# RRP Medical Reference Service

**An RRP Foundation Publication**

**edited by**

**Dave Wunrow and Bill Stern**


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## Preface

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

This issue focuses on a selection of references with abstracts from recent (2003 and later) RRP related publications.These listings are sorted in approximate reverse chronological order as indicated by the "Unique Identifier" 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
Unique identifier

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

*Otolaryngol Head Neck Surg. 2003 Jun;128(6):788-94.*

**Intralesional cidofovir for the treatment of severe juvenile recurrent respiratory papillomatosis: long-term results in 4 children.**

Milczuk HA.

Department of Otolaryngology-Head and Neck Surgery, Oregon Health and Science University, Portland, OR 97239-3096, USA. milczukh@ohsu.edu

OBJECTIVE: We sought to determine the efficacy of intralesional injection of cidofovir in improving resolution of recurrent respiratory papillomatosis (RRP).Study design and setting We conducted a prospective, observational trial at an academic tertiary children's hospital. RESULTS: Four children with RRP requiring more than 6 surgical excisions per year were treated with intralesional cidofovir. Cidofovir (5 mg/mL) was injected into airway sites where papillomas had just been excised using sharp technique. Each patient had 6 treatments performed 6 to 8 weeks apart. Biopsies confirmed benign papilloma lesions in all cases. During treatment with intralesional cidofovir there was diminished growth of the papillomas in each patient. Once cidofovir treatment was stopped, the rate of regrowth and frequency of surgical excision returned to pretreatment levels in 3 of the 4 patients. CONCLUSIONS: Intralesional cidofovir may provide benefit in reducing the rate of RRP growth while under treatment, but RRP severity returned to pretreatment levels once cidofovir treatment was stopped using this treatment program.

Unique Identifier – 22709067

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*Stat Med. 2003 Jun 30;22(12):1989-98.*

**Implications of genetic traits on vaccine efficacy.**

Murthy BN.

National Institute of Epidemiology, Mayor V.R. Ramanathan Road, Chetput, Chennai-600 031, Tamil Nadu, India.

Literature on genetic screening in the community suggests that people having specific genotypes may either get or protect from infection, for example, malaria, human papilloma virus, and haemophilic influenza, for which vaccines are either already developed or being targeted. In such a situation, the evaluation of the efficacy of vaccine in the community needs to be examined with caution. In this paper, I present a method for the estimation of vaccine efficacy (VE) in the presence of genetic traits/component (theta) and the sample size required

to estimate the 95 per cent CI with a given relative width for the estimated vaccine efficacy. Considering true efficacy ranging from 40 to 80 per cent and the possible values of the genetic component (theta) ranging from 0 to 60 per cent, the VE was estimated. The 95 per cent confidence intervals (CI) for the estimated VE for relative widths (R) 1.0 and 0.1 were computed. The sample sizes required for each of the unvaccinated and vaccinated cohorts were computed for estimating the 95 per cent CI for given incidence rates in the unvaccinated (Iu) cohort. In the presence of genetic traits I found that the VE was consistently overestimated. There existed change in the location as well as the asymmetry of the 95 per cent CIs over the point estimate of VE. The sample size required for estimating 95 per cent CI of VE was substantially reduced, resulting in savings. The more the genetic component (theta) affecting disease in the community, the more the savings in sample size. I examined the above estimators for (i) VE, (ii) 95 per cent CI for VE and (iii) sample size required for estimating 95 per cent CI of VE using the real-life data from the Haemophilus influenzae type b vaccine trial conducted in Finland and the global genetic structure of encapsulated H. influenza. Because of escalated VE and large savings in sample size for estimating the 95 per cent CI for VE, I recommend that the design should consider the genetic component that causes/protects from infection/disease for the evaluation of efficacy of vaccine in the field. 

Unique Identifier – 22687301

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*Zhonghua Er Bi Yan Hou Ke Za Zhi. 2002 Aug;37(4):296-9.*

**[Phonomicrosurgical management of the disease of vocal fold]**

[Article in Chinese]

Zhang X, Yang D, Wang N, Liu D, Cheng J.

Department of Otorhinolaryngology, China-Japan Friendship Hospital, Beijing 100029, China. jncheng@21cn.com

OBJECTIVE: To find a way of reserving normal high quality phonatory function after vocal cord surgery. METHODS: Various benign lesions (vocal nodules, polyp of vocal cord, cyst of vocal cord, etc) as well as premalignant lesion and early glottic cancer were treated with minimally excision, lateral microflap, medial microflap, submucosal infusion, mucosal stripping or epithelium stripping of phonomicrosurgical techniques to achieve minimally invasion. RESULTS: The 1,044 (99.8%) patients suffering from vocal nodules, polyp or cyst and 12 Reinke's edema achieved a normal phonation within a week. The recovery of normal phonation in 20 Reinke's edema, 31 vocal cases needed 1-3 months, by mucosal stripping. The restoration of phonation on 5 papilloma, 36 early malignancy were better than trans-cervical operation. After 5 year follow-up, 3 cases of vocal cord premalignant lesions received the re-stripping operation. 32 cases of early glottic cancer remained tumor free, 5 cases relapsed and 2 cases received the re-stripping operation, and 2 cases received

laryngectomy operation. CONCLUSION: The phonomicrosurgery may cure vocal disease and reserves good vorce function.

Unique Identifier – 22657484

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*Zhonghua Er Bi Yan Hou Ke Za Zhi. 2000 Oct;35(5):384-6.*

**[The relationship between tracheotomy and intra-tracheal papilloma progression in children]**

[Article in Chinese]

Chen X, Liu D.

Department of Otorhinolaryngology Head and Neck Surgery, Affiliated Beijing Tongren Hospital, Capital University of Medical Sciences, Beijing 100730, China. iamsuperstar@263.net

OBJECTIVE: To clarify the relationship between tracheotomy and intra-tracheal papilloma progression and introduce the experience of managing dyspnea in the hospital. METHODS: Children who were treated in ENT department of Tongren Hospital between 1992 and 1997 were reviewed in this essay. There were totally sixty-two children (thirty-two boys and thirty girls) with laryngeal papilloma and recurrent respiratory papillomatosis enroled in the series. RESULTS: Among 33 non-tracheotomied children the intra-tracheal lesions were found in only 2 cases (6.1%). There were 17 (80.9%) cases presented intra-tracheal lesions in 21 tracheotomied cases, and it showed great statistical difference (chi 2 = 27.4, $P < 0.005$). There were no difference of onset age, sex and the first sites of papilloma lesions between the non-tracheotomied and tracheotomied groups($P > 0.05$). CONCLUSION: We found papilloma has a week potential to progress into trachea. Tracheotomy is the most important factor of intra-tracheal papilloma progression in many cases. The tracheotomy can be avoided.

Unique Identifier – 22653867

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*Zhonghua Er Bi Yan Hou Ke Za Zhi. 1999 Apr;34(2):106-7.*

**[Study on the association between squamous cell carcinoma of larynx and HPV subgene by PCR]**

[Article in Chinese]

Wang L, Zhang T, Zhang F.

Department of Otorhinolaryngology, First Affiliated Hospital, Medical College of Jinan University, Guangzhou 510630.

