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, molecular 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 (2000 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

(Accepted for publication in *Arch Otolaryngol Head Neck Surg*)

Can Mumps Vaccine Induce Remission in Recurrent Respiratory Papilloma?

N.R.T. Pashley

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Study Objective: To describe our experience using laser excision and locally injected mumps vaccine to induce remission in patients with recurrent respiratory papilloma (RRP).
Design: Pilot study group of 11 children, subsequent case series of 18 children and 20 adults.
Setting: Tertiary care regional medical center.
Participants: Initially, 11 children with RRP all treated with laser excision at regular intervals for at least a year without any adjuvant therapy. Later 18 children and 20 adults with RRP, some of whom had used various adjuvant therapy with interval laser excision.
Interventions: Both patient groups continued their same interval laser excision, using the same of similar laser, same clinical setting, same surgeon. Locally injected mumps vaccine was then administered into the excision site after each laser removal of papilloma.
Outcome measures: Larynx and trachea were observed micro-photographically with each treatment. Two consecutive disease free intervals and a follow up of at least one year were required criteria for remission.
Results: In the pilot study, remission was induced in 9/11 patients (81.8%) by 1 to 10 injections, with follow up of 5 to 19 years. In the subsequent series, remission was induced in 29/38 patients (76.3%) by 4 to 26 injections and follow up was 2 to 5 years.
Conclusions: Combined with serial laser excision, mumps vaccine positively influences induction of remission in children with RRP. The mechanisms of this effect are unclear but the treatment is readily available, cheap, and has a low risk of side effects.

Unique Identifier: Not yet assigned.

Prim. Care Update Ob Gyns 2001 Jul;8(4):163-169

Interferon therapy in primary care.

Piper JM, Wen TT, Xenakis EM.

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Interferons are proteins produced by human blood cells in response to stimulation (viral infection). The natural roles of interferons are host defense and modulation of the immune system. Therapeutic uses are based on these roles. Interferon-alpha has been widely used for malignancies, skin conditions, viral infections, and myeloproliferative disorders. Interferon-beta is a standard treatment for relapsing multiple sclerosis. Interferon-gamma therapy is currently used for chronic granulomatous disease and skin lesions (human papilloma virus related and keloids), but further research is ongoing. Side effects of interferon therapy are common and limit utility. Flulike symptoms are reported by more than 75% and depression by 10-40% of interferon users. Severe adverse effects are less common but may be life threatening, including autoimmune diseases, thrombotic-thrombocytopenic purpura, and acute renal failure. Limited use of interferon therapy during pregnancy has been described, with successful maternal and neonatal outcomes. Use of interferon therapy during early pregnancy is not an indication for termination.

Unique Identifier: Not yet assigned.

Curr Opin Mol Ther 2001 Aug;3(4):413-417

Technology evaluation: HspE7, StressGen Biotechnologies Corp.

Hunt S.

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StressGen is developing HspE7 (SGN-00101) as a potential therapy for human papillomavirus (HPV)-associated conditions. It is a recombinant fusion protein comprising the HPV E7 antigen and the heat shock protein, hsp65, from Mycobacterium bovis. By November 2000, it was in phase III trials for HPV-related anal dysplasia [405228]. Under an aggrement formed in November 1999, the US National Cancer Institute (NCI) is carrying out clinical trials with StressGen in diseases caused by HPV [347155].

Unique Identifier: 21416381

Chang Gung Med J 2001 Jun;24(6):393-398

Carbon dioxide laser induced airway fire during larynx surgery: case report.

Chou AK, Tan PH, Yang LC, Sun GC, Hsieh SW.

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The precision intrinsic hemostatic properties of the laser have led to its wide use in modern clinical medicine especially in microscopic airway surgery. However, the intense heat

generated by the high energy density of the surgical laser can convert combustible tubes into veritable torches, cause catastrophic fires, and result in severe injury to the patient. This is of particular importance when high energy is used on the continuous mode or when the endotracheal tube is repeatedly hit by the laser at the same spot. Most reported laser-induced complications result from the laser beam inadvertently falling on the areas that are not intended to be exposed. We report a case of a trans-tracheostomy tube fire occurring during carbon dioxide (CO2) laser surgery. Aluminum-tape wrapping did not prevent this complication. It was found that the ignition of a trans-tracheostomy tube was caused by the laser striking an unprotected portion of the tube during resection of granuloma of the trachea.

Unique Identifier: 21404639

J Eur Acad Dermatol Venereol 2000 Nov;14(6):484-488

Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS. A pilot study.

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BACKGROUND: Cidofovir is a nucleoside analogue of deoxycytidine with a strong activity against several DNA viruses, including herpes, pox and human papilloma virus (HPV). MATERIAL AND METHODS: Fourteen acquired immunodeficiency syndrome patients, 10 with extensive HPV lesions and four with molluscum contagiosum (MC) infections, unresponsive to conventional therapies, were treated with a cream containing cidofovir 1%. All the subjects had been on treatment with highly active antiretroviral therapy for almost 1 year before starting the cream. Measured end-points of therapy were efficacy, tolerability, side-effects and freedom from recurrence. RESULTS: Thirteen of the 14 patients (92.8%) completed the therapy, one dropped out. These 13 eventually cleared their MC or warts, over varying periods of time. In nine, the lesions regressed 2 weeks from the end of the first cycle of therapy. Three patients needed two cycles and the last three consecutive courses of topical therapy before the cutaneous lesions healed. No recurrence was observed in nine patients over an average follow-up period of 24.1 months (range 12-30 months). Four patients had isolated relapses, which were successfully treated with simple curettage. SIDE-EFFECTS: All the patients experienced side-effects where they applied the cream. Inflammation, erosion and a burning sensation were the most frequent. Postinflammatory hyperpigmentation was observed in six cases, while two developed a transient alopecia on the beard area. No systemic side-effects or alteration of laboratory data were noted. CONCLUSION: Cidofovir appears to offer an effective therapeutic alternative option for lesions that are unresponsive to conventional methods. Appropriate clinical trials are required, however, to confirm the true efficacy and safety of topical cidofovir.

Unique Identifier: 21337177

Gynecol Oncol 2001 Jul;82(1):77-83

Synthetic peptides induce a cytotoxic response against human papillomavirus type-18.

Castellanos MR, Hayes RL, Maiman MA.

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OBJECTIVES: Over 90% of cervical carcinomas express human papillomavirus (HPV) E6 and E7 proteins. These unique antigens are ideal targets for the development of cytotoxic T-lymphocytes (CTL) for antitumor immunotherapy. In this study we identify peptides from HPV-18 E6 and E7 proteins that bind to HLA class I molecules. We further show that these peptides are able to induce peptide-specific CTL from an HLA-A2-positive (+) peripheral blood donor in vitro. METHODS: A computer-assisted algorithm was devised to identify peptides from HPV-18 E6 and E7 proteins that bind to HLA-A2 molecules. Peptides that were predicted to bind were synthesized and their binding activity was determined. HLA-A2(+) irradiated stimulator cells pulsed with HPV-18 peptides were incubated with HLA-A2(+) peripheral blood mononuclear cells. Cytotoxicity assays were performed to assess specific cell lysis. RESULTS: Of 295 possible sequences, the computer-assisted algorithm predicted 10 peptides that would have a high probability of binding to HLA-A2. The 4 strongest binding peptides were analyzed for their ability to induce cytotoxic cells against HPV-18 peptide-pulsed targets. Two of the peptides induced significant lysis. CONCLUSIONS: There are limited data on peptide-based immunotherapy for HPV-18(+) tumors. The combination of our computer-assisted algorithm and binding assay permits rapid selection of potential CTL epitopes. We identified two peptides that were able to induce peptide-specific lysis. These two epitopes are candidates for a peptide-based vaccine against HPV-18(+) tumors. The model described has broad applications and can be used in the development of immunotherapy for other types of cancers. Copyright 2001 Academic Press.

