoxynucleotides in the treatment of papillomavirus in a cottontail rabbit model (CRPV). METHODS: Twenty rabbits were infected with CRPV; 10 were treated with 11 weekly CpG inoculations while treatment control rabbits received intralesional saline solution. Eight rabbits (4 treatment, 4 control) were rechallenged with CRPV 17 weeks after the initial viral challenge and monitored for new papilloma development. RESULTS: Papillomas developed in all 20 rabbits (100%) within 4 weeks of infection. The diagnosis was confirmed histologically. There was no difference in the average tumor burden between the treatment and control groups after 11 weeks of CpG treatments or after 9 additional weeks of observation. There was no difference between the groups in papilloma size at the site of the injections, nor was there eradication of papillomas at remote sites in either group. No new papillomas developed in any of the 8 animals that were rechallenged. CONCLUSIONS: We have reproduced an effective mammalian papilloma model for preclinical immunotherapeutic testing. Despite the potency of CpG in triggering host immunity, CpG oligodeoxynucleotide did not show a therapeutic effect against the large papilloma burdens tested in this study. The lack of effect suggests that either enhanced papilloma antigen presentation or targeting of immune-evasive mechanisms used by the papillomas is needed to treat bulky disease with an immunotherapeutic strategy.

PMID: 16240926

[*Laryngoscope.* 2005 Oct;115\(10\):1848-54.](#)

Tracheal, bronchial, and pulmonary papillomatosis in children.

[Soldatski IL](#), [Onufrieva EK](#), [Steklov AM](#), [Schepin NV](#).

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OBJECTIVES: To compare the clinical course of tracheal, bronchial, and pulmonary papillomatosis with clinical course of laryngeal papillomatosis in children. **STUDY DESIGN:** The records of the 448 children with recurrent respiratory papillomatosis treated in St. Vladimir Moscow Children's Hospital between 1988 and 2003 were reviewed. In all cases, the diagnosis was confirmed histologically. Age at onset of symptoms, age at first surgery, number of surgical procedures, mean duration of surgical interval, possible causes, and age at a point of papillomatosis spread in the lower airways and course of the disease were analyzed. **SETTING:** Academic children's hospital. **RESULTS:** Papillomas extension down to lower airways was observed in 40 children (8.9%). Among 40 patients with lower airway recurrent respiratory papillomatosis, 8 (20%) demonstrated pulmonary involvement. The basic cause of papilloma extension to lower airways appeared to be tracheotomy performed in children with laryngeal papillomatosis (92.5% of cases). Incidence of satellite pharyngeal and esophageal papillomatosis is significantly higher in patients with lower airways papillomatosis, presenting evidence of larger process extension. The clinical course of lower airways papillomatosis is more aggressive as compared with laryngeal papillomatosis, and treatment efficacy in such children is lower. **CONCLUSIONS:** All the patients with laryngeal papillomatosis having a history of tracheotomy require a regular endoscopic control and chest radiographs or computed tomography scanning because tracheal or pulmonary papillomatosis may occur in such patients even several years after decannulation. The prognosis for the disease after development of pulmonary papillomatosis is always serious.

PMID: 16222208

[Eur J Gastroenterol Hepatol.](#) 2005 Nov;17(11):1233-7.

Esophageal squamous papillomatosis.

[Kao PC](#), [Vecchio JA](#), [Schned LM](#), [Blaszyk H](#).

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Esophageal squamous papillomatosis is rare and has been associated with gastroesophageal reflux and recurrent respiratory papillomatosis. We report a case of extensive esophageal papillomatosis, no airway involvement and a slowly progressive clinical course with progressive strictures and ultimately fatal squamous cell carcinoma. In-situ hybridization performed on biopsy specimens was negative for high-risk human papilloma virus types. Due

to the paucity of reported cases, little is conclusively known about the etiology, natural course and best clinical management of this disease. Human papilloma virus has been linked to some, but not all, cases, and the clinical course has been reported to vary from spontaneous regression to malignant transformation. Surveillance for malignancy by conventional endoscopic biopsies or computed tomography scan appears to have low sensitivity. This case illustrates the difficulties in clinical management and establishing a definite etiology in esophageal squamous papillomatosis.

PMID: 16215437

J Thorac Cardiovasc Surg. 2005 Oct;130(4):1190-3.

Clinical-pathologic conference in general thoracic surgery: malignant transformation of recurrent respiratory papillomatosis.

[Kozower BD](#), [Javiden-Nejad C](#), [Lewis JS](#), [Safdar S](#), [Cooper JD](#), [Patterson GA](#).

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No abstract available.

PMID: 16214538

J Huazhong Univ Sci Technolog Med Sci. 2005;25(3):351-3, 364.

Relationship between the expression of CD44v6 and development, progress, invasion and metastasis of laryngeal carcinoma.

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Department of Otorhinolaryngology Head and Neck Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.

The expression of CD44v6 and its relationship with the development, progress, invasion and metastasis of laryngeal carcinoma was investigated. The expression and content of CD44v6 mRNA in tissues were detected by both RT-PCR and FCM which were respectively extracted from normal laryngeal mucosa, leukoplakia of larynx, laryngeal papilloma, polyp of vocal cord, tissues of laryngeal carcinoma, metastatic and nonmetastatic lymph nodes of neck, and tissues close to carcinoma. The outcome of RT-PCR indicated that the expression rate of CD44v6 mRNA involved in tissues of laryngeal carcinoma and metastatic lymph nodes of neck was the highest (90%-100%) compared with that of leukoplakia of larynx, laryngeal papilloma, tissues close to carcinoma by 0.5 cm (55.56%-60.00%) and that of

normal laryngeal mucosa, polyp of vocal cord, nonmetastatic lymph nodes and tissues close to carcinoma by 1.0 cm was the lowest (13.33%-20%). The result from FCM was highly consistent with that from RT-PCR. It was suggested that CD44v6 was closely related with the development, progress, invasion and metastasis of laryngeal carcinoma. The outcome from the tissues close to carcinoma by different distance could do help to the determination of incisal edge in surgery abstractly.

PMID: 16201294

[Pediatrics](#). 2005 Oct;116(4):815-25.

Anogenital and respiratory tract human papillomavirus infections among children: age, gender, and potential transmission through sexual abuse.