OBJECTIVE: To measure the human papilloma virus(HPV) HPV-E1 in squamous cell carcinoma of larynx. METHODS: Polymerase chain reaction(PCR) was used to detect the HPV subgene in 25 specimens of laryngeal carcinoma and 6 normal larynges. RESULTS: Positive expression of HPV-E1 was detected in 17 of 25 cases(68%) with squamous cell carcinoma and all the recurrent cases. However, there was no positive expression of HPV-E1 in the normal larynges ($P < 0.01$). The expression rate was not significantly different among the histological grad groups. CONCLUSION: HPV-E1 infection was found in laryngeal carcinoma but not related to its histologic grading.

Unique Identifier – 22649875

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*Zhonghua Er Bi Yan Hou Ke Za Zhi. 2001 Dec;36(6):458-62.*

**[Clinical study of juvenile-onset recurrent respiratory papillomatosis]**

[Article in Chinese]

Cui S, Han D, Chen X.

Department of Otorhinolaryngology, Beijing Tongren Hospital, Capital University of Medical Science, Beijing 100730, China. shunjiu@263.net

OBJECTIVE: To study the clinical behavior of juvenile-onset recurrent respiratory papillomatosis in order to find some factors correlated to the development of this disease, and to sum up the significance and experience of CO2 laser surgery. METHOD: Sixty patients with juvenile-onset recurrent respiratory papillomatosis from September 1995 to December 1998 were retrospectively analyzed. RESULTS: The age of onset in 50 cases (83.3%) was below 4 years, and the peak-age was 2 years. The rates of recurrence were 72.0% and 45.7% ($chi 2 = 4.71$, $P < 0.05$) below and over 2 years, respectively. The rates of aggressive disease were 88.0% and 54.3% ($chi 2 = 7.66$, $P < 0.01$) below and over 2 years, respectively. The predominant sites of the disease were the vocal cords, the false vocal cords, the laryngeal ventricle, the laryngeal surface of the epiglottis and the subglottic region. Tracheostomy induced the development of tracheal papilloma, therefore should be avoided as possible. Laryngeal papilloma might be divided into four types on the basis of the growth manner and surface form corresponding to clinical behaviors. Five patients were followed-up for 1.5 years without recurrence, 18 patients had fewer recurrences following treatment, 33 patients were under treatment, and 3 patients died. Nineteen patients lost follow-up. The major complications included laryngeal and tracheal stenosis. CONCLUSION: Clinical behaviors of juvenile-onset recurrent respiratory papillomatosis were relevant to the age, growth form and tracheotomy. CO2 laser was an ideal instrument for ablation of the laryngeal papillomas with the following advantages: simple management, less bleeding, preservation of laryngeal structure and avoidance of tracheostomy.

Unique Identifier – 22647141

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*Acta Ophthalmol Scand. 2003 Apr;81(2):193-6.*

**Topical alpha-interferon in recurrent conjunctival papilloma.**

De Keizer RJ, De Wolff-Rouendaal D.

Department of Ophthalmology, Leiden University Medical Centre, Leiden, the Netherlands.

PURPOSE: To report the effect of topical alpha-interferon (alpha-IF) in two cases of recurrent conjunctival papillomas. METHODS: One patient with a conjunctival papilloma and one patient with a limbus-based papilloma were treated with excision and cryotherapy. Recurrences included one in situ carcinoma. Retreatment included systemic and topical alpha-IF. RESULTS: In Case 1, the papillomas regressed with systemic alpha-IF followed by topical application of alpha-IF (2.8 x 106 U) for 1 year against recurrence. In Case 2, the papillomas disappeared with topical alpha-IF over 1 year. No recurrences were seen during follow-up (84 and 91 months, respectively). The possible side effect of topical alpha-IF was superficial keratitis. Retrospective polymerase chain reaction tests for HPV were positive and showed type 6 in Case 1 and type 33 in Case 2. CONCLUSION: Topical alpha-IF can be used as adjuvant therapy in recurrent conjunctival papillomas.

Unique Identifier – 22636964

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*Rev Laryngol Otol Rhinol (Bord). 2002;123(5):315-20.*

**[In Process Citation]**

[Article in French]

Coulombeau B, Nusa Naiman A, Ceruse P, Froehlich P.

Hopital Universitaire Edouard Herriot, Pavillon U, 5 Pl d'Arsonval, F-69437 Lyon, France.

Laryngeal papillomatosis, due to type 6 and 11 papova-virus A, causes devastating lesions leading to difficult clinical situations (severe dysphonia, or laryngeal dyspnea). Recurrence requires repeated endoscopy with CO2 laser treatment to keep the airways free and prevent the lesions spreading. In patients presenting aggressive papillomatosis, such repeated intervention causes irreversible lesions which have a very negative impact on the vocal prognosis. In this context, developing a form of minimally invasive surgery would help avoid vocal sequelae as far as possible. Thus, anti-viral agents can be injected directly into the lesion per-operatively so as best to preserve the healthy mucosa and muscles, thereby

managing the lesions with precision and less iatrogenic impact than with CO2 laser. Twenty six patients since 1998 have undergone Cidofovir endoscopy. Total remission was achieved in eight of them (31%), after between two and eight interventions. Twenty seven (65%) showed clinically significant partial remission. Such positive results were obtained in both adults and children. Associated lesion excision was required in cases of obstructive or persistent papilloma. Intralesion Cidofovir injection thus seems to have proved highly effective in the clinical management of laryngeal papillomatosis. Combined Cidovir injection and surgical excision remains necessary in case of large or persistent papillomas. These results have lead us to indicate this procedure as primary treatment for laryngeal papillomatosis in adults and children.

Unique Identifier – 22626911

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*Asian J Surg. 2003 Apr;26(2):112-6.*

**Recurrent respiratory papillomatosis.**

Long YT, Sani A.

Department of Otorhinolaryngology, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia. ytlong@tm.net.my

A 6-year-review of patients who presented with recurrent respiratory papillomatosis (RRP) to our hospital from January 1996 to December 2001 was carried out. Ten cases were identified, of which six were juvenile-onset RRP. Hoarseness was the most common symptom, noted in nine (90%) patients. Other clinical presentations included cough, stridor and aphonia. All patients had glottic papillomas; two had multiple sites of involvement. One patient underwent a tracheostomy that revealed papillomas over the trachea, bronchus and lung parenchyma. Half of the patients were Chinese. Of the six cases of juvenile-onset RRP, three patients were Malay, two Chinese and one Indian. Three Chinese and one German patient had adult-onset RRP. Among the juvenile-onset RRP cases, the mean age at presentation was 2 years, while for adult-onset RRP, it was 42 years. Juvenile-onset RRP was more common in females. There were more papillomas over more sites in patients with juvenile-onset RRP than with adult-onset disease. Subglottic involvement was noted in the juvenile-onset RRP cases. All patients were treated with CO2 laser therapy, but there was complete remission of the papillomas in only two cases.

Unique Identifier – 22617515

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*Ann Otol Rhinol Laryngol. 2003 Apr;112(4):298-302.*

**Molecular transformation of recurrent respiratory papillomatosis: viral typing and p53 overexpression.**

Go C, Schwartz MR, Donovan DT.

Department of Otolaryngology, Baylor College of Medicine, Houston, Texas 77030, USA.