Unique Identifier: 21320636

Teratog Carcinog Mutagen 2001;21(4):303-313

Protective effect of Picroliv, the active constituent of Picrorhiza kurroa, against chemical carcinogenesis in mice.

Rajeshkumar NV, Kuttan R.

Amala Cancer Research Centre, Thrissur, Kerala, India.

Cancer chemoprevention of chemically induced tumours by Picroliv, an iridoid glycoside mixture purified from Picrorhiza kurroa, was studied on 20-methylcholanthrene (20-MC)-induced sarcoma model and 7,12-dimethylbenz[a]anthracene (DMBA)-initiated papilloma formation in BALB/c mice. Administration of Picroliv (100 and 200 mg/kg, p.o) inhibited the

sarcoma development by 47 and 53% as estimated on day 200 after 20-MC administration. Control animals started dying of tumour burden 76 days after 20-MC administration and all animals were dead by day 170, while 60 and 66% of the animals survived in the Picroliv treated group, 100 and 200 mg/kg, respectively. Picroliv exhibited anti-tumour-promoting activity on a two-stage carcinogenesis test on mouse skin using DMBA as an initiator and croton oil as a promoter. Topical application of Picroliv (1 and 5 mg/mouse) 30 minutes prior to that of croton oil application resulted in a 50 and 60% reduction in the number of animals that developed papillomas, and 48 and 64% reduction in the number of papillomas per mouse. There was also a delay in the onset of first skin tumour in the group of animals treated with Picroliv. Oral administration of Picroliv (150 mg/kg, p.o.) prior to DMBA application delayed the onset of papillomas and the percent of mice (60%) with tumours indicates that Picroliv inhibited the tumour initiation induced by DMBA. Picroliv administration was also found to increase the life span of transplanted Dalton's Lymphoma Ascites (DLA) and Ehrlich Ascites Carcinoma (EAC) harboring mice and reduced the volume of transplanted solid tumours.

Unique Identifier: 21299923

Toxicol Lett 2001 May 31;122(1):33-44

Topical and oral administration of the natural water-soluble antioxidant from spinach reduces the multiplicity of papillomas in the Tg.AC mouse model.

Nyska A, Lomnitski L, Spalding J, Dunson DB, Goldsworthy TL, Grossman S, Bergman M, Boorman G.

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The Tg.AC mouse carrying the v-Ha-ras structural gene is a useful model for the study of chemical carcinogens, especially those acting via non-genotoxic mechanisms. This study evaluated the efficacy of the non-toxic, water-soluble antioxidant from spinach, natural antioxidant (NAO), in reducing skin papilloma induction in female hemizygous Tg.AC mice treated dermally five times over 2.5 weeks with 2.5 microg 12-O-tetradecanoylphorbol-13-acetate (TPA). The TPA-only group was considered as a control; the other two groups received, additionally, NAO topically (2 mg) or orally (100 mg/kg), 5 days/week for 5 weeks. Papilloma counts made macroscopically during the clinical observations showed a significant decrease in multiplicity ($P<0.01$) in the NAO topically treated group. According to histological criteria, papilloma multiplicity were lower in both topical-NAO and oral-NAO groups, but significantly so only in the oral-NAO mice ($P<0.01$). The beneficial effect of NAO in the Tg.AC mouse is reported.

Unique Identifier: 21291454

Virology 2001 May 25;284(1):82-98

Detection of viral DNA and E4 protein in basal keratinocytes of experimental canine oral papillomavirus lesions.

Nicholls PK, Doorbar J, Moore RA, Peh W, Anderson DM, Stanley MA.

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We studied experimental canine oral papillomavirus (COPV) infection by in situ hybridization and immunohistochemistry of weekly biopsies. After 4 weeks, viral DNA in rete ridges suggested a keratinocyte stem cell target. Abundant viral DNA was seen in E4-positive cells only. E4 was predominantly cytoplasmic but also nuclear, being concentrated in the nucleoli during wart formation. Infected cells spread laterally along the basal layer and into the parabasal layers, accompanied by E7 transcription and increased mitoses. Most of the lower epithelium was positive for viral DNA, but, in mature warts, higher levels of E4 expression and genome amplification occurred in only sporadic superficial cells. L1 expression was late and in only a subset of E4-positive cells. During regression, viral DNA was less abundant in deep epithelial layers, suggesting downregulation of replication prior to replacement of infected cells from beneath. Detection of viral DNA in post-regression tissue indicated latent infection.

Unique Identifier: 21251392

Med Pediatr Oncol 2001 May;36(5):564-567

Retinoid chemoprevention in patients at high risk for skin cancer.

DiGiovanna JJ.

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Patients who develop large numbers of skin cancers suffer increased morbidity and mortality. A high skin cancer risk can result from inherited disorders such as xeroderma pigmentosum (abnormal repair of UV-induced DNA damage) or the nevoid basal cell carcinoma syndrome (tumor suppressor gene abnormality). The efficacy of systemic retinoid skin cancer chemoprevention was first demonstrated in these disorders. Since the mechanism of cancer prevention was not thought to involve correction of the underlying defect causing the disorder, individuals at high risk for new skin cancers from other causes may also benefit from this approach. With the success of organ transplantation, there is a growing population

of transplant recipients living long, active lives who also have sustained chronic UV damage. This population is at high risk for developing aggressive squamous cell carcinomas. In this population, extensive skin involvement with human papilloma virus induced warts and actinic keratoses results in difficulty with diagnosis and monitoring for these dangerous malignancies. Patients who have received treatment with agents that cause DNA damage, such as X-radiation, may also have a high skin cancer risk. Retinoid chemoprevention may also be of benefit in the management of selected patients with these iatrogenic conditions. This evolving therapeutic role has heightened the need for the development of new retinoids, with more efficacy and less toxicity, for cancer chemoprevention.

Unique Identifier: 21238489

Ear Nose Throat J 2001 Apr;80(4):194-195

Papillomata masquerading as vocal fold nodules.

Dean CM, Hawkshaw M, Sataloff RT.

American Institute for Voice and Ear Research, Philadelphia, USA.

No abstract available.

Unique Identifier: 21237313

J Med Microbiol 2001 May;50(5):468-471

Poor antibody response against human papillomavirus in adult-onset laryngeal papillomatosis.

Aaltonen LM, Auvinen E, Dillner J, Lehtinen M, Paavonen J, Rihkanen H, Vaheri A.