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OBJECTIVES: To evaluate human papillomavirus (HPV) presentation among children <13 years of age and its association with suspected child sexual abuse (CSA), and to assess sexual abuse consideration among different clinical services treating these children. **METHODS:** Records of children <13 years of age from 1985 to 2003 were selected for review if the children had a HPV-related International Classification of Diseases, Ninth Revision, code or had been examined in the CSA clinic. Abstracted data included demographic features, clinical findings, clinical services involved, age at diagnosis, age when care was first sought, and age when symptoms were first noted. **RESULTS:** HPV was identified by clinical examination and/or biopsy for 124 children, 40 with laryngeal lesions, 67 with anogenital lesions, 10 with oral lesions, and 7 with both anogenital and oral lesions. The mean age at HPV diagnosis was 4.0 +/- 2.9 years, compared with 6.4 +/- 3.0 years for 1565 HPV-negative children. Among 108 HPV cases with data for age when symptoms were first noted, the mean age was 3.3 +/- 2.9 years (median: 2.2 years) for children with anogenital and oral HPV and 2.4 +/- 2.3 years (median: 1.9 years) for children with laryngeal HPV. Among HPV-positive patients, 56% were female, compared with 82% of HPV-negative children. Fifty-five (73%) of 75 children with anogenital HPV infections were referred to the CSA clinic for evaluation, compared with none of 49 children with laryngeal or oral HPV infections treated by the otolaryngology service. Laryngeal cases presented earlier than anogenital and oral lesions. Abuse was considered at least possible for 17 of 55 children with any CSA evaluation. The mean age of likely abused, HPV-positive children was 6.5 +/- 3.8 years (median: 5.3 years), compared with 3.6 +/- 2.3 years (median: 2.6 years) for likely not abused, HPV-positive children. The likelihood of possible abuse as a source of HPV infection increased with age. The positive predictive value of HPV for possible sexual abuse was 36% (95% confidence interval: 13-65%) for children 4 to 8 years of age and 70% (95% confidence interval: 35-93%) for children >8 years of age. **CONCLUSIONS:** The data from this epidemiologic study of HPV suggest that many anogenital and laryngeal HPV infections

among preadolescent children are a result of nonsexual horizontal transmission, acquired either perinatally or postnatally. It seems that many children >2 years of age acquire HPV infection from nonsexual contact. Different subspecialties vary greatly in their suspicion and evaluation of CSA. At this time, there remains no clear age below which sexual abuse is never a concern for children with anogenital HPV infections. Every case needs a medical evaluation to determine whether enough concern for abuse exists to pursue additional investigations.

PMID: 16199688

[Clin Cancer Res.](#) 2005 Sep 1;11(17):6155-61.

Epidermal growth factor-induced cyclooxygenase-2 expression is mediated through phosphatidylinositol-3 kinase, not mitogen-activated protein/extracellular signal-regulated kinase kinase, in recurrent respiratory papillomas.

[Wu R](#), [Abramson AL](#), [Shikowitz MJ](#), [Dannenberg AJ](#), [Steinberg BM](#).

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PURPOSE: Recurrent respiratory papillomas, caused by human papillomaviruses, are premalignant tumors that overexpress the epidermal growth factor receptor (EGFR). The goals of this study were as follows: (a) to evaluate the expression of cyclooxygenase-2 (COX-2) in papillomas, (b) to investigate the role of EGFR signaling in COX-2 expression, and (c) to determine whether COX-2 activity is important for the growth of papilloma cells. **EXPERIMENTAL DESIGN:** Immunohistochemistry, Western blotting, and real-time PCR were used to determine levels of COX-2 in papilloma and normal laryngeal tissue. Explant cultures of both normal laryngeal and papilloma cells were used to define the signaling pathways that regulate COX-2 expression and investigate the potential of targeting COX-2 as a strategy to suppress papilloma growth. **RESULTS:** COX-2 levels were markedly increased in papillomas. In vitro studies suggested that overexpression in papillomas reflected activation of EGFR-->phosphatidylinositol 3-kinase signaling. Treatment with prostaglandin E2 (PGE2) induced COX-2, whereas celecoxib, a selective COX-2 inhibitor, suppressed levels of COX-2, suggesting a positive feedback loop. Moreover, treatment with PGE2 stimulated papilloma cell growth, whereas celecoxib suppressed proliferation and induced apoptosis. **CONCLUSIONS:** Overexpression of COX-2 in papillomas seems to be a consequence of enhanced EGFR-->phosphatidylinositol 3-kinase signaling. We propose a positive feedback loop for COX-2 expression, with induction of COX-2 resulting in enhanced PGE2 synthesis and further expression of COX-2 that contributes to the growth of papillomas in vivo. These data strengthen the rationale for evaluating whether nonsteroidal anti-inflammatory drugs, prototypic COX inhibitors, will be useful in the management of respiratory papillomas.

PMID: 16144915

[Ann Otol Rhinol Laryngol.](#) 2005 Jul;114(7):499-503.

Use of the Pediatric Quality of Life Inventory to assess the health-related quality of life in children with recurrent respiratory papillomatosis.

[Lindman JP](#), [Lewis LS](#), [Accortt N](#), [Wiatrak BJ](#).

Department of Surgery, Division of Otolaryngology, University of Alabama at Birmingham, Birmingham, Alabama, USA.

OBJECTIVES: The objective of this study was to use the Pediatric Quality of Life Inventory (PedsQL), a 23-question modular instrument designed to measure the health-related quality of life (HRQOL) in children and adolescents, to compare the HRQOL in children with recurrent respiratory papillomatosis (RRP) with the HRQOLs reported for healthy children and children with other chronic medical conditions. **METHODS:** The PedsQL version 4.0 Generic Core Scales consist of 23 questions in 4 subscales (Physical, Emotional, Social, and School Functioning) for parent-proxy reporting on the HRQOL in children ages 2 to 4 years, parent reporting for children 5 to 18 years, and child self-reporting for ages 5 to 7 years (age-adjusted questions and rating scales) and 8 to 18 years. The questionnaires were administered in person or by telephone to 22 children with RRP and (or, for children 2 to 4 years of age) one parent recruited from a tertiary pediatric otolaryngology practice. The results were compared with validated norms for healthy children and scores for children whose parents reported a chronic medical condition. **RESULTS:** Compared with healthy controls, the children 5 to 18 years of age with RRP self-reported a significantly ($p < .05$) worse HRQOL as measured by the PedsQL Total Score, Psychosocial Health score (a combination of Emotional, Social, and School Functioning Scores), and Social Functioning and School Functioning scores. Self-reported scores for the children 5 to 18 years of age with RRP compared with children with other chronic illnesses followed the same trend, and the difference approached statistical significance ($p = .05$) for the School Functioning Subscale scores. The parent-proxy report (for children 2 to 18 years of age) scores for children with RRP were significantly lower ($p < .0001$) on every scale and in total compared with scores for healthy children. Compared with scores of children with other chronic medical conditions, the parent-proxy report scores were significantly lower for psychosocial health ($p = .005$) and school functioning ($p < .0001$). **CONCLUSIONS:** Children with RRP report a lower quality of life than do those who are healthy, and a quality of life similar to that of those who have other chronic medical problems. The parent reports also reflect a lower quality of life for children affected by this disease, as compared with healthy children. The PedsQL demonstrated a statistically significant low HRQOL in children with RRP; however, the clinical implications of this finding appear trivial. A distinct, disease-specific survey for RRP, if developed, would have enhanced responsiveness and sensitivity to change (due to the natural course of the disease and/or surgical treatments).

PMID: 16134343

[Lasers Surg Med.](#) 2005 Sep;37(3):192-200.

Raman spectroscopy for optical diagnosis in the larynx: preliminary findings.