Recurrent respiratory papillomatosis (RRP) is a histologically benign disease of the larynx, trachea, and bronchi. Here we report on the histologic and molecular characteristics of 7 cases of malignant transformation of RRP to squamous cell carcinoma (SCCA). The clinical histories of 7 patients with RRP who developed SCCA were carefully reviewed. Sequential biopsies were available from 5 of the 7 cases of spontaneous transformation of RRP to SCCA and were reviewed. In addition, p53 protein overexpression and human papillomavirus (HPV) typing for all cases was examined. The average age of patients with juvenile-onset RRP was 3 years, and that of patients with adult-onset RRP was 31 years. The average age of onset of transformation to SCCA was 28 years. All patients had laryngeal involvement with RRP, and 3 of the 7 patients had tracheal extension of disease. Five patients were tracheotomy-dependent. Four of the 7 patients developed SCCA of the lung, while 3 patients developed laryngeal SCCA. There was no consistent histologic progression from squamous papilloma to papilloma with dysplasia, and all but 1 of the SCCAs were well differentiated. The overexpression of p53 protein was variable in each of the 5 patients. We detected HPV types 6/11 in papillomas from 3 patients, and HPV types 6/11, 16/18, and 31/33/51 in a papilloma of a fourth patient. No HPV DNA was detected in papillomas of 2 patients. We found HPV 6/11 in 4 of the carcinomas. We conclude that the spontaneous transformation of RRP to SCCA is not characterized by a histologic progression through dysplasia over time. Transformation can result in the loss of HPV expression. It does not appear that p53 is a molecular marker for monitoring the transformation process. Thus, these cancers may be very difficult to diagnose histologically and clinically early in the course of the transformation of the disease.

Unique Identifier – 22616707

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*Otolaryngol Head Neck Surg. 2003 Apr;128(4):603; author reply 603-4*

**Phonomicrosurgical techniques for treatment of RRP in children.**

Derkay CS.

No abstract available.

Unique Identifier – 22612955

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*Pediatr Dent. 2003 Mar-Apr;25(2):149-53.*

**Condyloma acuminatum and human papilloma virus infection in the oral mucosa of children.**

Kui LL, Xiu HZ, Ning LY.

Department of Oral Pathology, West China College of Stomatology, Sichuan University, Chengdu, Sichuan, The People's Republic of China. laikuiliu@sina.com

PURPOSE: The purpose of this study was to investigate the clinicopathological features of oral condylomas in children and condylomatous lesions of their mothers. Moreover, the authors sought to determine the mode of transmission of this disease and to find the genotype of human papilloma virus (HPV) in the children's oral condyloma. METHODS: Nine instances of oral condyloma acuminatum in children and lesions in their mothers were reviewed. Their HPV genotypes were evaluated by in situ hybridization (ISH). RESULTS: This study revealed that the lesions appeared during 3 years of age and the most common location was the hard and soft palate. Seven of the 9 mothers had experienced vulva and/or oral cavity condylomata during pregnancy. Social evaluation confirmed sexual abuse in 1 girl, and probable sexual abuse in another girl. The results of ISH demonstrated HPV 16/18 DNA being positive in 5 of the 9 cases, and HPV 6 and HPV 11, HPV 6 and HPV 16/18, HPV 6, and HPV 11 DNA being positive, respectively, in 1 case. HPV DNA types in mother-child pairs were not concordant. CONCLUSIONS: Oral condyloma acuminatum in children is probably induced by HPV 16/18. The mode of transmission by sexual abuse is the most likely route. Prenatal transmission of HPV to children is rare. This study provides further confirmation of possible different genotype and transmission in oral CA of children and adults.

Unique Identifier – 22609069

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*Methods Find Exp Clin Pharmacol. 2003 Jan-Feb;25(1):53-76.*

**Gateways to clinical trials.**

Bayes M, Rabasseda X, Prous JR.

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Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies knowledge area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: 81C6; Adefovir dipivoxil, Agalsidase alfa, AGM-1470, albumin interferon alfa, alefacept, alosetron hydrochloride, anakinra, anti-CTLA-4 Mab, aprepitant, aripiprazole, atazanavir; BAY-43-9006, BBR-3438, beta-L-Fd4C, bimatoprost, bortezomib, bosentanBR96-doxorubicin;

Caspofungin acetate, ciclesonide, cilengitide, cilomilast, COL-1621, COL-3, CpG-7909, cyclosporine; DCVax-Brain, dexmethylphenidate hydrochloride, dexosome vaccine (melanoma), donepezil hydrochloride, drotrecogin alfa (activated), DTI-015, [99Tc]-DTPA-mannosyldextran, duloxetine hydrochloride; Emivirine, emtricitabine, entecavir, epothilone B, estradiol-MNP, etonogestrel/etonogestrel/ethinylestradiol, etoricoxib; Febuxostat, fondaparinux sodium, fosamprenavir calcium; Gefitinib, GVS-111; Heparinase I, HspE7, human alpha-glucosidase, human insulin; Imatinib mesylate, INGN-241, interferon alfa B/D hybrid, interferon alfa Biphasix, ISIS-14803; Lanicemine hydrochloride, 1311-lipiodol, liposome-encapsulated mitoxantrone, lixivaptan, lumiracoxib, lupus-AHP, LY-466700; Marimastat, MEN-10755, micafungin sodium; Nitronaproxen, NSC-683864 Omalizumab, oral insulin; Palonosetron hydrochloride, peginterferon alfa-2a, pimecrolimus, pralnacasan, pramlintide acetate, pregabalin, pyrazoloacridine; R-165335, ranolazine, risperidone, RPR-109881;, RSD-1235, Satraplatin, seocalcitol, sertindole, SMART anti-interferon gamma antibody, sulfasalazine; T-138067, TAK-013, tegaserod maleate, telithromycin, tenofovir disoproxil fumarate, teriparatide, tiotropium bromide, tipifarnib, TP-38; Valdecoxib, vatalanib succinate, voriconazole; ZD-9331.

Unique Identifier – 22577389

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*Obstet Gynecol. 2003 Apr;101(4):645-52.*

**Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis.**

Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV.

Department of Epidemiology, Baltimore, Maryland 21205-2179, USA. msilverb@jhsph.edu

OBJECTIVE: To assess the risk of juvenile-onset recurrent respiratory papillomatosis conferred by a maternal history of genital warts in pregnancy, and to identify additional cofactors such as the method of delivery (cesarean versus vaginal) and procedures or complications during pregnancy. METHODS: A retrospective cohort design was used to evaluate maternal and infant characteristics associated with respiratory papillomatosis among Danish births between 1974 and 1993. Using data from Danish registries, we identified 3033 births with a maternal history of genital warts during pregnancy. Fifty-seven respiratory papillomatosis cases were identified by review of medical records from ear, nose, and throat departments. RESULTS: Seven of every 1000 births with a maternal history of genital warts resulted in disease in the offspring, corresponding to a 231.4 (95% confidence interval 135.3, 395.9) times higher risk of disease relative to births without a maternal history of genital warts. In women with genital warts, delivery times of more than 10 hours were associated with a two-fold greater risk of disease. Cesarean delivery was not found to be protective against respiratory papillomatosis, and no other procedures or complications during pregnancy were observed to increase the risk of respiratory papillomatosis. CONCLUSION: A maternal history of genital warts in pregnancy is the strongest risk factor for respiratory

papillomatosis in the child. Future studies should examine the efficacy of genital wart treatment for the prevention of disease.

