Recurrent respiratory papillomatosis: update 2008

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Purpose of review

Recurrent respiratory papillomatosis (RRP) is the most common benign neoplasm of the larynx in children. Over the past several years some exciting new therapeutic options as well as some relevant research into the disease process has emerged that may offer new insight and methods in managing this frustrating disease.

Recent findings

Recent investigations have resulted in the following findings: more accurate prevalence estimates of human papilloma virus in women in the United States; correlation of socioeconomic status and disease severity; the malignant potential of human papilloma virus in head and neck cancer; the role of the host immune system in RRP; the efficacy of a vaccine preventing human papilloma virus; the emergence of pulsed dye laser and potassium-titanyl-phosphate laser as a therapy for RRP; the efficacy of cidofovir as an adjunctive therapy for RRP; and the role of cyclooxygenase-2 in the molecular biology of RRP.

Summary

The management of RRP is ever evolving. Despite several new therapies discussed in this study, it is still a disease with the potential for high morbidity. As the focus of therapy shifts from treatment to prevention, it will take many years to determine whether prevention strategies are effective in limiting the spread of this disease. In the mean time, further research is needed to gain better control of this disease process.

Keywords

cidofovir, human papilloma virus, human papilloma virus vaccine, pulsed dye laser, recurrent respiratory papillomatosis

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Introduction

Recurrent respiratory papillomatosis (RRP) is the most common benign neoplasm of the larynx in children. Although a benign disease, it is frustrating to manage owing to its unpredictable nature and its tendency to recur and spread throughout the respiratory tract. Additionally, it possesses the potential for airway compromise and a 3–7% risk of malignant conversion [1,2••]. Exposure of the neonatal larynx to infected cervical tissue during transit through the birth canal is the proposed method of transmission. However, this is not absolute and other unknown factors are present in transmission of this disease. RRP treatment requires multiple surgical debridements and hospital admissions to control, costing an estimated $123 million annually. This number does not take into account the substantial human cost as well [2••]. This study reviews the epidemiology, etiology, and management of RRP and presents recent advancements from the medical literature.

Epidemiology

RRP demonstrates a bimodal distribution: juvenile onset and adult onset. Juvenile-onset recurrent respiratory papillomatosis (JORRP) occurs in children younger than 5 years. The second age peak, known as adult-onset recurrent respiratory papillomatosis (AORRP), occurs between the ages of 20 and 40 years old with a mode of transmission thought to be either latent virus present from birth or adult exposure through sexual contact. The younger the patient's age at diagnosis, the more likely the patient will have severe disease [2••,3–6]. Estimates of incidence and prevalence of RRP are imprecise. The RRP Task Force using the national registry for JORRP estimates an incidence in the pediatric population of 1.7–4.3 per 100 000 children and 1.8 per 100 000 adults [7,8].

RRP tends to affect families of lower socioeconomic status at a higher rate than more affluent families. In 2004, Wiatrak *et al.* [4] performed a longitudinal, prospective

analysis demonstrating a statistically significant association between higher disease severity scores and patients with Medicaid insurance (versus those with private insurance). Three years later, Leung *et al.* [2••] performed a cross-sectional study of the active JORPP patients at their institution in Toronto, Canada, looking to correlate socioeconomic status and disease severity. Instead of just looking at the patient's insurance as an indicator of socioeconomic status, they used more comprehensive measures that included family income, occupation, level of education, and community status. Although they did not find a statistically significant correlation, they noted that 45% of all the patients with JORRP were living below the poverty level (defined as 14–17th percentile). This finding suggests that poorer families are at greater risk for the disease.

Cause

Human papilloma virus (HPV) has been implicated as the etiologic agent of RRP. This small, DNA containing, nonenveloped icosahedral (20 sided) capsid virus is 7900 base pairs long with nearly 120 different subtypes of HPV identified [5]. RRP is almost universally caused by HPV types 6 and 11, the same types that cause genital warts. [9]. HPV type 11 is more likely to cause severe disease and is associated with earlier presentation. It tends to require more frequent debridement, has a higher risk of bronchopulmonary spread, and more often requires tracheotomy [4]. Additionally, HPV is the most common sexually transmitted disease in the United States. Dunne *et al.* [10•] determined that the overall prevalence of HPV infection among women (age 14–59 years) in the United States to be 26.8%, with the highest prevalence (44.8%) among women aged 20–24 years. The overall prevalence of HPV among women aged 14–24 years was 33.8%. This corresponds with 7.5 million women with HPV in the United States. When broken down into the prevalence of certain types, HPV types 6, 11, 16, and 18 were detected in 3.4% of the study participants.

Vaccination

HPV types 16 and 18 cause approximately 70% of cervical cancers worldwide. The FUTURE II study group performed a randomized, double-blinded trial in 12 167 women between 15 and 26 years to receive either three doses of a quadrivalent vaccine against HPV 6, 11, 16, and 18 or placebo to evaluate prevention of high-grade cervical lesions. The women were followed for 3 years after receiving their first vaccine dose and achieved a 98% efficacy for prevention of high-grade cervical lesions [11••]. On the basis of this phase III study and several well designed phase II studies [12], the Advisory Committee on Immunization Practices (ACIP) published their recommendations regarding use of the vaccine (Gardisil, Merck & Co., Inc., Whitehouse Station, New Jersey, USA) licensed on 8 June 2006 by the US Food and Drug Administration. The report recommended that the vaccine be administered to all girls 11–12 years and as early as 9 years with catch-up for women aged 13–26 who have not been previously vaccinated [13••]. This recommendation set the stage for the vaccine to be part of the Vaccine for Children (VFC) program that supplies vaccine to all states for use by participating providers. The program saves patients and providers out-of-pocket expenses for vaccine purchases and provides cost savings to states through Centers for Disease Control (CDC) vaccine contracts. Indirectly, it results in lower vaccine prices and ensures that all states pay the same contract prices. In addition, the American Academy of Pediatrics' Committee on Infectious Diseases published a policy statement [14••] mirroring the ACIP recommendations.