[Lau DP](#), [Huang Z](#), [Lui H](#), [Anderson DW](#), [Berean K](#), [Morrison MD](#), [Shen L](#), [Zeng H](#).

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BACKGROUND AND OBJECTIVES: Raman spectroscopy (RS) provides information about molecular structure and is a potential tool for non-invasive tissue diagnosis. To determine if Raman spectra could be obtained rapidly from laryngeal tissue in vitro, and compare Raman spectra from normal, benign, and cancerous laryngeal tissue. **STUDY DESIGN/MATERIALS AND METHODS:** Forty-seven laryngeal specimens were studied using RS with signal acquisition times (SAT) between 1 and 30 second(s). Multivariate analysis was used to determine the diagnostic ability of RS compared to standard histology (n = 18, 13, and 16 respectively for normal tissue, carcinoma, and squamous papilloma). **RESULTS:** Good quality spectra were obtained with 5-second SAT. Spectral peak analysis showed prediction sensitivities of 89%, 69%, and 88%, and specificities of 86%, 94%, and 94% for normal tissue, carcinoma, and papilloma. **CONCLUSIONS:** In the larynx, spectral differences appear to exist between normal tissue, carcinoma, and papilloma. The ability to obtain spectra rapidly supports potential for future in vivo studies. Copyright 2005 Wiley-Liss, Inc.

PMID: 16127671

[Ann Otol Rhinol Laryngol.](#) 2005 Jun;114(6):463-71.

Use of interferon-alpha in recurrent respiratory papillomatosis: 20-year follow-up.

[Gerein V](#), [Rastorguev E](#), [Gerein J](#), [Jecker P](#), [Pfister H](#).

Department of Pediatric Pathology, Institute of Pathology, Johannes Gutenberg University of Mainz, Germany.

OBJECTIVES: The aim of this study was analysis of the results of use of interferon-alpha (IFN-alpha) in patients with recurrent respiratory papillomatosis (RRP) and correlation of the results with human papillomavirus (HPV) type. **METHODS:** A multicenter prospective series (42 patients from 22 hospitals) yielded 20 years of follow-up of patients with RRP and

HPV typing who were treated with IFN-alpha in doses of 3 MU/m² 3 times per week.

RESULTS: During long-term follow-up (mean +/- SD, 172 +/- 36.8 months), the rate of event-free survival evaluated by Kaplan-Meier analysis was 42.8%, and the overall survival rate was 82.6%. The HPV typing revealed an association of HPV 11 with a more aggressive disease course (64% of HPV 11 patients versus 24% of HPV 6 patients), a lower incidence of long-term response to IFN-alpha therapy (14% of HPV 11 patients versus 64% of HPV 6 patients), and a higher incidence of malignant transformation and mortality during follow-up (36% and 24%, respectively, of HPV 11 patients versus 0% of HPV 6 patients).

CONCLUSIONS: The obtained results revealed maximal effectiveness of IFN-alpha therapy in RRP patients with HPV 6 as compared with HPV 11. The association of HPV 11 with a worse long-term response to IFN-alpha therapy and a higher incidence of malignant transformation and mortality is clinically important and indicates the necessity of HPV typing in RRP patients after the first biopsy.

PMID: 16042104

[*In Vitro Cell Dev Biol Anim.* 2005 Mar-Apr;41\(3-4\):111-7.](#)

Phosphatidylinositol 3-kinase regulates early differentiation in human laryngeal keratinocytes.

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Epidermal growth factor receptor (EGFR) signaling regulates a variety of cellular functions, including proliferation, gene expression, and differentiation. Infection of laryngeal epithelial cells by human papillomaviruses causes recurrent respiratory papillomas, benign tumors characterized by an altered pattern of differentiation. Papilloma cells overexpress the EGFR and have constitutively active extracellular signal-regulated kinase (ERK) and enhanced phosphatidylinositol 3-kinase (PI3K) activity, but overexpression of the lipid phosphatase PTEN (Phosphatase and Tensin Homolog) reduces activation of Akt by PI3K. We hypothesized that the altered differentiation of papillomas reflects these changes in signaling from the EGFR-ERK and PI3K-Akt pathways and that one or both of these pathways is required for the normal differentiation process in mucosal epithelium. Inhibiting either the enzymatic activity or the synthesis of PI3K in uninfected laryngeal cells blocked expression of keratin-13 (K13), a protein induced during normal differentiation. In contrast, inhibiting activation of ERK had minimal effect. Using ribonucleic acid interference to reduce protein levels of integrin-linked kinase 1 or phosphoinositide-dependent protein kinase 1, intermediates in the activation of Akt by PI3K, or reducing levels of Akt-1 itself did not inhibit K13 expression by normal laryngeal keratinocytes. We conclude that PI3K activation is an important regulator of expression of K13, a marker for the normal differentiation process in human mucosal keratinocytes, that this function does not require activation of Akt-

1, and that the failure to express K13 in papilloma cells is not because of reduction in activated Akt.

PMID: 16029072

[Pharmacotherapy](#). 2005 Jul;25(7):977-89.

Cidofovir for the treatment of recurrent respiratory papillomatosis: a review of the literature.

[Shehab N](#), [Sweet BV](#), [Hogikyan ND](#).

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Recurrent respiratory papillomatosis (RRP) is a rare but potentially severe disease caused by papillomavirus, most often types 6 and 11. The disease, which occurs in both juvenile and adult forms, is characterized by benign epithelial tumors of the airway that most frequently affect the larynx but can also spread along the entire aerodigestive tract. Recurrent respiratory papillomatosis is the most common benign neoplasm of the larynx in children and the second most frequent cause of childhood hoarseness. Standard treatment, which is palliative only, consists of surgical excision of papillomata to maintain airway patency and improve voice quality. Recurrence despite repeated surgical procedures is the rule. To date, incorporation of adjuvant treatments has not been reliably beneficial in altering the disease course. Several case series have described promising results with cidofovir, a cytosine nucleoside analog with antiviral activity. To evaluate the data available on the safety and efficacy of cidofovir for the treatment of RRP, we conducted a MEDLINE search for all case reports or series from January 1966-August 2004 describing cidofovir therapy in either adults or children with RRP. The bibliographies of qualifying articles were also searched for relevant references. In both adults and children with mild-to-severe RRP, intralesional administration of cidofovir directly into the site of papillomata was associated with partial-to-complete regression of papillomata, improvement in voice quality and airway status, and decreased need for surgery. Wide variation in intralesional cidofovir dose (2-57 mg), frequency (every 2-8 wks), and duration (4 mo-4 yrs) was found. Successful outcomes have also been reported with intravenous cidofovir, but data are limited to three case reports. Rash, headache, and precordialgia were the only adverse effects reported with intralesional cidofovir. Nephrotoxicity and neutropenia secondary to either intralesional or intravenous cidofovir were not observed. Long-term risks associated with intralesional administration remain to be seen. Further studies are necessary to determine the most appropriate dose, frequency, and duration of therapy, and to fully characterize the safety profile of cidofovir when given intralesionally.