Unique Identifier – 22569186

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*Int J STD AIDS. 2002 Dec;13 Suppl 2:38-41.*

**Vaccine candidates in STD.**

Fletcher MA.

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Sexually transmitted diseases (STDs) are caused by organisms that infect the mucosal surfaces of the genitourinary tract. In spite of its public health importance, current STD vaccine research lags behind work against pathogens that target another mucosal region, the respiratory tract. In the latter case, live-attenuated viral vaccines, killed whole-cell bacterial vaccines, subunit/protein bacterial vaccines, and bacterial polysaccharide vaccines have been enormously successful. To move STD vaccine research forward, complex issues must be resolved. Those include selection of an appropriate antigen (e.g. scientific feasibility and intellectual property rights), the manufacture of the vaccine (e.g. delivery systems, formulation processes, and production steps), and the appropriate public health approach (e.g. medical indications and marketing aspects). Particular scientific problems have delayed STD vaccine development, like incomplete attenuation (human herpes simplex virus type 2), accentuated immunopathology (Chlamydia trachomatis), poor immunogenicity (Treponema pallidum), and broad antigenic heterogeneity (Neisseria gonorrhoeae). Nevertheless, efforts continue with the use of protein antigens: for example, the haemolysin toxoid of Haemophilus ducreyi; the major outer membrane protein(s) of N. gonorrhoeae and C. trachomatis; the glycoprotein D of human herpes simplex virus type 2; and the proteins E6 and E7 of human papilloma virus. It may be predicted that eventual STD vaccines (administered either for prophylaxis or for therapy) will use approaches that include (1) live-attenuated viruses, (2) subunit proteins or inactivated whole organisms given with mucosal adjuvants or with cellular immune response adjuvants, and (3) DNA plasmids expressing the vaccine antigen.

Unique Identifier – 22493572

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*Hua Xi Kou Qiang Yi Xue Za Zhi. 2002 Feb;20(1):27-9.*

**[A retrospective study of clinical manifestation and human papilloma virus detection of oral condyloma acuminate in children]**

[Article in Chinese]

He Z, Liu L, Chen Y.

College of Stomatology, West China University of Medical Sciences.

OBJECTIVE: The aim of this study is to study genotype, transmission, clinical and pathological characteristics, and prognosis of oral condyloma acuminate (CA) in children. METHODS: The authors retrospected the clinical characteristics and slices of HE staining of six cases which have been diagnosed as oral CA and, performed inmunohistochemistry (IHC) and in situ hybridization (ISH) analysis to detect the DNA of human papilloma virus in 5 cases. RESULTS: Oral CA often happened in the hard or soft plates of children of two-year-old. Most of them came from the families had been infected by human papilloma virus (HPV). Histological examination demonstrated that koilocytes were common in the upper spinous and corneal layers. HPV was detected in all cases. HPV16/18-E6 antigen was positive in 4 of 5 cases examined. The result of ISH only show one case was HPV6- and HPV11-positive, and the other case was HPV-positive, but HPV could not be detected when recurring. CONCLUSION: The pathogen leading to oral condyloma acuminate (CA) and the transmission way of children may be different from that of adults.

Unique Identifier – 22481630

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*J Otolaryngol. 2002 Dec;31(6):333-5.*

**Observations on the early results of treatment of recurrent respiratory papillomatosis using cidofovir.**

El Hakim H, Waddell AN, Crysdale WS.

Department of Otolaryngology, The Hospital for Sick Children, Toronto, Ontario.

OBJECTIVE: To document the response of two patients with severe recurrent laryngeal papillomatosis following treatment with intralesional cidofovir in conjunction with carbon-dioxide laser evaporation. Setting: Tertiary referral centre. METHODS: Retrospective review of treatment of two patients followed up over a 12-month period. INTERVENTION: Microlaryngoscopy and carbon-dioxide laser evaporation of lesions followed by intralesional injection of cidofovir. OUTCOME MEASURES: Photodocumentation and descriptive statistical representation of intervals between endoscopic treatment. The disease was staged according to severity on endoscopy. RESULTS: Initially, both patients showed a marked improvement of disease. However, the disease relapsed to a significant extent. Overall, there

was no demonstrable change in the frequency of required endoscopies despite subjective improvement of the airway. CONCLUSION: Cidofovir may be of some benefit in the management of recurrent respiratory papillomatosis, but further studies are still required.

Unique Identifier – 22480978

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*Hum Gene Ther. 2003 Jan 1;14(1):45-57.*

**Treatment of human papillomavirus (HPV) type 16-infected cells using herpes simplex virus type 1 thymidine kinase-mediated gene therapy transcriptionally regulated by the HPV E2 protein.**

Sethi N, Palefsky J.

Department of Medicine and Department of Stomatology, University of California, San Francisco, San Francisco, CA 94143, USA.

Human papillomavirus type 16 (HPV-16) is associated with development of anogenital squamous cell cancers (SCCs) and their precursor, intraepithelial neoplasia (IN). Few approaches to the treatment of IN to prevent SCC are targeted specifically to HPV. We have designed an HPV-specific therapy using the herpes simplex virus type 1 thymidine kinase (HSV-1 TK) gene driven by an HPV-specific promoter in the HPV-16 long control region (LCR) (nucleotide 7450-nucleotide 104), which is regulated by the HPV E2 protein. Expression of the HSV-1 TK gene is designed to render HPV-infected cells sensitive to the prodrugs ganciclovir (GCV) and acyclovir (ACV). To assess the E2 specificity of gene expression driven by the HPV-16 LCR, we measured luciferase expression in HPV-positive and HPV-negative cell lines. Significant induction of luciferase activity was observed in HPV-positive cells when compared with four different HPV-negative epithelial cell lines. Cotransfection of an HPV-negative cell line, MDCK, with an HPV-16 E2-expressing plasmid resulted in 15- to 20-fold induction of luciferase activity, suggesting specific activation by E2 protein. A plasmid expressing the HSV-1 TK gene driven by the LCR was transfected into CaSki and SiHa cells. Treatment of transfected cells with either GCV or ACV (20-30 microg/ml) for 6-10 days resulted in 80-95% cell death. Cell death was progressive, dose dependent, and mediated by apoptosis. These results suggest that direct gene transfer of the HSV-1 TK gene into HPV-16-infected cells expressing E2 protein, accompanied by treatment with either GCV or ACV, may be a clinically feasible therapeutic strategy.

Unique Identifier – 22461634

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*Int J Pediatr Otorhinolaryngol. 2003 Jan;67(1):7-10.*

**The changing indications for paediatric tracheostomy.**

Hadfield PJ, Lloyd-Faulconbridge RV, Almeyda J, Albert DM, Bailey CM.

Department of Paediatric Otolaryngology, Great Ormond Street Hospital for Children, London WC1N 3JH, UK.

OBJECTIVE: To investigate whether the incidence and indications for paediatric tracheostomy in this unit have changed over recent years. METHODS: All paediatric tracheostomies performed between 1993 and 2001 were identified from our departmental database. The indications for these were ascertained by retrospective case note review. RESULTS: Over the 9-year period studied 362 tracheostomies were performed, the number increased slightly between the first and second half of the period, with peaks in 1997 and 1999. The commonest indication was prolonged ventilation due to neuromuscular or respiratory problems. CONCLUSIONS: This large series shows that the increase in frequency of paediatric tracheostomy performed in this unit over the past decade has been due to conditions such as subglottic and tracheal stenosis, respiratory papillomatosis, caustic alkali ingestion and craniofacial syndromes. Conditions in which tracheostomy are now less common are subglottic haemangioma and laryngeal clefts. Prolonged ventilation remains the commonest indication overall.