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To investigate whether adult-onset laryngeal papillomatosis induces serum antibodies to the human papillomavirus (HPV), 60 patients underwent a clinical examination, and HPV DNA from their laryngeal biopsy was assayed by PCR and HPV serology with virus-like particles as the antigen. Patients and controls (n = 53) showed no differences in their HPV 6 and 16 antibodies. Patients more often had HPV 11 antibodies, female patients more often than female controls or male patients. Of the female patients, 5 of 15 had a history of genital condylomas and, at the follow-up visit, 5 of 9 had cervical cytology consistent with genital HPV infection. The fact that HPV antibodies did not correlate with clinical features of the

laryngeal disease or with HPV DNA detected in the larynx, suggests that HPV antibodies in female patients were induced by genital rather than laryngeal HPV infection. The high prevalence of abnormal Pap smears indicates that gynaecological examination of female adult-onset laryngeal papilloma patients is warranted.

Unique Identifier: 21235845

Int J Pediatr Otorhinolaryngol 2001 May 11;58(3):233-238

Recurrent respiratory papillomatosis with esophageal involvement.

Batra PS, Hebert RL 2nd, Haines GK 3rd, Holinger LD.

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OBJECTIVE: To report a case of recurrent respiratory papillomatosis with diffuse involvement of the esophagus in a child. DESIGN: Retrospective case report and literature review. SETTING: Tertiary Children's Hospital. CONCLUSION: Endoscopy is recommended for detection of esophageal papillomas, especially in patients with significant laryngeal lesions or post-cricoid involvement.

Unique Identifier: 21233331

Pediatr Transplant 2001 Apr;5(2):142-144

Successful ribavirin therapy for life-threatening laryngeal papillomatosis post liver transplantation.

Balauff A, Sira J, Pearman K, McKiernan P, Buckels J, Kelly D.

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A 3-yr-old girl developed severe progressive juvenile laryngeal papillomatosis (JLP) 2 yr after liver transplantation (Tx) for biliary atresia. The papillomata were resistant to withdrawal of immunosuppression, to laser surgery, and to subcutaneous interferon (3 MU/m2, three times weekly), necessitating tracheostomy. Oral ribavirin therapy (25 mg/kg/day) in combination with no immunosuppression effectively prevented the rapid recurrence of JLP over 5 yr. Hence, oral ribavirin is a potentially useful therapy in this life-threatening situation and may also be of benefit in other children with severe JLP.
Unique Identifier: 21227306

J Calif Dent Assoc 2000 Dec;28(12):922-927

Papillary lesions of the oral cavity: relationship to human papillomaviruses.

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Human papillomaviruses are a group of genetically related organisms that infect stratified squamous epithelium. Unlike many other viruses that infect oral epithelium and induce lysis of the cells they penetrate, HPVs induce proliferative changes in these cells that result in both benign and malignant tumors. The common skin wart (verruca vulgaris) is induced by HPV 2 and 4. Genital warts (condylomas) and the common solitary oral papilloma are associated with HPV 6 and 11. Either HPV 13 or 32 causes focal epithelial hyperplasia. All of these wart-like lesions are benign growths of the stratified squamous lining of the oral cavity and lips and can be treated by surgical excision or laser ablation. HPV 16 and other less frequently encountered genotypes are associated with uterine cervix cancer in 95 percent to 98 percent of cases, and the evidence for a causal role is robust. There are emerging data that implicate HPV in certain subsets of oral cancer, particularly those that arise in the oropharynx/tonsillar region. Some instances of the various histologic subtypes subsumed under proliferative verrucous leukoplakia and verrucous carcinoma also harbor HPV.

Unique Identifier: 21222044

Virology 2001 Apr 25;283(1):31-39

Regression of canine oral papillomas is associated with infiltration of CD4+ and CD8+ lymphocytes.

Nicholls PK, Moore PF, Anderson DM, Moore RA, Parry NR, Gough GW, Stanley MA.

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Canine oral papillomavirus (COPV) infection is used in vaccine development against mucosal papillomaviruses. The predictable, spontaneous regression of the papillomas makes this an attractive system for analysis of cellular immunity. Immunohistochemical analysis of the timing and phenotype of immune cell infiltration revealed a marked influx of leukocytes during wart regression, including abundant CD4+ and CD8+ cells, with CD4+ cells being most numerous. Comparison of these findings, and those of immunohistochemistry using TCRalphabeta-, TCRgammadelta-, CD1a-, CD1c-, CD11a-, CD11b-, CD11c-, CD18-, CD21-, and CD49d-specific monoclonal antibodies, with previously published work in the human, ox, and rabbit models revealed important differences between these systems. Unlike bovine papillomavirus lesions, those of COPV do not have a significant gamma/delta T-cell

infiltrate. Furthermore, COPV lesions had numerous CD4+ cells, unlike cottontail rabbit papillomavirus lesions. The lymphocyte infiltrate in the dog resembled that in human papillomavirus lesions, indicating that COPV is an appropriate model for human papillomavirus immunity. Copyright 2001 Academic Press.

Unique Identifier: 21214660

Acta Anaesthesiol Scand 2001 May;45(5):645-648

Laryngeal papillomatosis with airway obstruction in an infant.

Mikkelsen PG.

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Laryngeal papillomatosis in infants and children is a benign condition, but the location and a marked tendency for recurrence makes the disease both dangerous and troublesome. This case report deals with a little girl who had suffered hoarseness and wheezing since she was born. The diagnosis of laryngeal papillomatosis was made when she was 17 months old. By that time, the tumour had reached a size that necessitated a tracheotomy to secure the airway. The symptoms and differential diagnoses are discussed, and it is stressed that chronic hoarseness and wheezing sounds in infants and children should make a doctor suspect laryngeal papillomatosis. Laser treatment and anaesthetic management of small children with a compromised airway are discussed. As tracheal intubations and tracheotomy increase the risk of the disease spreading to the trachea and bronchi, an example is given of treating laryngeal papillomatosis with potassium titanyl phosphate (KTP) laser, using a laryngeal mask as an airway to avoid tracheal intubation. Whether this procedure can reduce the need to perform a tracheotomy in some of these small patients remains to be seen.

Unique Identifier: 21205579

Arch Otolaryngol Head Neck Surg 2001 Apr;127(4):442-446

Latex allergy: an update for the otolaryngologist.

Kashima ML, Tunkel DE, Cummings CW.

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OBJECTIVE: To describe the clinical manifestations of latex allergy in otolaryngology

patients. DESIGN: Descriptive case series. SETTING: Tertiary academic otolaryngology practice. PATIENTS: Otolaryngology patients with documented allergic reactions to latex during surgery and confirmatory laboratory test results for latex allergy. MAIN OUTCOME MEASURES: Clinical description of latex reactions; identification of risk factors for latex allergy. RESULTS: We describe 3 patients, 2 children and 1 young adult, with severe latex allergy manifested by intraoperative cardiorespiratory changes and confirmed by positive latex-specific IgE test results. A 9-year-old boy with a tracheotomy and a history of multiple procedures for laryngeal stenosis developed a rash and unexplained bronchospasm during an open laryngeal procedure. Surgery was aborted, and subsequent surgery was performed uneventfully 4 weeks later using a latex-safe environment. A 13-year-old boy with recurrent respiratory papillomatosis and a ventriculoperitoneal shunt had sudden unexplained arterial oxygen desaturation and a rash during laser endoscopy. He was then treated successfully using latex-safe protocols. A 23-year-old man with a parotid malignancy developed unexplained hypotension and ventilatory difficulties in the operating room during preparation for surgery. He responded to medical treatment for anaphylaxis. CONCLUSION: The otolaryngologist should share in the increased awareness of latex allergy. Our patients who have had multiple surgical procedures or who are exposed to latex on a long-term basis may be at increased risk. Latex allergy should be considered when unexplained cardiorespiratory compromise occurs during surgery.