PMID: 16006276

[Klin Lab Diagn.](#) 2005 May;(5):51-3.

[RT-PCR-based evaluation of the activity of human papilloma virus infection in relapsing papillomatosis of the larynx]

[Article in Russian]

[Manzeniuk OIu](#), [Ashurov ZM](#), [Moskalets OV](#), [Kadyrova EV](#), [Sloeva AI](#).

RT-PCR-based examination of papilloma samples obtained from patients with relapsing papillomatosis of the larynx showed an incidence rate of human papilloma virus (HPV) amounting to 89%. The viral load level of the studied samples, when measured by concurrent RT-PCR HPV, differed by more than 130 times. It made, in the untreated patient, $1.2 \times 10(9)$ hormonal equivalents/ml, i.e. 13-fold higher versus the patient who received pathogenetic therapy. Thus, the approach in question provides for a possibility to monitor the activity of papilloma viral infection and to evaluate the efficiency of different variations of pathogenetic therapy because the "classic" variant of PCR-detection is not informative in the discussed case.

PMID: 15986802

[Vestn Ross Akad Med Nauk.](#) 2005;(5):25-8.

[Treatment of patients with respiratory papillomatosis: experience analysis]

[Article in Russian]

[Zegner VG](#), [Ashurov ZM](#), [Sloeva AI](#).

The authors of the article analyze clinical observations of 240 patients with respiratory papillomatosis (aged 7 months to 56 years), treated in the ETN clinic of Moscow Regional Research Clinical Institute in 1984-2003 using endolaryngeal microsurgical techniques, such as ultrasound desintegration and laser photodestruction of papillomas. Additional therapy included immunocorrection with T-activin and leukomax, discrete plasmapheresis, antiviral therapy with zovirax, and photodynamic therapy. Having compared various methods and their combinations, the authors conclude that "clinical recovery" (no relapses within more than 2.5 years), was achieved in 41.4 +/- 0.5% - 77.8 +/- 0.2% patients.

PMID: 15960200

[N Engl J Med.](#) 2005 Jun 16;352(24):e22.

Images in clinical medicine. Recurrent respiratory papillomatosis with lung involvement.

[Glikman D](#), [Baroodv FM](#).

University of Chicago, Chicago, IL 60637, USA.

No abstract available.

PMID: 15958801

[Arkh Patol](#). 2005 Mar-Apr;67(2):27-9.

[Clinical and morphological characteristics of laryngeal papillomatosis in children]

[Article in Russian]

[Zaitsev VS](#), [Tsinzerling VA](#), [Tsvetkov EA](#).

Respiratory papillomatosis was studied clinically and morphologically in 35 children with immunohistochemical detection of human papilloma virus. More frequent detection of viral antigen in the superficial layers of the epithelium in children with frequent recurrences was observed. Correlation between clinical efficiency of prospidine and immunohistochemical findings was noted. Suggestion on the indirect link between viral damage and intranuclear inclusions (although viral antigen in these inclusion was not observed) was made.

PMID: 15938116

[Otolaryngol Pol](#). 2005;59(1):119-21.

[A case of laryngeal papilloma with sudden dyspnea]

[Article in Polish]

[Pabiszczak M](#), [Wierzbicka M](#), [Borucki L](#), [Iwanik K](#).

Klinika Otolaryngologii i Onkologii Laryngologicznej w Poznaniu.

Laryngeal papilloma is one of the most common non-malignant tumors of the larynx. In adult they are included to pre-cancerous diseases. In morphological examination, it is a solid tumor. Often it is possible to cure them during one surgical procedure. The disease is mostly localized on the anterior commissurae region, vocal fold, ventricles, and on the laryngeal

surface of the epiglottis. If the malignant transformation is suspected, a large excision with margin has to be performed, completed by a histological evaluation. A case of a huge laryngeal papilloma with dyspnea is presented.

PMID: 15915931

[Ann Otol Rhinol Laryngol.](#) 2005 Apr;114(4):289-95.

Role of vascular endothelial growth factor-A in recurrent respiratory papillomatosis.

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Vascular endothelial growth factor-A (VEGF-A) is known to play an important role in the angiogenic response essential for tumor growth in a variety of human and experimental tumors. This study was designed to investigate whether VEGF-A may play a role in the pathogenesis of recurrent respiratory papillomatosis (RRP). A retrospective study with institutional review board approval was performed at a tertiary care medical center on 12 patients with a history of laryngeal RRP. Their ages at the time of initial diagnosis ranged from 19 to 96 months (mean, 56 months). All patients had involvement of right and left true vocal cords. All patients required multiple endoscopic procedures (range, 4 to 66; mean, 12). Normal pediatric larynx samples from 5 autopsy patients were used as controls. Formalin-fixed, paraffin-embedded sections of laryngeal squamous papillomas from the 12 patients with a diagnosis of RRP and the 5 control patients were examined by in situ hybridization for the presence of messenger RNA (mRNA) for VEGF-A and vascular endothelial growth factor receptor 1 (VEGFR-1) and vascular endothelial growth factor receptor 2 (VEGFR-2). The biopsy specimens were from the true vocal cord (N = 10) or subglottis (N = 2) in the patients with RRP and consisted of large sections of larynx including the true vocal cord in the control patients (N = 5). Strong expression of VEGF-A mRNA was noted in the squamous epithelium of papillomas of all 12 patients. Strong expression of VEGFR-1 and VEGFR-2 was noted in the endothelial cells of the underlying vessels in all 12 patients. Neither strong labeling of VEGF-A mRNA nor labeling of its receptors was noted in the control patients. We conclude that the angiogenic growth factor VEGF-A is strongly expressed in the epithelium of squamous papillomas in RRP. Also, VEGFR-1 and VEGFR-2 mRNAs are strongly expressed by underlying vascular endothelial cells, suggesting an important role in the pathogenesis of RRP.

PMID: 15895784

[Int J Pediatr Otorhinolaryngol.](#) 2005 May;69(5):597-605.

Extraesophageal acid reflux and recurrent respiratory papilloma in children.

[McKenna M](#), [Brodsky L](#).

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OBJECTIVE: Recurrent respiratory papillomatosis (RRP) is a benign infectious disease which is caused by the human papilloma virus (HPV). When it infects the larynx, hoarseness and airway obstruction are often the presenting symptoms. Latent virus is found in the laryngeal mucosa of many more patients than exhibit the disease. The factors which lead to virus activation have not been identified, however, extra-esophageal acid reflux disease (EERD) has been suggested as one of these factors. **METHODS:** This is a case series of four patients with RRP who had increase in severity of their disease with the recognition of concurrent extra-esophageal acid reflux. The clinical course of the papillomatosis and the diagnosis and treatment of reflux are compared over time. **RESULTS:** In all four cases, with identification and treatment of the EERD, control of the RRP improved, and in at least two patients, was complete with resolution of the EERD. Lapses in compliance with medications or behavioral and dietary recommendations in three out of four patients led to a rebound in symptoms and signs of RRP, including worsening of vocal quality and the endoscopic appearance of the larynx. **CONCLUSION:** The clinical course of these patients suggests a link between the presence of EERD and RRP. The inflammation induced by chronic acid exposure may result in the expression of HPV in susceptible tissues. Prompt diagnosis and effective treatment of EERD should be considered in all patients with difficult to control RRP or with clinical presentation or endoscopic signs of EERD.