Unique Identifier – 22447099

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*Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2001 Jun;15(6):251-2.*

**[Clinical analysis of 62 cases laryngeal papilloma in children]**

[Article in Chinese]

Zheng Y, Ou Y, Chen J, Huang X, Zou H, Ding J, Xu Y.

Department of Otorhinolaryngology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University of Medical Sciences, GuangZhou 510012.

OBJECTIVE: To investigate the clinical features of laryngeal papilloma in children. METHOD: In a group of 62 patients with laryngeal papilloma in children, the tumors of 28 patients were cut under the direct laryngoscope, 34 patients were treated with laryngeal micro-laser operation. RESULT: The post-operation followup ranged from 2 to 5 years, the cure rate of 2 years was 51.61%. CONCLUSION: The clinical features of this disease include rapid development, a large lesion, and it is often found in the infraglottic cavity. Furthermore, we believe that in order to eliminate the tumors more accurately and decrease recurrence, micro-laser surgery and the use of interferon is very necessary.

Unique Identifier – 22429991

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*Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003 Jan;95(1):80-4.*

**Human papillomavirus, type 40-associated papilloma, and concurrent Kaposi's sarcoma involving the anterior hard palate of an HIV-positive man.**

Anderson KM, Allen CM, Nuovo GJ.

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A number of oral lesions have been reported in association with HIV, including lesions caused by other viruses such as the epitheliotropic human papillomavirus (HPV). More than 90 types of HPV have been identified, with the less commonly encountered strains of HPV tending to show association with immunodeficiency states. In addition, HIV-infected patients may have Kaposi's sarcoma develop, a malignancy thought to be caused by human herpes virus, type 8. Recent evidence suggests a sexual mode of transmission for this virus. We report an HIV-positive man with a large, HPV type 40-associated papilloma of the anterior palate and a previously undiagnosed focus of Kaposi's sarcoma.

Unique Identifier – 22426826

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*Ann Otol Rhinol Laryngol. 2003 Jan;112(1):7-10.*

**Treatment of recurrent respiratory papillomatosis in children with the microdebrider.**

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The mainstay of treatment of children with recurrent respiratory papillomatosis has been CO2 laser laryngoscopy. Powered microdebriders allow precise removal of laryngeal lesions without thermal damage. The microdebrider may reduce costs by reducing operative time and limiting the need for expensive laser-related equipment. To compare the use of the microdebrider with that of the CO2 laser in children undergoing surgery for recurrent respiratory papillomatosis, we retrospectively reviewed the charts of 18 patients from 2 institutions covering a treatment period between December 1998 and October 2001. These patients were initially treated with the CO2 laser, but were switched to microdebrider resection during the review period. We recorded the number of procedures, the technique(s) of resection used, and the operative time for each procedure. We identified 18 patients, 11 male and 7 female, ages 18 months to 14 years. A total of 127 procedures were performed

with the CO2 laser, and a total of 50 procedures were performed with the microdebrider. The mean number of procedures per patient was 10 (range, 2 to 17 procedures). The mean surgical time per procedure using the CO2 laser was 59.2 minutes (range, 8 to 130 minutes). The mean time per procedure with the microdebrider was 32.4 minutes (range, 12 to 47 minutes). This reduction in operative time was clinically and statistically significant (p = .0001, unpaired Student's t-test). We concluded that microdebrider resection of laryngeal papilloma in children allowed more rapid surgery with potentially reduced treatment costs. Other advantages of this technique include precise excision without thermal injury. Our report details useful refinements of technique with the microdebrider.

Unique Identifier – 22424337

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*J Virol. 2003 Feb;77(3):1927-39.*

**HLA class II polymorphisms and susceptibility to recurrent respiratory papillomatosis.**

Gelder CM, Williams OM, Hart KW, Wall S, Williams G, Ingrams D, Bull P, Bunce M, Welsh K, Marshall SE, Borysiewicz L.

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Recurrent respiratory papillomatosis (RRP) is characterised by multiple laryngeal papillomas. Left untreated, the lesions enlarge, spread, and endanger the airway. Medical treatments are unsatisfactory, and repeated surgery remains the mainstay of therapy. RRP is caused by human papillomavirus (HPV) infection. However, since oral HPV infection is common and RRP is rare, other host and/or viral factors may contribute to pathogenesis. In an attempt to identify such factors, we have investigated 60 patients. The patients were HLA class I, II, and tumor necrosis factor TNF typed by sequence-specific primer PCR, and the results compared to those for 554 healthy controls by using Fisher's exact test. Peripheral blood mononuclear cell proliferative responses of 25 controls and 10 patients to HPV-11 L1 virus-like particles (VLP) were compared. Short-term VLP-specific T-cell lines were established, and recognition of L1 was analyzed. Finally, the L1 open reading frames of HPV isolates from four patients were sequenced. Susceptibility to RRP was associated with HLA DRB1*0301 (33 of 60 patients versus 136 of 554 controls, P < 0.0001). The three most severely affected patients were homozygous for this allele. A range of T-cell proliferative responses to HPV-11 VLP were observed in DRB1*0301-positive healthy donors which were comparable to those in DRB1*0301-negative controls. Individuals with juvenile-onset RRP also mounted a range of VLP responses, and their magnitude was negatively correlated with the clinical staging score (P = 0.012 by the Spearman rank correlation). DRB1*0301-positive patients who responded to L1 recognized the same epitope as did matched controls and produced similar cytokines. Sequencing of clinical isolates excluded the possibility that nonresponsiveness was the result of mutation(s) in L1.

Unique Identifier – 22413706

*Ear Nose Throat J. 2002 Dec;81(12):850-1.*

**Applications of the diode laser in otolaryngology.**

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We undertook a study to determine the usefulness and effectiveness of a relatively new, portable 980-nm wavelength diode laser with a fiberoptic delivery system. We tested the laser in several clinical situations, both in the operating room and in the office. We used it while performing 14 turbinate reduction procedures, one nasal polypectomy, one ablation of an oral papilloma, and one photocoagulation of nasal telangiectasias. Our preliminary findings indicate that the use of this laser was helpful in alleviating nasal congestion in the patients with turbinate dysfunction and in controlling epistaxis in the patient with telangiectasias. It was also effective in treating the polyp and papilloma patients. We did not experience any intra- or postoperative complications. The laser's flexible fiber delivery system is compatible with hollow instruments, allows for coaxial vision, and is ideally suited for intranasal use. Its portability and functional diversity make it an attractive alternative to the conventional carbon dioxide, argon, and neodimium:yttrium-aluminumgarnet lasers.

Unique Identifier – 22405078

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*Laryngoscope. 2003 Jan;113(1):139-43.*

**Microdebrider versus CO2 laser removal of recurrent respiratory papillomas: a prospective analysis.**

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Division of Otolaryngology--Head and Neck Surgery, The University of Alabama at Birmingham, USA.