Unique Identifier: 21191813

Otolaryngol Head Neck Surg 2001 Apr;124(4):421-425

A new laser treatment for vocal cord papilloma--585-nm pulsed dye.

Valdez TA, McMillan K, Shapshay SM.

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OBJECTIVES: Microvascular targeting with the 585- nm pulsed dye laser (PDL) may provide a new form of therapy to control symptoms caused by recurrent respiratory papillomatosis (RRP). METHODS: Ten patients with RRP underwent 13 procedures under general anesthesia with the 585-nm PDL. A micromanipulator (11 procedures) and a flexible nasolaryngoscope (2 procedures) were used to deliver the laser pulses. Patients were followed postoperatively according to protocol. RESULTS: Clinical examination revealed regression of papillomas in all patients. Seven patients had complete regression after PDL surgery, and 2 patients had partial response to treatment. One patient was lost to follow-up. No complications were present during this prospective nonrandomized pilot study. CONCLUSION: Patients treated with PDL experienced regression of their papillomas. PDL may provide patients with RRP with an alternative treatment without the risks associated with CO(2) laser surgery. This procedure also has potential to be delivered on an outpatient basis with flexible fiberoptic laryngoscopes.
Unique Identifier: 21179707

J Laryngol Otol 2001 Apr;115(4):302-303

Deliberate removal of incisor teeth to allow access for laryngoscopy.

Saravanappa N, Ward VM, Harries ML.

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This paper describes a clinical situation where it was impossible to obtain a biopsy of a lesion at the anterior commissure in a patient with progressive hoarseness of voice using standard microlaryngoscopy techniques. Due to anatomical difficulties and a histological suggestion of laryngeal papillomatosis the incisor teeth were deliberately removed to allow an adequate view of the larynx and to facilitate further access.

Unique Identifier: 21172972

Appl Immunohistochem Molecul Morphol 2001 Mar;9(1):86-91

Topoisomerase alpha II, retinoblastoma gene product, and p53: potential relationships with aggressive behavior and malignant transformation in recurrent respiratory papillomatosis.

Gupta D, Holden J, Layfield L.

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Recurrent respiratory papillomatosis (RRP) has a juvenile aggressive form and an adult more indolent form. Most cases of RRP are cytologically benign; however, some undergo malignant transformation. At present, there are no known markers that help identify patients at risk for aggressive disease. We investigated by immunohistochemistry expressions of topoisomerase alpha II, MIB-1, p53, p21, E-cadherin, retinoblastoma (RB) gene protein product, HER-2/neu, and steroid hormone receptors in a case of juvenile respiratory papillomatosis with malignant transformation to determine whether these markers are associated with malignant transformation. Histologic examination of the pulmonary lobectomy specimen revealed well-differentiated squamous carcinoma and invasive papillomatosis. Increased staining was found in areas of invasive papillomatosis for topoisomerase alpha II, p53, and MIB-1, with highest labeling indices in areas of squamous carcinoma. Staining intensity for RB gene protein product showed gradual decline from benign papilloma (3+) and invasive papillomatosis (2+) to squamous carcinoma (0-1+). Expression of p21 was similar in benign papilloma and invasive papillomatosis but showed reduction in squamous carcinoma. Expressions of E-cadherin, HER-2/neu, and steroid hormone receptors did not appear to correlate with biologic behavior. Increased topoisomerase alpha II and p53 expression along with reduced RB gene protein product and

p21 expression may serve as markers of transformation to invasive papillomatosis and squamous carcinoma.

Unique Identifier: 21171021

J Oral Sci 2000 Dec;42(4):189-193

Design of a unique PCR primer for detection of oral HPV infection.

Kuroki T, Tsuzukibashi O, Saito M, Kuribayashi S, Shimpuku Y, Makimura M.

Department of Comprehensive Dentistry, Nihon University School of Dentistry at Matsudo, Chiba, Japan.

Human papillomavirus (HPV) has been known as a pathogen of oral dysplasia. However, suitable PCR primers for the detection of oral HPV infection have not been reported. The aim of this study was to design unique consensus primers. The consensus primers were designed by homologues analyses between subtypes 2, 6, 11, 13, 16, 18, 30, 32 and 58, which frequently infect the oral membrane. PCR, with our designed primer, detected HPV DNA subtypes 2, 6, 11, 16, 18 and 58, and also showed PCR product from a clinical papilloma sample. These results indicate that our designed consensus primer can be used for the study of the relationships between oral disease and HPV infection.

Unique Identifier: 21165864

J Pharmacol Exp Ther 2001 Apr;297(1):1-10

2001 ASPET Otto Krayer Award Lecture. Molecular targets for antiviral agents.

De Clercq E.

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There are a number of virus-specific processes within the virus replicative cycle or virus-infected cell that have proven to be attractive targets for chemotherapeutic intervention, i.e., virus adsorption and entry into the cells, reverse (RNA --> DNA) transcription, viral DNA polymerization, and cellular enzymatic reactions that are associated with viral DNA and RNA synthesis and viral mRNA maturation (i.e., methylation). A variety of chemotherapeutic agents, both nucleoside (and nucleotide) and non-nucleoside entities, have been identified that specifically interact with these viral targets, that selectively inhibit virus replication, and that are either used or considered for clinical use in the treatment of virus infections in humans. Their indications encompass virtually all major human viral pathogens, including

human immunodeficiency virus (HIV), hepatitis B virus (HBV), herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), human papilloma virus (HPV), orthomyxoviruses (influenza A and B), paramyxoviruses [e.g., respiratory syncytial virus (RSV)] and hemorrhagic fever viruses (such as Ebola virus).

Unique Identifier: 21160047

Vaccine 2001 Mar 21;19(17-19):2549-2556

Clinical studies of human papilloma vaccines in pre-invasive and invasive cancer.

Adams M, Borysiewicz L, Fiander A, Man S, Jasani B, Navabi H, Lipetz C, Evans AS, Mason M.

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Cervical cancer is the second most common cause of cancer death in women worldwide. It is almost invariably associated with infection with human papilloma virus (HPV) particularly types 16 and 18. The ubiquitous expression of E6 and E7 oncogene products has been recognised as an attractive target for CTL-mediated immunotherapy. In-vivo expansion of an HPV oncogene product specific MHC class 1 restricted response has been demonstrated using intradermally administered live vaccinia virus HPV 16 and 18 E6/E7 gene construct (TA-HPV, Cantab Pharmaceuticals). Responses have been seen in 1/3 evaluable patients with advanced cervical cancer, and 3/12 CIN3 volunteers, and in 4/29 patients with early invasive cervical cancer (Rankin et al. Proceedings of 91st AACR Meeting, San Francisco, April 2000). In addition, the adoptive transfer of ex vivo HPV 16 or 18 positive autologous tumour lysate pulsed dendritic cells is currently being tested as an alternative means of expanding HPV specific CTL in advanced cervical cancer patients. So far an HLA-A*O201 restricted CD8 T cell response has been recorded in the single HLA-A*O201 patient whose tumour was shown to be HPV16 positive. It appears therefore feasible to induce HPV specific CTL responses in patients with cervical cancer using several vaccine strategies. However, further clinical trials are needed to determine the full anti-tumour potential of this vaccine based immunotherapy.