PMID: 15850681

[J Voice](#). 2005 Mar;19(1):146-50.

Subglottic jet ventilation for suspension microlaryngoscopy.

[Rubin JS](#), [Patel A](#), [Lennox P](#).

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High-frequency subglottic jet ventilation was used in 142 consecutive adults with grade I airways treated with suspension microlaryngoscopy. All cases were managed by the senior anesthesiologist (AP) and the large majority by the senior surgeon (JR), between 2000 and 2002. The laser was used in 30% of cases. There were few complications, none serious, associated with this technique in this series. The subglottic catheter never proved impossible to insert and only needed to be replaced by the supraglottic catheter in two patients because

of limitation of visualization of the posterior glottis. The technique was used in a wide variety of surgical pathology from benign hyperfunction-related laryngeal pathology through paralytic vocal fold conditions through papilloma. Advantages and disadvantages over traditional intubation techniques and supraglottic jet ventilation are reviewed, including such issues as ease of intubation/ventilation, surgical exposure/control, maintenance of O₂ and CO₂ levels, and use in the limited/borderline airway.

PMID: 15766860

[J Clin Virol](#). 2005 Mar;32 Suppl 1:S59-66.

Human papillomavirus (HPV) in head and neck cancer.

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The term "head and neck cancer" has been widely adopted in the recent literature, to include the lesions at several anatomic sites: the lip, oral cavity, nose and para-nasal sinuses, nasopharynx, oro-pharynx, hypo-pharynx, and larynx. In this communication, the data on human papillomavirus (HPV) involvement in oral, oro-pharyngeal, sino-nasal, and laryngeal carcinomas are reviewed. Our group was the first to present evidence on the involvement of HPV infections in both laryngeal and oral carcinogenesis, prompted by the discovery of morphological similarities between oral and cervical squamous cell lesions. The latest meta-analyses of the epidemiological studies as well as the multi-centre case-control studies have confirmed HPV as an independent risk factor for oral cancer, with a range of odds ratios (OR) between 3.7 and 5.4. Until 2002, 4768 oral carcinomas have been analysed for HPV DNA, and 22% were reported to contain HPV by any of the detection techniques. Of all non-genital cancers, tonsillar carcinomas appear to have the highest prevalence of HPV. By the end of 2002, 422 cases of tonsillar carcinoma have been analyzed for the presence of HPV DNA, with the overall detection rate of 51%. HPV 16 is the most prevalent HPV type found in 84% of HPV DNA-positive tumours. HPV seems to be mainly episomal in tonsillar carcinomas, but the significance of this observation is still obscure. Interestingly, patients with HPV 16-positive tumours seem to have a better overall- and disease-specific survival, as compared with the HPV-negative group. To date, 1041 sino-nasal papillomas have been analysed for HPV and 347 (33%) cases have been positive, whereas of the 322 sino-nasal carcinomas analysed so far, 70 (22%) have been positive for any HPV type. Laryngeal squamous cell papilloma and recurrent respiratory papillomatosis (RRP) are well-established HPV-induced tumours, whereas the role of HPV in laryngeal carcinomatosis remains controversial. The molecular mechanisms of HPV-associated carcinogenesis of the head and neck require further study.

PMID: 15753013

[Acta Otorrinolaringol Esp.](#) 2005 Jan;56(1):22-4.

[Cidofovir activity in infantile recurrent respiratory papillomatosis]

[Article in Spanish]

[Palomar Asenjo V](#), [Palomar Garcia V](#), [Soteras Olle J](#), [Ruiz Giner A](#).

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We report the case of a 4 year old boy that arrived to our department referring a 4 months history of dysphony complicated in the last week with inspiratory estridor. He was diagnosed of respiratory papillomatosis. In the next 10 months he underwent 6 operations to remove papillomas with CO2 laser. In the last operation we decided to add adjuvant therapy with intralesional injections of cidofovir once all papillomas had been removed. After more than a year of monitoring he remains disease free.

PMID: 15747720

[Otolaryngol Head Neck Surg.](#) 2005 Mar;132(3):392-4.

Incidence, age at onset, and potential reasons of malignant transformation in recurrent respiratory papillomatosis patients: 20 years experience.

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Forty-two patients with recurrent respiratory papillomatosis (RRP) were accepted into a multicenter prospective study in 1983 to 1990, treated with alfa-IFN 3 MU/m 2 3 times a week and then followed-up until August 1, 2003. All the patients who had disease progression with pulmonary spread were characterized by insufficient response to IFN-therapy and detection of HPV type 11. Five patients (4/5 smokers) presented malignant transformation in lungs or nasopharynx (mean RRP duration was 27.2 +/- 8 years from RRP onset and 14.6 +/- 6.3 years from pulmonary spread until malignant transformation) with persistent RRP in larynx. The results of long-term follow-up in RRP patients with HPV 11 underline the necessity of reanalyzing the current therapy.

PMID: 15746849

[Laryngoscope](#). 2005 Mar;115(3):552-4.

Delivery of cidofovir to respiratory papillomas of the distal trachea.

[Cullen RD](#), [Zdanski C](#).

Department of Otolaryngology-Head and Neck Surgery, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina, USA.

No abstract available.

PMID: 15744176

[Arch Otolaryngol Head Neck Surg](#). 2005 Feb;131(2):99-105.

Clinical trial of photodynamic therapy with meso-tetra (hydroxyphenyl) chlorin for respiratory papillomatosis.

[Shikowitz MJ](#), [Abramson AL](#), [Steinberg BM](#), [DeVoti J](#), [Bonagura VR](#), [Mullooly V](#), [Nouri M](#), [Ronn AM](#), [Inglis A](#), [McClay J](#), [Freeman K](#).

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OBJECTIVE: To determine the efficacy of photodynamic therapy (PDT) with meso-tetra (hydroxyphenyl) chlorin (m-THPC) photosensitizer for recurrent respiratory papillomatosis. **DESIGN:** Parallel-arm, randomized trial of patients requiring surgery at least 3 times yearly with single PDT 6 or 18 months after enrollment and 12-month follow-up. Disease extent was scored and papillomas were removed during direct endoscopy every 3 months after enrollment. **SETTING:** Tertiary medical centers. **PATIENTS:** Of 23 patients aged 4 to 60 years enrolled in the study, 15 patients, plus 2 in the late group without PDT owing to airway risk, completed the study. Six patients withdrew voluntarily after PDT. **INTERVENTION:** Intravenous administration of m-THPC 6 days before direct endoscopic PDT with 80 to 100 J of light for adults and 60 to 80 J for children. **MAIN OUTCOME MEASURES:** Difference in severity scores between the early and late groups and between pre- and post-PDT scores for all patients. Secondary measures were the associations between baseline characteristics and response and changes in immune response and the prevalence of latent viral DNA. **RESULTS:** There were significant differences between groups, with marked improvement in laryngeal disease across time after PDT ($P = .006$). Five of 15 patients were in remission 12 to 15 months after treatment, but there was recurrence of disease after 3 to 5 years. Tracheal disease was not responsive to PDT. No change occurred in the prevalence of latent human papillomavirus DNA. The immune response to virus improved with clinical response. **CONCLUSIONS:** Use of m-THPC PDT reduces the severity of laryngeal papillomas,

possibly through an improved immune response. Failure to maintain remission with time suggests that this is not an optimal treatment.