OBJECTIVE: To compare postoperative patient discomfort, voice quality, and procedure time and cost for removal of recurrent respiratory papillomas using the microdebrider versus the CO2 laser. STUDY DESIGN: A randomized prospective study comparing children undergoing excision of recurrent respiratory papillomas by CO2 laser versus excision by microdebrider. METHODS: For the 6-month study, patients for whom removal of recurrent respiratory papillomas was indicated were randomly assigned by birth year to microdebrider or CO2 laser therapy. Disease severity was scored as the sum of ratings of 1+ (minimal), 2+ (moderate), or 3+ (severe) for involvement of 27 areas of the aerodigestive tract by direct microlaryngoscopy immediately before treatment. Parents scored patient discomfort and improvement in voice quality 24 hours after surgery, using a 5-point (0 = no pain; 4 = worst pain) and a 10-point (1 = minimal change; 10 = significant improvement) scale, respectively.

RESULTS: Nineteen patients ranging in age from 2.5 to 20 years underwent 32 procedures in all. Groups did not differ significantly in age, sex, or severity of disease. For disease of equivalent severity, microdebrider treatment was associated with equivalent 24-hour-postoperative pain scores, greater improvement in voice quality, shorter procedure times, and lower overall procedure cost. CONCLUSIONS: Immediate postoperative results indicate that the microdebrider may be as safe as and, at some institutions, might be more cost-effective than the CO2 laser for removal of recurrent respiratory papillomas.

Unique Identifier – 22402100

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*Ear Nose Throat J. 2002 Nov;81(11):790-1.*

**Bilateral vocal process papillomas: report of a case.**

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We describe a case of bilateral vocal process lesions in a 65-year-old man. His history was strongly suggestive of vocal process granulomas: previous gastroesophageal reflux, intubation, smoking, and oral squamous cell carcinoma. Medical management with a proton-pump inhibitor, reflux precautions, voice therapy, and adequate hydration yielded no results. Subsequent surgical intervention revealed that he had squamous papillomas. We also provide a brief review of vocal process granulomas and squamous papillomas.

Unique Identifier – 22360395

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*Medicina (Kaunas). 2002;38(5):499-504.*

**[Prevalence of papillomavirus infection among patients with laryngeal papillomatosis and the effects of some risk factors on the persistence of papillomaviruses in the upper respiratory tract]**

[Article in Lithuanian]

Velyvyte D, Laiskonis A, Uloza V, Gozdzicka-Jozefiak A.

Kauno medicinos universiteto Infekciniu ligu klinika ir Ausu, nosies, gerkles ligu klinika, Eiveniu 2, 3007 Kaunas. velyv@takas.lt

Infection with high-risk human papillomaviruses is a significant risk factor of various benign and malignant human lesions in the upper respiratory tract, skin and the genital tract. The

identification of particular human papillomaviruses types is important for identifying patients with premalignant lesions who are at risk of progression to malignancy. Our aim was to establish the prevalence of human papillomaviruses infection in the upper respiratory tract of patients with laryngeal papillomatosis, to identify viral types, to evaluate the relationship between some risk factors and persistence of human papillomaviruses in the upper respiratory tract and to determine the pattern of human papillomaviruses infection. MATERIAL AND METHODS: The group of 36 patients with laryngeal papillomatosis and control group of 108 persons without any complains of respiratory system was examined. Epidemiologic characteristics and objective data were analyzed and routine laryngological examination was performed. Pharyngeal swabs of all persons and laryngeal biopsies of 17 patients were taken and analyzed for the presence of human papillomaviruses DNA. Viral typing using the polymerase chain reaction was performed. RESULTS: Human papillomaviruses DNA was detected in all except one case of laryngeal papillomatosis; then only 23.15% of persons without complaints of respiratory system were found human papillomaviruses positive. Human papillomaviruses 6, 11 types were predominant (in 88.9% of patients and 19.4% of persons from control group). High-risk human papillomaviruses were detected in 52.78% of laryngeal papillomatosis cases and in 9.26% of control cases. Risk factors were noted statistically significantly more often in human papillomaviruses positive cases. CONCLUSIONS: The prevalence of human papillomaviruses infection in the upper respiratory tract of patients with laryngeal papillomatosis is high; human papillomaviruses 6, 11 types are predominant. High-risk human papillomaviruses were noted statistically significantly more often in the group of patients with laryngeal papillomatosis. Inclination to diseases of respiratory system, dental caries, smoking, low living standard are statistically significantly related to human papillomaviruses persistence in the upper respiratory tract.

Unique Identifier – 22355222

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*Arch Inst Pasteur Madagascar. 2000;66(1-2):65-7.*

**[Diagnostic pitfalls in childhood acute obstructive dyspnea]**

[Article in French]

Tovone XG, Rasamoelisoa JM, Rakoto F, Rakotovao F, Ramialiharisoa A, Rakotoarimanana DR.

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Diagnosis of an acute obstructive dyspnea is very difficult because there are many possible causes. The authors reported the case of a 3.5-year-old boy with an atopic status who presented iterative asthma attacks which evolute to severity in spite of an appropriate therapy. Then suffocation occurred with a serious infectious context. The cause of the disease was diagnosed by respiratory tract endoscopic exam which allowed to detect a laryngeal papillomatis. The surgical extraction of this tumour cured the patient. Physiopathology of

acute obstructive dyspnea in child was discussed. Upper airway obstructions are separated from lower pulmonary diseases. Two syndromes are very difficult to separate among upper airway obstructions: spasmodic laryngitis and subglottal laryngitis. They are considered in fact as different outward signs of the same disease: subglottal laryngitis is the infectious evolutive form of a spasmodic laryngitis in which atopic status exists. Laryngeal papillomatosis would be a favourising factor of infection. The authors conclude that respiratory tract endoscopic exam is very important to diagnose childhood acute obstructive dyspnea.

Unique Identifier – 22351424

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*Neoplasma. 2002;49(5):285-9.*

**Therapeutic vaccines against HPV16-associated tumors. Minireview.**

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Human papilloma viruses (HPV) were found to be closely associated with several types of anogenital tumors, particularly with cervical carcinomas (CC). Of more than 100 HPV types characterized until now, 11 have been classified as high-risk types and detected in human tumor tissue by molecular and immunological techniques. Immunological intervention against HPV can be envisaged at two levels, prophylactic and therapeutic. The therapeutic vaccines constructed to counteract tumors which are already developed utilize two nonstructural early proteins coded by HPV, the products of their E6 and E7 oncogenes. These E6/E7 oncoproteins are the only HPV-coded proteins expressed in CC; they are involved in malignant transformation of HPV-infected cells, their presence is necessary for the maintenance of the malignant phenotype of the cells, and their expression correlates with the transforming potential of HPV. Therefore, the E6/E7 oncoproteins are used for the construction of therapeutic vaccines against HPV-associated neoplasms. The purpose of this review is to discuss the results obtained with HPV16 E6/E7 oncoprotein based therapeutic vaccines in animal tumor models, as well as the prospects and limitations of the vaccines.

Unique Identifier – 22346104

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*Virus Res. 2002 Nov;89(2):275-84.*

**The status of HPV16-specific T-cell reactivity in health and disease as a guide to HPV vaccine development.**

van der Burg SH, de Jong A, Welters MJ, Offringa R, Melief CJ.