Unique Identifier: 21157772

Antimicrob Agents Chemother 2001 Apr;45(4):1201-1209

Combination treatment with intralesional cidofovir and viral-dna vaccination cures large cottontail rabbit papillomavirus-induced papillomas and reduces recurrences.

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Pathology, The Jake Gittlen Cancer Research Institute, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033.

We used the cottontail rabbit papillomavirus (CRPV) New Zealand White rabbit model to test a combination treatment of large established papillomas with intralesional cidofovir and DNA vaccination to cure sites and reduce recurrences. Intralesional 1% (wt/vol) (0.036 M) cidofovir treatment of rabbit papillomas led to elimination, or "cure," of the papillomas over a 6- to 8-week treatment period (N. D. Christenson, M. D. Pickel, L. R. Budgeon, and J. W. Kreider, Antivir. Res. 48:131-142, 2000). However, recurrences at periods from 1 to 8 weeks after treatment cessation were observed at approximately 50% of cured sites. DNA vaccinations with CRPV E1, E2, E6, and E7 were initiated either after or at the time of intralesional treatments, and the recurrence rates were observed. When DNA vaccinations were started after intralesional cures, recurrence rates were similar to those of vector-vaccinated rabbits. A small proportion of recurrent sites subsequently regressed (4 out of 10, or 40%) in the vaccinated group versus no regression of recurrences in the vector-immunized group (0 out of 19, or 0%), indicating partial effectiveness. In contrast, when DNA vaccinations were conducted during intralesional treatments, a significant reduction of recurrences (from 10 out of 19, or 53%, of sites in vector-immunized rabbits to 3 out of 20, or 15%, of sites in viral-DNA-immunized rabbits) was observed. DNA vaccination without intralesional treatments had a minimal effect on preexisting papillomas. These data indicated that treatment with a combination of antiviral compounds and specific immune stimulation may lead to long-term cures of lesions without the ensuing problem of papilloma recurrence.

Unique Identifier: 21156971

Laryngoscope 2001 Mar;111(3):404-408

The predictive value of serum interleukins in recurrent respiratory papillomatosis: a preliminary study.

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OBJECTIVE: IL-2 is the primary interleukin responsible for activation of the cell-mediated (Th1) arm of the immune response. Our objective was to determine whether a correlation existed between circulating levels of interleukin-2 as well as its soluble receptor (sIL-2R) and the clinical course of recurrent respiratory papillomatosis. METHODS AND MATERIALS: Fifteen children with a histological diagnosis of RRP were recruited. Age at the time of study, time since first diagnosis, and number of surgical interventions were recorded. The number of surgically treated recurrences per year was then calculated. We obtained serum samples from each of these 15 children and from 10 normal control subjects. We then performed in vitro determination of serum IL-2 and soluble IL-2 receptor levels using

enzyme-linked immunosorbent assay (ELISA) techniques. RESULTS: IL-2 was significantly lower (136.6 vs. 199.9 pg/mL, P =.035) in papilloma patients than in control subjects. IL-2R was also lower in papilloma patients (531.7 vs. 785.8 U/mL, P =.025). There was no statistical age difference between the papilloma and control groups. Among patients with papillomatosis, IL-2 and sIL-2R levels were significantly higher in those with aggressive disease (>4 surgically treated recurrences per year) versus non-aggressive disease (179.2 vs. 99.2 pg/mL, P =.024; and 697 vs. 387 U/mL, P =.022). Age was also significantly lower in the aggressive papilloma group (P =.002). CONCLUSIONS: Levels of interleukin-2 and IL-2 receptor were significantly lower in patients with recurrent respiratory papillomatosis compared with normal children. These data support the presence of an aberrant cell-mediated immune response in children with recurrent respiratory papillomatosis.

Unique Identifier: 21126443

Int J Pediatr Otorhinolaryngol 2001 Mar;57(3):189-193

Acoustic analysis in the diagnosis of voice disorders in children.

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The main aim of this study was to describe the changes in acoustic analysis in diagnosing voice disorders in children. The secondary goal was the attempt at differentiation of organic and functional disorders by means of acoustic analysis. The study included 112 children in treated due to laryngeal papilloma, gastro-esophageal reflux, atopic disease and noduli vocales. The following values have been determined: basic frequency F(o), jitter, shimmer, F(o) tremor and the harmonics to noise ratio (HNR). The study results confirmed that the HNR value was the most sensitive indicator of changes in the voice organ.

Unique Identifier: 21125346

J Cutan Pathol 2001 Mar;28(3):131-134

Dermal dendritic cells in anogenital warty lesions unresponsive to an immune-response modifier.

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BACKGROUND: Human papilloma viruses (HPV) are responsible for a variety of

proliferative epithelial lesions including anogenital condylomas. These lesions may regress during treatment with an immune-response modifier such as imiquimod. The release of specific cytokines from the monocyte-macrophage lineage induces a cascade of events abating the HPV replication. METHOD: A total of 14 persistent warty anogenital lesions were excised 4 to 7 weeks after completing a 4-month imiquimod treatment. Another series of 25 untreated condylomas and 8 bowenoid papulosis served as controls. All examined lesions had been excised in otherwise healthy individuals with a normal immune status. Lesions were examined for the presence of Langerhans cells and subpopulations of the monocyte/macrophage/dendrocyte lineage using immunohistochemical detection of L1-protein, CD68, lysozyme and Factor-XIIIa. CD45R0-positive T lymphocytes were also identified. HPV capsid antigens and genotypes were searched for using immunohistochemistry and in situ hybridization, respectively. RESULTS: The persistent although treated anogenital lesions were identified as 10 viral condylomas, 3 bowenoid papulosis and 1 basal cell carcinoma. The inflammatory cell densities and distributions were similar in the untreated and imiquimod-resistant condylomas with the exception of Factor XIIIa-positive dendrocytes. These dermal dendritic cells were slim and rare in all imiquimod-resistant lesions. In contrast, about two-thirds of the untreated condylomas were enriched in these cells. CONCLUSION: As dermal dendritic cells play a role in the immune surveillance, their low densities in some lesions might be a key feature responsible for low cytokine local production and failure of imiquimod treatment. The combined apparent lack of Langerhans cell activation might suggest that both intraepidermal and intradermal compartments of antigen-presenting cells are affected in imiquimod-resistant lesions.

Unique Identifier: 21102768

Braz Dent J 2000;11(2):105-110

AgNORs in hyperplasia, papilloma and oral squamous cell carcinoma.

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Ten inflammatory fibrous hyperplasias, ten papillomas, and nineteen oral squamous cell carcinomas were analyzed by the AgNOR technique to determine if different disturbances of oral epithelia presented different AgNOR counts. The papilloma group showed higher mean AgNOR counts (3.15 +/- 0.58) than the hyperplasia group (1.98 +/- 0.24) and smaller than the well-differentiated oral squamous cell carcinoma group (6.56 +/- 1.25) and poorly differentiated oral squamous cell carcinoma group (7.07 +/- 1.60). The differences among the groups of lesions were statistically significant ($P < 0.05$) except between the well differentiated oral squamous cell carcinoma group and the poorly differentiated oral squamous cell carcinoma group. Our findings suggest that the cellular proliferation ratio in papillomas is greater than hyperplasias and smaller than carcinomas.
Unique Identifier: 21078742

Gen Dent 2000 Jan;48(1):62-64

Oral condyloma acuminatum.