PMID: 15723939

[Lin Chuang Er Bi Yan Hou Ke Za Zhi](#). 2004 Sep;18(9):516-8.

[Clinical pilot study of HPV6b L1 virus-like particles as immune therapy for juvenile larynx papillomatosis]

[Article in Chinese]

[Chen B](#), [Zhao K](#), [Liu X](#), [Xu Y](#), [Xiang S](#), [Yang J](#), [Chen X](#).

Department of Otolaryngology, the Second Affiliated Hospital of Wenzhou Medical College, Wenzhou, 325027, China.

OBJECTIVE: To study the safety and the immunogenicity of HPV6b virus-like particles (VLP) in children with juvenile laryngeal papilloma (JLP). The result of therapy is observed. **METHOD:** HPV6b VLP were expressed with HPV6b L1 recombinant baculovirus in sf-9 insect cells. Ten case of recurrent JLP were immunized with HPV6b VLP in 5, 10, 25 microg doses progressively and any local or systemic adverse events were recorded. By ELISA was used to detect the serum HPV6b VLP antibody (Ab) of JLPs samples in therapy different stage. Seven cases of JLP were used DTH test. To understand the effects of VLP on disease prognosis subjects will be examined by fibrolaryngoscope. **RESULT:** All subjects did not experience local or systemic adverse events and specific serum antibody against HPV6b L1VLP was produced in JLP immunized. The A value of sera antibody in the first dose group have completed (0.310 +/- 0.012) were higher than that of pro-immune (0.110 +/- 0.035) (t = 4.673, P < 0.01). There was a significant difference of serum mean HPV6b Ab A value between JLP's patients immunized (0.772 +/- 0.013) and the control group (0.153 +/- 0.014) (t = 15.45, P < 0.01), 7 samples have male response of DTH test. All patients didn't recurrent papilloma after receiving treatment. **CONCLUSION:** HPV6b VLP have immunogenicity and safety as therapy for JLP patients, and HPV6b VLP may be used in prophylactic and therapeutic vaccine for JLP.

PMID: 15696942

[Vestn Ross Akad Med Nauk](#). 2004;(12):36-9.

[Papilloma virus infection in pretumor and tumor masses of the larynx]

[Article in Russian]

[Balukova OV](#), [Shcherbak LN](#), [Savelov NA](#), [Ungiadze GV](#), [Zborovskaia IB](#).

There has been recent evidence suggesting that papilloma virus infection is of no small importance in the pathogenesis of tumors of the head and neck. This study has involved a screening of the mucosa having laryngeal pretumors and tumors for papilloma virus infection by polymerase chain reaction and immunohistochemistry. Specimens were studied in 130 patients. All the patients with laryngeal papillomatosis were found to have human papilloma virus (HPV) types 6 and 11. HPV-18 was detected in 6 (13%) of 48 cases of laryngeal cancer and in 4 (9%) of 46 cases of laryngeal mucosal precancer. Mixed HPV infection of 2-3 different types was revealed in 6 (20%) of 30 HPV-positive patients. Such a wide survey of laryngeal pretumors and tumors in the Russian population for virus infection has been conducted for the first time.

PMID: 15678687

[Hum Pathol](#). 2004 Nov;35(11):1419-22.

Metachronous squamous cell carcinomas evolving from independent oropharyngeal and pulmonary squamous papillomas: association with human papillomavirus 11 and lack of aberrant p53, Rb, and p16 protein expression.

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Squamous cell carcinoma evolving from squamous papilloma in both the upper and lower respiratory tract in the same patient is uncommon. The molecular mechanisms underlying the progression have not been well investigated. We herein describe a case of squamous cell carcinoma arising from respiratory papilloma in two independent occasions. The patient initially had oropharyngeal squamous cell carcinoma arising in a squamous papilloma at the age of 25 years. He subsequently developed squamous cell carcinoma in the left lower lobe of the lung, which was also associated with squamous papilloma, 8 years after the complete excision of the oropharyngeal lesion. Polymerase chain reaction-based broad-spectrum human papillomavirus DNA amplification and typing showed the presence of human papillomavirus type 11 DNA in both oropharyngeal and pulmonary tumors. Immunohistochemical studies showed that the expression status of p53, Rb, and p16 proteins was unaltered during tumor progression. These observations indicate that human papillomavirus 11-associated neoplastic transformation and tumor progression in the respiratory tract may not involve aberrant regulation of the p53 and Rb signaling pathways.

PMID: 15668901

[J Clin Pathol. 2005 Jan;58\(1\):51-5.](#)

The characteristics of human papillomavirus DNA in head and neck cancers and papillomas.

[Major T](#), [Szarka K](#), [Sziklai I](#), [Gergely L](#), [Czegledy J](#).

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AIM: To determine the prevalence, type, physical state, and viral load of human papillomavirus (HPV) DNA in cases of head and neck cancer and recurrent respiratory papillomatosis (RRP). METHODS: The prevalence and type of HPV DNA was determined in 27 fresh frozen tissue specimens from patients with head and neck cancers and 16 specimens from 10 patients with RRP by MY09/MY11 and GP5+/GP6+ nested polymerase chain reaction (PCR) and subsequent restriction enzyme cleavage. The physical state of HPV DNA was analysed by E1, E2, and E1E2 specific PCRs and Southern blot hybridisation (SBH). RESULTS: HPV DNA was detected in 13 of 27 cancers and 10 of 10 papillomas. Both low risk HPV-6 and HPV-11 and high risk HPV-16 were present in cancers in low copy numbers, whereas papillomas exclusively harboured low risk HPV-6 and HPV-11. E1E2 PCRs failed to determine the physical state of HPV in cancers except one case where HPV-6 DNA was integrated. In contrast to cancers, all papillomas showed the episomal state of HPV DNA and a relatively higher viral load. CONCLUSIONS: Based on the prevalence, type, physical state, and copy number of HPV DNA, cancers and papillomas tend to show a different HPV DNA profile. The 100% positivity rate of low risk HPV types confirms the role of HPV-6 and HPV-11 in the aetiology of RRP.

PMID: 15623482

[J Med Virol. 2005 Feb;75\(2\):332-5.](#)

Successful use of intralesional and intravenous cidofovir in association with indole-3-carbinol in an 8-year-old girl with pulmonary papillomatosis.