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Human papilloma viruses (HPV) are among the most common sexually transmitted pathogens in young adults. In the majority of individuals, anti-viral immunity is capable of suppressing viral infection but in a minority of patients viral infection is not cleared in time to prevent the development of malignancies. In these cases, HPV16-specific immunity may develop too late, is not strong enough, and/or is possibly of the wrong type. The influence of pre-existing immunity on the efficacy of vaccines is largely unknown. Nor has it been studied what the effect is of vaccines on the various types of pre-existing HPV-specific T-cell immunity. Animal models showing that vaccines are able to protect against a subsequent tumor challenge and even to treat transplantable tumors, are not qualified to address this point because tumor development is not preceded by persistent viral infection. Therefore, the comparison between fully characterized pre-existing HPV-specific immunity in patients and healthy subjects is a prerequisite for the full appreciation of vaccine-efficacy as well as for further development of next-generation vaccines.

Unique Identifier – 22337978

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*Otolaryngol Head Neck Surg. 2002 Nov;127(5):465-6.*

**Concurrent respiratory and cutaneous papillomatosis with human papillomavirus type 11.**

Brown L, Wiatrak B.

University of Alabama at Birmingham, The Children's Hospital of Alabama, USA.

No abstract available.

Unique Identifier – 22337506

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*Laryngoscope. 2002 Nov;112(11):1926-9.*

**Laryngopharyngeal reflux and laryngeal web formation in patients with pediatric recurrent respiratory papillomas.**

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OBJECTIVE: To determine whether treatment of laryngopharyngeal reflux reduces the laryngeal soft tissue complications encountered in surgery for recurrent respiratory papillomas. STUDY DESIGN: Retrospective chart review. METHODS: Retrospective chart review of all pediatric patients treated for laryngeal recurrent respiratory papillomas between 1984 and 1999 was performed. Thirty-one such patients were identified. Twenty-four were at "high risk" for developing complications based on the number of operating suite visits and the presence of disease at the anterior commissure. Twelve patients underwent 24-hour double pH probe testing. RESULTS: Overall, 13 of 31 patients (42%) developed laryngeal webs. No other soft tissue complications were encountered. Of the patients who had pH probe testing, 12 of 12 (100%) had at least one pharyngeal episode of acid exposure. Of the "high-risk" patients, 10 were treated for reflux and only 2 of 10 (20%) developed webs. Eleven of 14 (79%) of the "high-risk" patients who were not treated for reflux developed webs. The difference in rate of web formation between patients treated for reflux and those not treated for reflux was statistically significant (P =.011). CONCLUSIONS: Antireflux treatments for patients undergoing surgery for laryngeal recurrent respiratory papillomas may reduce the soft tissue complications, especially scarring and web formation. Prophylactic antireflux therapy may be warranted in any patient undergoing surgery during which laryngeal mucosal disruption is anticipated.

Unique Identifier – 22326884

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*Eur Arch Otorhinolaryngol. 2002 Nov;259(10):516-20. Epub 2002 Jun 27.*

**Expression of the the cyclin-kinase inhibitors p21(WAF1) and p27(Kip1) and the p53 tumor suppressor genes in adult-onset laryngeal papillomas.**

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Different types of human papilloma virus are known to be closely associated with laryngeal papillomas. On the other hand, the proliferation of epithelial cells is associated with various abnormalities in the mechanisms of cellular regulation. In this study, we detected the expressions of p53, p21 and p27 proteins in adult-onset laryngeal papillomas by immunohistochemical techniques. The objective of this study is to evaluate the expression of these factors in adult-onset laryngeal papillomas and to determine whether such expression is correlated with the existence of dysplastic epithelium covering the papillomas. Eighteen patients with adult-onset papillomas who were surgically treated at the Department of Otolaryngology at the University of Istanbul between January 1994 and December 1999 were included in this study. Anti-p21, -p27 and -p53 antibodies were used to perform immunostaining. Positive nuclear staining for p21 was detected in 14 of the 18 (78%) cases, especially in the parabasal layer. Also, in 78% of the cases, weak to strong immunoreactivity was observed for p27. In all cases, negative immunoreactivity was observed for p53

throughout the epithelium except for the basal and parabasal cells. A negative correlation was observed between the existence of dysplastic epithelium and p21 expression (P=0.02). In conclusion, variable p21 and p27 expression was detected by immunohistochemistry in our series of 18 cases of adult-onset laryngeal papillomatosis, and a statistically significant inverse correlation was detected between p21 expression and the existence of dysplastic epithelium covering the papillomas. Further prospective studies are warranted to determine the prognostic values of these variables and to evaluate their role in the pathogenesis of adult-onset laryngeal papillomas.

Unique Identifier – 22321215

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*Radiographics. 2002 Oct;22 Spec No:S215-30.*

**Nonneoplastic lesions of the tracheobronchial wall: radiologic findings with bronchoscopic correlation.**

Prince JS, Duhamel DR, Levin DL, Harrell JH, Friedman PJ.

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Nonneoplastic diseases of the central airways are uncommon but can be categorized as either focal or diffuse, although there is some overlap. Focal diseases include postintubation stenosis, postinfectious stenosis, posttransplantation stenosis, and various systemic diseases that may involve the airways and lead to focal stenosis (eg, Crohn disease, sarcoidosis, Behcet syndrome). Diffuse diseases of the central airways include Wegener granulomatosis, relapsing polychondritis, tracheobronchopathia osteochondroplastica, amyloidosis, papillomatosis, and rhinoscleroma. Conventional radiography is often the first step in the evaluation of suspected central airway disease and may be adequate in itself to identify the abnormality. However, computed tomography (CT) improves both the detection and characterization of central airway disease. Bronchoscopy remains the primary procedure for the diagnostic work-up of these disease entities. Nevertheless, a thorough radiologic evaluation with radiography and CT may demonstrate specific imaging findings (eg, calcification) that can help narrow the differential diagnosis and aid in the planning of bronchoscopy or therapeutic intervention.

Unique Identifier – 22264048

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*Virology. 2002 Sep 15;301(1):176-87.*

**Chimeric human papilloma virus-simian/human immunodeficiency virus virus-like-particle vaccines: immunogenicity and protective efficacy in macaques.**

Dale CJ, Liu XS, De Rose R, Purcell DF, Anderson J, Xu Y, Leggatt GR, Frazer IH, Kent SJ.

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Vaccines to efficiently block or limit sexual transmission of both HIV and human papilloma virus (HPV) are urgently needed. Chimeric virus-like-particle (VLP) vaccines consisting of both multimerized HPV L1 proteins and fragments of SIV gag p27, HIV-1 tat, and HIV-1 rev proteins (HPV-SHIV VLPs) were constructed and administered to macaques both systemically and mucosally. An additional group of macaques first received a priming vaccination with DNA vaccines expressing the same SIV and HIV-1 antigens prior to chimeric HPV-SHIV VLP boosting vaccinations. Although HPV L1 antibodies were induced in all immunized macaques, weak antibody or T cell responses to the chimeric SHIV antigens were detected only in animals receiving the DNA prime/HPV-SHIV VLP boost vaccine regimen. Significant but partial protection from a virulent mucosal SHIV challenge was also detected only in the prime/boosted macaques and not in animals receiving the HPV-SHIV VLP vaccines alone, with three of five prime/boosted animals retaining some CD4+ T cells following challenge. Thus, although some immunogenicity and partial protection was observed in non-human primates receiving both DNA and chimeric HPV-SHIV VLP vaccines, significant improvements in vaccine design are required before we can confidently proceed with this approach to clinical trials.