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Oral condyloma acuminatum is a papillomatous lesion that is transmitted sexually and associated with the human papilloma virus. Condyloma acuminatum generally appears one to three months after exposure to an infected partner and presents in multiple form in the oral cavity.

Unique Identifier: 21070674

J Gen Virol 2001 Jan;82(Pt 1):201-213

Oestrogen and progesterone increase the levels of apoptosis induced by the human papillomavirus type 16 E2 and E7 proteins.

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Human papillomavirus (HPV) type 16 infects the genital tract and is generally acknowledged to be a causative agent of cervical cancer. HPV infection alone is not sufficient to induce cervical cancer and other factors such as steroid hormones are thought to play a role in the establishment and/or progression of this disease. The HPV-16 E2 protein is required for virus replication and modulates viral gene expression whereas the HPV-16 E7 protein is required for cell transformation. We and others have shown that both the E2 and E7 proteins can induce apoptotic cell death in HPV-transformed and non-HPV transformed cell lines. Here we show that the steroid hormones oestrogen and progesterone can both increase the levels of E2- and E7-induced apoptosis. The oestrogen metabolite 16 alpha-hydroxyoestrone also increases E2- and E7-induced cell death and the dietary component indole-3-carbinol, which reduces the formation of 16alpha-hydroxyoestrone from oestrogen, blocks the effects of oestrogen. Thus the metabolism of oestrogen to 16 alpha-hydroxyoestrone appears to be required for the effects of this hormone on E2- and E7-induced cell death. We also show that the oestrogen receptor antagonist 3-hydroxytamoxifen blocks the effects of oestrogen on E2- and E7-induced cell death, whereas the anti-progesterone RU486 blocks the effects of both progesterone and oestrogen. We discuss these results in terms of the origin and progression of cervical cancer.

Unique Identifier: 21064573

Pediatr Dev Pathol 2001 Jan;4(1):68-72

Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus-6-associated disease.

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The aim of this study was to determine whether viral type (HPV-6 vs. HPV-11) could predict the clinical course of recurrent respiratory papillomatosis in children. Viral typing, using the polymerase chain reaction, was performed on laryngeal biopsies of 61 patients treated at Children's Hospital of Michigan. HPV-6 was detected in 29 of the patients' biopsies and HPV-11 in 32 biopsies. HPV-11 was more common among the African-American patients than among Caucasians (P = 0.001). Patients with HPV-11 were diagnosed at a younger age (36.2 vs. 48.2 months; P = 0.04) and were more likely to have active disease (P = 0.0311) at the time of this study. They tended to have longer periods of disease activity (8 years vs. 5 years; P = 0.026), required more surgical procedures (42 procedures/patient vs. 13.6; P = 0.02), and more procedures per patient, per year (2.9 vs. 5.3; P = 0.0164). Three of the patients infected with HPV-11 developed invasive papillomatosis and bronchogenic squamous cell carcinoma, and two of these patients died of disease. Our findings suggest that HPV-11 infection confers a more aggressive course to recurrent respiratory papillomatosis.

Unique Identifier: 21041793

Cell Stress Chaperones 2000 Nov;5(5):401-405

Immunotherapy of a human papillomavirus type 16 E7-expressing tumor by administration of fusion protein comprised of Mycobacterium bovis BCG Hsp65 and HPV16 E7.

Chu NR, Wu HB, Wu TC, Boux LJ, Mizzen LA, Siegel MI.

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Human papillomavirus type 16 (HPV16) infection has been linked to the development of cervical and anal dysplasia and cancer. One hallmark of persistent infection is the synthesis of the viral E7 protein in cervical epithelial cells. The expression of E7 in dysplastic and transformed cells and its recognition by the immune system as a foreign antigen make it an ideal target for immunotherapy. Utilizing the E7-expressing murine tumor cell line, TC-1, as a model of cervical carcinoma, an immunotherapy based on the administration of an adjuvant-free fusion protein comprised of Mycobacterium bovis BCG Hsp65 linked to HPV16 E7 (HspE7) has been developed. Initial in vitro analyses indicate that immunization with HspE7 results in the induction of a type 1 immune response based on the pattern of secreted cytokines and the presence of cytolytic activity following antigenic recall. It has been

previously shown that prophylactic immunization with HspE7 protected mice against challenge with TC-1 cells and that these tumor-free animals are also protected against rechallenge with TC-1 cells. The present report shows that a single therapeutic immunization with HspE7 induces regression of palpable tumors, confers protection against tumor rechallenge, and is associated with long-term survival (>253 days). In vivo studies using mice with targeted mutations in CD8 or MHC class II or depleted of CD8 or CD4 lymphocyte subsets demonstrate that tumor regression following therapeutic HspE7 immunization is CD8 dependent and CD4 independent. These studies extend previous observations on the induction of CTL by Hsp fusion proteins and are consistent with the clinical application of HspE7 as an immunotherapy for human cervical and anal dysplasia and cancer.

Unique Identifier: 21036313

Lin Chuang Er Bi Yan Hou Ke Za Zhi 1998 Jul;12(7):298-301

The detection of basement membrane and dendritic cells in laryngeal carcinoma.

[Article in Chinese]

Hu S, Fei Q, Wen S.

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The state of basement membrane(BM) and dendritic cells(DC) were observed by immunohistochemical methods with the use of anti-laminin antibody, anti-type IV collagen antibody, anti-S-100 protein antibody in 68 cases of laryngeal carcinoma and 21 cases of non-cancer laryngeal tissues. The results showed that among 68 patients with laryngeal carcinoma 39 cases had discontinuous BM. A continuous, linear BM was found mostly in normal larynx, atypia hyperplasia and papilloma, only 3 cases had discontinuous BM. 43 positive DC were detected in 68 cases of laryngeal carcinoma. There were rarely positive DC in non-cancer laryngeal tissues. The poorer the differentiation of carcinoma, the more the discontinuous BM and the lesser the number of DC. The discontinuous BM and DC(-) were seen more in advanced stages of carcinoma. The five-year survival rate in patients with continuous BM was significantly higher than that in patients with discontinuous BM, the five-year survival rate in patients with DC positive was also higher than that in patients with DC negative; the survival rate was highest in patients with continuous BM and DC positive. Our results indicated that the detection of the state of BM and dendritic cells were of value to the prognostic analysis in patients with laryngeal carcinoma.

Unique Identifier: 21031565

Laryngoscope 2001 Jan;111(1):57-69

Recurrent respiratory papillomatosis.

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Recurrent respiratory papillomatosis (RRP) is the most common benign neoplasm of the larynx in children. Despite its benign histology, RRP has potentially morbid consequences and is often difficult to treat because of its tendency to recur and spread throughout the respiratory tract. Long neglected from an epidemiological standpoint, recent initiatives to better understand this disease process have been launched through coordination between the Centers for Disease Control and Prevention and the American Society of Pediatric Otolaryngology. In this clinical review, I discuss what we currently know regarding the etiology, epidemiology, and transmission of this disease. Clinical features including pertinent aspects of the history, physical examination, airway endoscopy, and other considerations are highlighted. A detailed description of the surgical and anesthetic management of these challenging cases is presented. Adjuvant modalities of surgical and nonsurgical treatment and their indications are discussed. Ongoing research initiatives and the Practice Guidelines of the Recurrent Respiratory Papillomatosis Task Force are also included.