[de Bilderling G](#), [Bodart E](#), [Lawson G](#), [Tuerlinckx D](#), [Remacle M](#), [Naesens L](#), [De Clercq E](#), [Snoeck R](#).

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We report the history of an 8-year-old girl who was treated for suspected lung lesions of respiratory papillomatosis with Indole-3-Carbinol, local and intravenous injections of Cidofovir for 27 months. This is the first report where a complete cure of the lung lesions occurred in a child, and was sustained for at least 24 months.

PMID: 15602729

[Ann Otol Rhinol Laryngol.](#) 2004 Nov;113(11):859-62.

Serial office-based intralesional injection of cidofovir in adult-onset recurrent respiratory papillomatosis.

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Intralesional injection of cidofovir is used in the treatment of recurrent respiratory papillomatosis as an adjuvant therapy after microsurgical excision and CO2 laser therapy. This is conventionally done in the operating room with the patient under general anesthesia. We report our experience with 5 patients with adult-onset recurrent respiratory papillomatosis who were treated with intralesional injections of cidofovir after recurrence of their papillomatosis. These injections were given monthly in the office without the use of general anesthesia. Before cidofovir injection, all patients required repeated CO2 laser treatments at intervals of less than 5 months. We injected 7.5 mg/mL of cidofovir transorally into the papillomas under office telescopic control. These injections were given monthly for 3 consecutive months. The patients were then followed up for 2 to 10 months after therapy to monitor the size of the papillomas. In all 5 patients, partial remission of the laryngeal papillomatosis was noted during the follow-up period. Their need for repeat microsurgery was delayed, and their vocal function improved. Intralesional injection of cidofovir in an office setting appears to be safe and effective. It might be more convenient and cost-effective than performing the same procedure in the operating room with the patient under general anesthesia.

PMID: 15562893

[J Laryngol Otol.](#) 2004 Oct;118(10):750-6.

2',5'-Oligoadenylate synthetase activity analysis and human papilloma virus typing as prognostic factors in patients with recurrent respiratory papillomatosis.

[Gerein V, Rastorguev E, Gerein J, Lodemann E, Pfister H, Draf W, Desloovere C.](#)

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OBJECTIVE: Determination of early prognostic factors in patients with recurrent respiratory

papillomatosis is extremely important, so the major goal of our prospective, multicentre study was to evaluate (1) the feasibility of various factors to determine prognosis of the clinical course, as well as (2) the response to interferon-alpha therapy in recurrent respiratory papillomatosis. **METHODS:** Forty-two patients with recurrent respiratory papillomatosis were treated with interferon-alpha (3 MU/m²) three times per week; mean therapy duration was 2.7 +/- 1.8 years) in 1983-1994 and followed-up until 2003. Human papilloma virus (HPV) type, recurrent respiratory papillomatosis severity and 2',5'-oligoadenylate synthetase activity were determined by standard methods and analysed for correlation with the results of long-term clinical outcome. **RESULTS AND CONCLUSION:** Patients with HPV type 11, a severity score >4, a high number of surgical procedures prior to interferon-alpha therapy and a high basal 2',5'-oligoadenylate synthetase activity should be considered at high risk of an aggressive clinical course, often with spread to lower airway passages, malignant transformation and death. Human papilloma virus type, score for recurrent respiratory papillomatosis severity, number of surgical procedures and 2',5'-oligoadenylate synthetase activity showed significant association with response to interferon-alpha therapy and the long-term clinical course, so these factors have value in predicting prognosis in recurrent respiratory papillomatosis.

PMID: 15550179

[Curr Opin Otolaryngol Head Neck Surg. 2004 Dec;12\(6\):532-7.](#)

Current diagnostic and management trends for recurrent respiratory papillomatosis.

[Silverman DA](#), [Pitman MJ](#).

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PURPOSE OF REVIEW: The purpose of this review is to discuss recent literature regarding diagnostic and management trends for recurrent respiratory papillomatosis (RRP) published within the past year. This includes a discussion of new information regarding the epidemiology and pathogenesis of RRP and an update on adjuvant therapy and new surgical techniques. **RECENT FINDINGS:** Epidemiological studies have confirmed that juvenile-onset RRP is the most common and most aggressive form of the disease. Age at diagnosis is the most important determinant of disease severity, with younger patients requiring significantly more annual surgeries and more likely to have multicentric disease. Distal tracheal or pulmonary RRP is rare, but carries a significant increase in morbidity and mortality. Research into the pathogenesis of RRP has focused on the genetics of HPV infection and host-virus interactions, suggesting a genetic basis for host susceptibility to RRP. At the present time, surgery remains the mainstay of treatment for RRP. However, recurrence after surgery is common and the search for effective adjuvant therapies is ongoing. The antiviral drug cidofovir has demonstrated efficacy against RRP and is considered a promising new adjuvant treatment of this disease. In an attempt to minimize the

untoward effects of surgery, the pulsed-dye laser (PDL) has emerged as a safe and efficacious treatment for select patients with RRP. SUMMARY: While a cure for RRP remains elusive, there has been substantial progress in the diagnosis and management of this disease. Significant advances in clinical and basic science research have dramatically improved our understanding of the epidemiology and pathogenesis of the disease and led to the development of promising new adjuvant therapies and surgical techniques. This has translated to an improved quality of life for many patients with RRP.

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Intralesional cidofovir for pediatric recurrent respiratory papillomatosis.

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OBJECTIVE: To compare disease response among children with recurrent respiratory papillomatosis (RRP) who underwent combined surgical debulking and intralesional cidofovir injections vs repeated surgical debulking only. DESIGN: Retrospective medical record review; follow-up range: 16 to 56 months. SETTING: Tertiary care children's hospital. PATIENTS: Seven children with RRP, including 4 subjects treated with cidofovir and 3 controls matched for age and initial papilloma staging score. INTERVENTIONS: Subjects treated with cidofovir underwent combined surgical debulking and intralesional cidofovir injection every 2 months until disease remission. Control subjects underwent repeated surgical debulking at individually determined intervals. MAIN OUTCOME MEASURES: Intraoperative endoscopic photographs were retrospectively assigned papilloma staging scores. Cidofovir and control group comparisons were made using nonparametric 2-sample Wilcoxon rank-sum (Mann-Whitney) testing, and comparisons of initial and final papilloma staging scores were made using nonparametric matched-pair Wilcoxon signed-rank testing. RESULTS: The final cidofovir group scores were significantly lower than the control group scores ($P < .05$). Within-group differences between initial and final scores were not significant (cidofovir group, $P = .07$; control group, $P = .29$). CONCLUSIONS: Four children with RRP were safely and successfully treated with intralesional cidofovir injection. Consideration should be given to using cidofovir more widely for treatment of pediatric RRP. Larger numbers in the cidofovir and control groups are needed in future studies to determine the true impact of cidofovir on management of this disease.

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[Diagn Cytopathol](#). 2004 Dec;31(6):407-12.