Unique Identifier – 22247914

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*Dermatol Nurs. 2002 Aug;14(4):268-70.*

**Imiquimod (Aldara): modifying the immune response.**

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Imiquimod 5% cream represents a new class of topically applied immune response modifiers that are capable of enhancing immune function. It stimulates both the innate arm of the immune system as well as cell-mediated immunity. It is currently indicated for treating genital human papilloma virus infection. However, because of its action on the immune system it shows promise for wide applicability in treating other viral skin infections as well as neoplastic and immune-mediated diseases of the skin.

Unique Identifier - 22226196

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*J Virol. 2002 Oct;76(19):9798-805.*

**Protective immunity to rabbit oral and cutaneous papillomaviruses by immunization with short peptides of L2, the minor capsid protein.**

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The papillomavirus minor capsid protein, L2, has been shown to exhibit immunogenicity, whereby a variety of B-cell epitopes, predominantly in the amino terminus of L2, have been deduced. However, immunity to L2 in vivo has not been examined extensively. Notably, a common neutralization epitope for human papillomavirus (HPV) types 6 and 16 was mapped to amino acids (aa) 108 to 120. The objectives of this study were to derive antisera from rabbits using the corresponding sequences from rabbit viruses and to assess the ability of these peptides to protect against infection. Synthetic peptides consisting of two overlapping sequences each in the region of aa 94 to 122 of the rabbit oral (ROPV) and cottontail rabbit (CRPV) papillomaviruses were used to immunize rabbits. Rabbits were then infected with both ROPV and CRPV and monitored for the development of oral and cutaneous papillomas, respectively. Serum derived from rabbits immunized with either of the two peptides was shown to (i) react to purified L2 from the cognate virus, (ii) specifically recognize L2 within virus-infected cells, and (iii) neutralize virus in vitro. Following viral challenge, cutaneous papilloma growth was completely absent in rabbits immunized with either CRPV peptide. Likewise, ROPV peptide-immunized rabbits were protected from oral papillomatosis. Challenge of CRPV peptide-immune rabbits with the viral genome resulted in efficient papilloma growth, suggesting a neutralizing antibody-mediated mechanism of protection. These results afford in vivo evidence for the immunogenicity provided by a distinct region of L2 and further support previous evidence for the ability of this region to elicit antiviral immunity.

Unique Identifier – 22199147

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*Oncogene. 2002 Aug 29;21(38):5940-5.*

**The DNA repair protein, O(6)-methylguanine-DNA methyltransferase is a proteolytic target for the E6 human papillomavirus oncoprotein.**

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We have previously shown that O(6)-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein that protects tissues against toxic and carcinogenic effects of alkylating

agents, is degraded through ubiquitination-dependent proteolysis. Here, we investigated the role of the human papillomavirus (HPV) E6 protein in MGMT degradation. In three pairs of isogenic human tumor cell lines in which a member of each pair expressed the E6 protein through stable transfection (HCT116/HCT116-E6, MCF7/MCF7-E6, and RKO/RKO-E6), we found a consistent 40-55% reduction in the MGMT protein level and its activity in all E6-expressing cells compared with the parent cells (P=<0.05). E6 expression did not, however, alter the levels of MGMT mRNA. Addition of the recombinant MGMT (rMGMT) protein to extracts of HCT116/E6 cells resulted in the binding of E6 to MGMT. Further, the purified E6 protein promoted the degradation of rMGMT in rabbit reticulocyte lysates. Immunoprecipitation assays showed the presence of a ternary protein complex between MGMT, E6, and the cellular ubiquitin-ligase E6-associated protein (E6-AP). Transient transfection of the p53-null H1299 lung tumor cells with an E6 construct also down-regulated the MGMT. The MGMT protein also showed structural features that are compatible for interaction with the E6, and E6-AP components. Collectively, these data suggest that the oncogenic E6 proteins enhance the ubiquitin-dependent proteolysis of MGMT.

Unique Identifier – 22173127

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*Expert Opin Pharmacother. 2002 Aug;3(8):1091-9.*

**Pharmacotherapy of recurrent respiratory papillomatosis.**

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Recurrent respiratory papillomatosis (RRP) is a disease which affects both children (juvenile-onset RRP) and adults (adult-onset RRP). While a greater amount of information is known about the epidemiology of juvenile-onset than adult-onset RRP, fundamental work is still needed to more fully describe areas such as the mode of transmission. The primary management approach focuses on the removal of the papillomas by surgical debulking, although persistence of the human papillomavirus genome and subsequent recurrence of disease is the typical outcome. In a minority of patients, surgical management must be supplemented with adjuvant medical therapy, with IFN being the best studied and most commonly used. Other adjuvant treatments being employed include photodynamic therapy, indole-3-carbinol, ribavirin and cidofovir. Large controlled trials are lacking for all but IFN, making it extremely difficult to assess clinical benefit and risk in a systematic fashion at the current time. As with surgical management, viral persistence occurs following treatment with these adjuvant modalities, further contributing to the challenge of managing patients with this potentially devastating disease.

Unique Identifier – 22146180

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*Magy Onkol. 2002;46(1):35-41. Epub 2003 Feb 03.*

**[Causal association between human papilloma virus infection and head and neck and esophageal squamous cell carcinoma]**

[Article in Hungarian]

Szentirmay Z, Szanto I, Balint I, Polus K, Remenar E, Tamas L, Szentkuti G, Melegh Z, Nagy P, Kasler M.

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HPVs commonly cause proliferative lesions of squamous epithelium, and infection with certain HPV types carries a high risk of malignant transformation. We used molecular techniques to detect and type HPV in papillomas and carcinomas in the oral cavity and esophagus. DNA was extracted from 150 fresh or paraffin embedded biopsy specimens, and analyzed for HPV by PCR with 15 sets of consensus primers directed to conserved regions of L1 gene, three sets of HPV16E6 primers (specific for the HPV 16 prototype and L83V variant), and sets of primers specific for the E6 gene of other mucosa type HPVs including HPV 6, 11, 16, 18, 52, 58, 66 and 73. Overall, HPV sequences were detected in 61 of 150 specimens. HPV DNA sequences were detected in 16/32 specimens in the oropharyngeal region, in 13/36 specimens in larynx and 32/82 specimens in esophagus. Papillomas contained only the episomal form of HPV 16.In the esophagus, the most common type was HPV 73. In all specimens examined, HPV 6/11 (4/150), HPV 16 (23/150), HPV 35 (1/150), HPV 45 (1/150), HPV 54 (1/150), HPV 58 (1/150), HPV 61 (1/150), HPV 66 (1/150), HPV 68 (2/150), HPV 70 (3/150), HPV 72 (1/150), HPV 73 (16/150), double HPV infection (2/150), and unidentified HPV type (4/150) was detected. Interestingly, HPV was found in all verrucous carcinomas and in 18/22 basaloid squamous cell carcinomas. HPV16E6 T350G mutant were observed only in two of eight carcinomas. Using correspondence analysis, a segregation of specific virus types in specific clinico-pathologic lesions (verrucous carcinoma and basaloid squamous cell carcinoma) was proved. It was shown that the relative rates of the HPV positive tumors were significantly higher in women than in men. The synergic action of mucosal irritation and HPV infection may be necessary for the development of the papillomas and the specific types of carcinomas in the oral cavity and in the esophagus.

Unique Identifier – 22045824

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