Unique Identifier: 21030708

Minerva Stomatol 2000 Jun;49(6):281-292

Papilloma virus. Note I: identification and related oral pathology. Review of the literature.

[Article in Italian]

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Viral pathology is constantly increasing, in particular forms correlated to papilloma virus infection, both on account of the spread of oral sexual practices and of the receptivity of the host who is often affected by immune deficiency induced by the increased use of immunosuppressive treatment and the spread of HIV. Viral pathologies caused by papilloma virus are pre-cancerous lesions with a high degree of malignant transformation and for this reason the oral clinician must be able to diagnose them and start appropriate therapy. This study highlights the general characteristics of hyman papilloma virus, the related oral

pathologies and the host's response.

Unique Identifier: 21029935

Laryngorhinootologie 2000 Nov;79(11):673-674

Indirect micro-phonosurgery.

[Article in German]

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No abstract available.

Unique Identifier: 21020538

West Afr J Med 2000 Jul-Sep;19(3):195-9.

Prevalence of human papilloma virus genital infections in sexually transmitted diseases clinic attendees in Ibadan.

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All patients, who presented at the Sexually Transmitted Disease clinic of the University College Hospital, Ibadan, between the period of August 1996 and January 1998 were included in this study. They were examined for genital infections in order to determine the prevalence rate of Human papilloma virus genital infection (genital warts) among them. Out of the 1,373 patients seen in the clinic during the period, 861 (62.71%) had STD while the remaining 512 (37.29%) had other conditions. Out of these 861 cases, 69 (8.01%) had HPV genital infection, while the remaining 792 (91.9%) had other STDS. Of these 69 cases of genital warts, 35 (50.7%) were males while 34 (49.3%) were females. Their ages ranged between 17 and 74 years, with the peak incidence in the 20-29 years age group. 32 (46.4%) had concurrent genital infections with non-gonococcal urethritis and cervicitis 9(13%) constituting the most common type. The highest incidence (36.2%) of this condition was found among petty traders while the lowest was found among the business executives and applicants. In 67 (97%) of these patients, the nature of sexual intercourse was vaginal, while in 1 (1.5%) it was oral and another 1 (1.5%) both vaginal and oral. 26 (37.7%) of the patients had just one sexual partner, while 7 (8.1%) had 2 or more. Only 2 (2.9%) admitted to have

had any sexual contact with commercial sex workers. The sites of warts in males include the shaft of the penis, the glans penis, perineum and intrameatum. In females, warts were found in the vulva, vagina, cervix, perineum and perianal regions. 42 (60.9%) of these patients were placed on 20% podophyllin on tincture of benzoin, 17 (24.6%) on cryotherapy and 1 (1.5%) on both. They all did well on the different treatment regimens except for 1 (1.5%) that had to change from podophyllin to cryotherapy when there was no reduction in size. 11 (15.9%) were however lost to follow up.

Unique Identifier: 21017097

Antiviral Res 2000 Nov;48(2):131-142

In vivo anti-papillomavirus activity of nucleoside analogues including cidofovir on CRPV-induced rabbit papillomas.

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A series of nucleoside analogues were tested for in vivo anti-papillomavirus activity using the cottontail rabbit papillomavirus (CRPV) domestic rabbit model. Compounds were delivered either topically, injected into growing papillomas, or delivered subcutaneously at a site remote from the papillomas. Compounds tested included cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine] (HPMPC); cyclic HPMPC (cHPMPC); cyclopentenylcytosine (CPE-C); lobucavir [1R(1alpha,2beta,3alpha)]-9-[2, 3-bis(hydroxymethyl)cyclobutyl]guanine; 9-((2-phosphonylmethoxy)propyl)adenine (PMPA); adefovir 9-((2-phosphonylmethoxy)ethyl)adenine(PMEA) and cyclopropyl 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine (cyclopropylPMEDAP). Dose response curves and time-course treatments were included for most compounds tested. Strong anti-viral activity was detected using cidofovir and cHPMPC when delivered either topically or by the intralesional route. Complete cures were obtained using 1% (w/v) topical cidofovir at dosing schedules of twice daily for 8 weeks beginning at 4 weeks after CRPV infection, which represents a time when papillomas were clearly visible. Complete cures of large established papillomas were obtained by intralesional injection of 1% cidofovir three times per week for 8 weeks. Topical treatments with adefovir had strong anti-viral activity, cyclopropyl PMEDAP had moderate anti-viral activity, and CPE-C, PMPA and lobucavir showed no effects. These data indicate that certain nucleoside analogues have strong in vivo anti-papillomavirus activity and that the CRPV/rabbit model is a good model for assessing clinical responses of anti-viral treatments for patients with HPV disease.

Unique Identifier: 29566418

Vestn Otorinolaringol 2000;5:54-57

The treatment of laryngeal papillomatosis with interferon inducers.

[Article in Russian]

Karimova FS, Ivanchenko GF, Grigorian SS.

Seventy three patients aged 16 to 88 years who had laryngeal papillomatosis (LP) were followed up. Microsurgical endolaryngeal removal of laryngeal papillomas was made in all the patients. The interferon inducers amixine and cycloferon as antirecurrent drugs were used in 45 patients by the regime the authors developed by taking into account the interferon status and cellular immunity of patients. The criteria for the efficiency of treatment were their improved interferon status and longer remission. The efficiency of treatment with amixine and cycloferon was 72 and 80%, respectively. Thus, the use of a sparing microsurgical intervention in combination with interferon inducers may be regarded as the method of choice in the LP treatment.

Unique Identifier: 20506079

Minerva Stomatol 2000 Apr;49(4):179-186

Papilloma virus. Review of the literature. Note II. Diagnosis and treatment.

[Article in Italian]

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Viral infections due to papilloma virus, are not always easy, for the oral clinician, to diagnose. In this paper the diagnostic procedures to detect infections due to papilloma virus and the available therapies to avoid possible recurrences are pointed out.

Unique Identifier: 20495419

Bangladesh Med Res Counc Bull 1999 Aug;25(2):46-50

Recurrent respiratory papillomatosis: a study of 24 cases.

Majumder SM, Ibrahim MF, Huda QK, Bhattacharjee N, Amin MN.

Deptt. of ENT, Mymensingh Medical College Hospital.

24 cases of recurrent respiratory papillomatosis (RRP) in children were treated by surgical removal with cup forceps and followed up for variable periods between 1990-95. Most of the

patients required multiple operations due to recurrence. No anaesthetic death or complication was recorded. Voice changes of different degrees were noted. Four patients has glottic web formation. The findings suggest that recurrence of RRP is very common & needs multiple session of surgery. For children with persistent and progressive voice change/cry, the necessity of precise & comprehensive endoscopic examination of the upper aerodigestive tract under general anesthesia (GA) is emphasized.

Unique Identifier: 20479007

Vestn Otorinolaringol 2000;4:22-25

Assessment of the formation of interferon neutralizing antibodies and their influence on the effectiveness of interferon therapy in children with juvenile respiratory papillomatosis.

[Article in Russian]

Nurmukhametov RK, Onufrieva EK, Soldatskii IL, Mezentseva MV, Kas'ianova NV, Tsvetnova MV, Kol'tsov VD.