Recurrent respiratory papillomatosis: cytopathological findings in an unusual case.

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Recurrent respiratory papillomatosis (RRP) primarily is a disease of children and adolescents. Most patients experience spontaneous regression at a later age, while others continue to be affected throughout their lives. Here, we present the case of a 26-yr-old man who presented with persistent cough, worsening dyspnea, and development of pneumothorax. Eight years prior, he had presented with similar complaints and an evaluation at that time had showed RRP. Follow-up since that time showed recurrent disease managed by multiple surgical procedures. At the most current admission, an ultrasound-guided fine-needle aspiration (FNA) of the lung showed numerous papillary tissue fragments and single atypical squamous cells consistent with recurrent RRP. To our knowledge, morphological findings of RRP have been reported rarely. copyright (c) 2004 Wiley-Liss, Inc.

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Prognostic factors of recurrent respiratory papillomatosis spread to lower airway passages.

[Valentin G](#).

No abstract available.

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Analysis of a staging assessment system for prediction of surgical interval in recurrent respiratory papillomatosis.

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INTRODUCTION: A staging system for assessment of recurrent respiratory papillomatosis (RRP) has been in use over the last 3 years for 17 patients at our children's hospital.

OBJECTIVE: To evaluate a staging system for assessment of RRP on the basis of the predictive value on the surgical interval of: anatomic staging system score, urgency of intervention, voice quality, and stridor. To assess effect on surgical interval of the age of patient at time of surgery and use of adjuvant therapy. To develop a model based on the staging criteria to predict need for adjuvant therapy. **DESIGN:** Validation cohort. **SETTING:** Academic children's hospital. **RESULTS:** Estimated time to surgery decreased by "x days": "independent variable" "(95% CI)" as follows. Four days: each 1 point in total anatomical score (0.2, 8); 120 days: total anatomical score >20 (37,203); 143 days: urgent versus scheduled surgery (42, 243); 100 days: aphonic versus normal voice (-211, 343); 31 days: abnormal versus normal voice (-281, 343); 125 days: stridor at rest versus no stridor (-31, 281); 109 days: stridor with activity versus no stridor (19, 198); 26 days: each 1 year decrease in age (22, 30). Adjuvant therapy delays next surgery by 32 days (-4, 69) and average scores decreased while on adjuvant therapy. **CONCLUSIONS:** Elements of our proposed staging system are effective in prediction of surgical interval with statistical significance achieved for total anatomical scores, urgency of intervention and stridor with activity versus no stridor. This study is pilot in nature and provides a framework upon which future studies can be based. The analysis of a larger, more severity diverse population could yield results which lead to a model capable of effectively predicting future surgical interval based on a weighted prediction score calculated from age, comorbidities, anatomic staging score, and clinical staging score.

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Recurrent respiratory papillomatosis in Ibadan, Nigeria.

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BACKGROUND: Recurrent respiratory papillomatosis (RRP), the most common benign neoplasm of the larynx, usually results in upper airway obstruction that is most often misdiagnosed as lower airway disease in children. The prevalence of RRP and various aspects of its clinical course are still unknown with a dearth of literature on this in Nigeria. This study aims at presenting the clinical profile of RRP as seen in the University College Hospital, Ibadan, Nigeria. **METHODOLOGY:** A retrospective study of 43 cases of histologically confirmed RRP over a fifteen-year period in the Otorhinolaryngology Department of the University College Hospital Ibadan. **RESULTS:** There were 28 (65.1%) males and 15 (34.9%) females with mean age of 8.7 years (range 2-23 years). Thirty-two

patients (74.4%) were between 110 years with the highest incidence occurring at the 6-10 year age group (39.5%). Forty-one patients (95.3%) belonged to low social classes V and IV. Thirty-one patients (72%) presented within 1 year of onset of symptoms. All the patients were hoarse with 70% of those dyspnoeic at presentation having emergency tracheostomy. The lesions involved the vocal cords and anterior commissure mostly. There were no recurrences in 23 patients (53.5%) while twenty patients (46.5%) had 2 to 5 recurrences. CONCLUSION: Sequelae of RRP in Children may be grave, thus a high index of suspicion is needed in a patient with progressive voice change exceeding six weeks and unresponsive to standard medical therapy.

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Remote intrapulmonary spread of recurrent respiratory papillomatosis with malignant transformation.

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Recurrent respiratory papillomatosis is the most common neoplasm of the larynx in childhood. Extension into lung parenchyma occurs in less than 1% of patients and has a low risk of malignant transformation. Treatment options for intrapulmonary spread have shown limited success. We describe a case of recurrent respiratory papillomatosis with extensive parenchymal involvement and adenosquamous carcinoma in a 14-year-old girl.

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Interferon alpha-2b as adjuvant treatment of recurrent respiratory papillomatosis in Cuba: National Programme (1994-1999 report).

[Nodarse-Cuni H](#), [Iznaga-Marin N](#), [Viera-Alvarez D](#), [Rodriguez-Gomez H](#), [Fernandez-Fernandez H](#), [Blanco-Lopez Y](#), [Viada-Gonzalez C](#), [Lopez-Saura P](#); [Cuban Group for the Study of Interferon in Recurrent Respiratory Papillomatosis](#).

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Respiratory papillomatosis is a life-spoiling disease due to its high recurrence rate. Interferon (IFN)alpha-2b treatment, adjuvant to surgery, was assessed for its contribution to disease control and patient quality of life improvement. One hundred and sixty-nine patients (85

children and 84 adults) were included after surgical removal of the lesions followed by intramuscular IFN alpha-2b (Heberon alfa R, Heber Biotec), starting with 10(5) IU/Kg weight in children or 6 x 10(6) IU in adults, three times per week. The dose was reduced monthly, if no relapses occurred, until a monthly maintenance with 5 x 10(4) IU/Kg of weight in children or 3 x 10(6) IU in adults up to two years. In case of relapse, it was surgically removed and the patient returned to the higher dose level. The relapse frequency decreased significantly in 77 percent (69/90) of the recurrent patients both in children (34/46, 74 per cent) and adults (35/44, 79 per cent). Among patients included after their first papilloma, 67 per cent (44/66) had complete (no relapses) or partial (only one relapse) responses (children: 15/33, 45 per cent; adults 29/33, 88 per cent). One hundred and eighteen patients (73 per cent) concluded the treatment without lesions (children: 58 per cent; adults 82 per cent), while the rest showed a significant reduction in the number and size of lesions. IFN was well tolerated. Sixty-two patients (38 per cent) did not have adverse events. The main adverse reactions were fever (59 per cent), chills (24 per cent), arthralgias and myalgias (14 per cent) and headache (10 per cent). One patient developed anti-IFN alpha neutralizing antibodies and became resistant to treatment with recombinant IFN alpha-2b; he responded to natural leucocyte IFN alpha. Treatment with IFN alpha-2b, as an adjuvant to surgery represents a favourable and safe therapeutic alternative for patients with recurrent respiratory papillomatosis.

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