Formation of neutralizing antibodies (NAB) to alpha-interferon (aINF) was assessed in the reaction of antiviral activity neutralization in 36 children with severe juvenile respiratory papillomatosis (JRP). Surgical removal of papillomas was combined with administration of recombinant aINF preparations (reaferon, intron A, viferon). High and moderate neutralizing activity was determined in 22 (61.1%) patients. 7, 2 and 13 of them received reaferon, intron A and viferon, respectively. NAB were not registered in the rest 14 (38.9%) patients. The frequency of NAB formation was not related to the preparation used, only in the group on reaferon it was insignificantly higher. It was found that the highest response to therapy occurred in children with low NAB titer (8 of 12 children, 66.7%), while children with high NAB titer (3 of 4 children, 75%) did not respond.

Unique Identifier: 20465956

Vestn Otorinolaringol 2000;4:17-21

Contemporary status of the issues in the treatment of children with respiratory papillomatosis.

[Article in Russian]

Zenger VG, Ashurov ZM.

For 15 years the authors treated 205 children aged 9 months to 15 years with respiratory papillomatosis. Besides surgical endolaryngeal removal of the papillomas, they applied immunomodulators, plasmapheresis and antiviral drugs. Of different methods of artificial lung ventilation, the best is thought to be transcatheter high-frequency artificial lung

ventilation. As shown by the studies of infection resistance, the combined treatment should incorporate such drugs as zovirax and leukomax. Ultrasound disintegration and laser photodestruction with Ho laser were introduced in surgical removal of the papillomas. The combined treatment shortens the treatment duration and prolongs recurrence-free period.

Unique Identifier: 20465955

Cancer Immunol Immunother 2000 Sep;49(7):347-360

A recombinant vaccinia virus containing the papilloma E2 protein promotes tumor regression by stimulating macrophage antibody-dependent cytotoxicity.

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Human papillomavirus infection is associated with cervical cancer. The E6 and E7 papillomavirus proteins are normally required for the maintenance of the malignant phenotype. Expression of these proteins in infected cells is negatively regulated by the binding of the papilloma E2 protein to the long terminal control region of the papilloma virus genome. The E2 protein can also promote cell arrest and apoptosis in HeLa cells. Therefore, it is clear that this protein has the potential of inhibiting the malignant phenotype. Because, anticancer vaccines based in vaccinia viruses have recently been shown to be an effective way to treat and to eradicate tumors, a recombinant vaccinia virus expressing the E2 gene of bovine papilloma virus (Modified Vaccinia Ankara, MVA E2) was created, to explore further the antitumor potential of the E2 protein. A series of rabbits, containing the VX2 transplantable papilloma carcinoma, were treated with MVA E2. An impressive tumor regression, up to a complete disappearance of tumor, was observed in most animals (80%). In contrast, very little or no regression was detected if the normal vaccinia virus was used. Lymphocytes isolated from MVA E2-treated rabbits did not show cytotoxic activity against tumor cells. However, in these animals a humoral immune response against tumor cells was observed. These antitumor antibodies were capable of activating macrophages to destroy tumor cells efficiently. These data indicate that injecting the MVA E2 recombinant vaccinia virus directly into the tumor results in a robust and long-lasting tumor regression. Data also suggest that antitumor antibodies are responsible, at least in part, for eliminating tumors by activating macrophage antibody-dependent cytotoxicity.

Unique Identifier: 20452090

Mod Pathol 2000 Aug;13(8):914-918

Squamous cell carcinoma arising in recurrent respiratory papillomatosis with pulmonary involvement: emerging common pattern of clinical features and human

papillomavirus serotype association.

Cook JR, Hill DA, Humphrey PA, Pfeifer JD, El-Mofty SK.

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Squamous papillomas of the lung are an uncommon feature of recurrent respiratory papillomatosis, occurring in fewer than 1% of cases. We describe a 23-year-old patient with pulmonary papillomas who developed a fatal squamous cell carcinoma of the lung. PCR-based human papillomavirus (HPV) typing showed the presence of HPV 11 DNA in both benign papillomas and invasive carcinoma. A review of the literature reveals four reports of malignant transformation of juvenile-onset recurrent respiratory papillomatosis in which HPV typing was performed. Similar clinical features are noted in all of the reports; specifically, each case has arisen in a young adult man with a history of papillomatosis since childhood. In each of the cases, HPV 11 was identified in association with the squamous cell carcinoma. Although HPV 11 is uncommonly associated with the development of invasive carcinoma at other sites, these findings suggest that it is correlated with malignant transformation in the setting of juvenile-onset recurrent respiratory papillomatosis.

Unique Identifier: 20410427

Clin Exp Immunol 2000 Aug;121(2):216-225

Immunotherapy of a human papillomavirus (HPV) type 16 E7-expressing tumour by administration of fusion protein comprising Mycobacterium bovis bacille Calmette-Guerin (BCG) hsp65 and HPV16 E7.

Chu NR, Wu HB, Wu T, Boux LJ, Siegel MI, Mizzen LA.

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Human papillomavirus type 16 (HPV16) infection has been linked to the development of cervical and anal dysplasia and cancer. One hallmark of persistent infection is the synthesis of the viral E7 protein in cervical epithelial cells. The expression of E7 in dysplastic and transformed cells and its recognition by the immune system as a foreign antigen make it an ideal target for immunotherapy. Utilizing the E7-expressing murine tumour cell line, TC-1, as a model of cervical carcinoma, an immunotherapy based on the administration of an adjuvant-free fusion protein comprising Mycobacterium bovis BCG heat shock protein (hsp)65 linked to HPV16 E7 (hspE7) has been developed. The data show that prophylactic immunization with hspE7 protects mice against challenge with TC-1 cells and that these tumour-free animals are also protected against re-challenge with TC-1 cells. In addition, therapeutic immunization with hspE7 induces regression of palpable tumours, confers protection against tumour re-challenge and is associated with long-term survival (> 253

days). In vitro analyses indicated that immunization with hspE7 leads to the induction of a Th1-like cell-mediated immune response based on the pattern of secreted cytokines and the presence of cytolytic activity following antigenic recall. In vivo studies using mice with targeted mutations in CD8 or MHC class II or depleted of CD8 or CD4 lymphocyte subsets demonstrate that tumour regression following therapeutic hspE7 immunization is CD8-dependent and CD4-independent. These studies extend previous observations on the induction of cytotoxic T lymphocytes by hsp fusion proteins and are consistent with the clinical application of hspE7 as an immunotherapy for human cervical and anal dysplasia and cancer.

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Incidence and prevalence of recurrent respiratory papillomatosis among children in Atlanta and Seattle.

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The incidence and prevalence of recurrent respiratory papillomatosis (RRP) for children aged <18 years were estimated in 2 US cities, Atlanta and Seattle, in 1996. All otolaryngologists in a 24-county area in metropolitan Atlanta (101 physicians) and an 8-county area in metropolitan Seattle (139 physicians) agreed to participate in the study. Medical record chart abstraction was performed only for children with documented current residence in the study area (21 patients in Atlanta and 14 patients in Seattle). The incidence rate for juvenile RRP was 1.11/100,000 population in Atlanta and 0.36/100, 000 in Seattle. The prevalence rate was 2.59/100,000 population in Atlanta and 1.69/100,000 in Seattle. In neither city did prevalences differ significantly when stratified by sex or race. Extrapolation of these estimates to the US population suggests that 80-1500 incident cases and 700-3000 prevalent cases of juvenile RRP will occur in the United States during 1999.

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