Additional vaccine-related studies have looked at the safety and persistent immunogenicity in preadolescent boys and girls. The vaccine is generally well tolerated and induced persistent anti-HPV serologic responses in both boys and girls that lasted at least 1 year following completion of the vaccine regimen [15•]. In Australia, the quadrivalent vaccine is registered for use in boys age 9–15 as well as girls age 9–16 [16]. Among others, Giuliano [17•] makes the argument for implementing a future vaccination program in men citing the UK-based rubella experience in which a resurgence of the disease occurred after an initial decline when women only were vaccinated. HPV infection among men appears to be as common as in women but is often asymptomatic, which contributes to the high rate of transmission between sexual partners. Genital warts among men are estimated at 250 out of 100 000 and have been increasing over the last few decades. Treatment costs have been estimated in men of about $1700 per case [17•].

Herd immunity may be necessary to protect unvaccinated women from cervical cancer. This places HPV vaccination as a men's health issue as well since men are responsible for half the cases of transmission of the virus, and vaccinating men, if found to be effective in reducing the transmission of HPV to women, could be an important mechanism for reducing the burden of cervical cancer. A policy of vaccinating one segment of the population for the primary purpose of reducing the incidence of disease in another segment was also successfully undertaken in the case of the rubella vaccine [18]. Block *et al.* [19] vaccinated boys with the quardrivalent HPV vaccine and found superior immunogenic responses to all four types of HPV covered by the vaccine. This suggests that the possibility of vaccinating persons of both sexes should be further evaluated as a policy option.

For more than a century it has been settled law that states may compel people to be vaccinated, and both federal

and state court decisions have consistently upheld vaccination mandates for children [20]. Requirements are usually based on ACIP recommendations. Mandating immunizations for school attendance has been shown to increase immunization rates [21]. Girls typically receive other immunizations, such as the diphtheria/pertussis and meningococcal vaccine between the ages of 11 and 12 so adding the HPV vaccine should not result in significant inconvenience to families. School-based immunization programs customarily feature exceptions that incorporate individual, medical, religious, and philosophical objections. HPV-vaccination mandates have been attacked as an unwarranted intrusion on individual and parental rights. Proposed legislation varies between opt-in programs that require a confirmatory effort by a parent, yet misses many children whose parents forget to opt-in, and opt-out approaches that increase vaccination rates among children whose parents have no real objection to the program while preserving parental autonomy. Opposition to mandated HPV vaccination reflect a growing movement toward parental refusal of vaccines based on the mistaken perception that many vaccines are more hazardous than the diseases that they prevent. Critics contend that abstinence is a safe alternative to vaccination but experience demonstrates that abstinence-only approaches to sex education do not delay the age of sexual initiation nor do they decrease the number of sexual encounters. Although only 13% of American girls are sexually experienced by 15 years of age, by 17 the proportion grows to 43% and by 19 to 70% [22]. School-based programs are crucial for reaching those at highest risk of contracting sexually transmitted diseases and are recommended to begin with children as young as 12 years. An additional fear among those who oppose mandatory HPV vaccination is that it will have a disinhibiting effect and thus encourage sexual activity among teens that might otherwise have remained abstinent. Even though pregnancy and AIDS are far more immediate threats than cervical cancer, sex education and distribution of condoms have not been shown to increase sexual activity and, in fact, delay initiation of sexual intercourse [23].

Although moral objections to requiring HPV vaccinations are largely emotional, public health officials may have more justifiable concerns about the merits of HPV vaccination based on the financial and logistic burdens that may be imposed on families and schools and also may legitimately worry about adverse-event rates in mass scale programs. It is estimated that the cost to fully immunize all 11-year-old girls will exceed $850 million per year [24]. This cost will have to be covered by the VFC program for uninsured, Medicaid and SCHIP families and by most private insurers.

Factors influencing pediatricians' intentions to recommend HPV vaccination and the views of pediatricians regarding effective strategies for HPV vaccine delivery have been recently studied [25,26]. The main factors driving intention to recommend vaccination include knowledge of HPV diseases and the health impact of the vaccine, vaccine cost and reimbursement, and parental factors. Almost all pediatricians surveyed favored universal rather than targeted vaccination but opinions regarding legislative mandates varied.

The bivalent L1 virus-like vaccine has also been found to be effective for cervical cancer prevention in 10–14-year-old and 15–25-year-old women [27,28]. However, as this vaccine does not cover HPV 6 or 11, it would not be anticipated to have any significant impact on the future incidence of RRP or genital warts [29••].

Although both vaccines have been found to have high prophylactic efficacy, a report from Costa Rica by Hildesheim on the bivalent vaccine demonstrates its lack of efficacy as a therapeutic vaccine. In this trial involving 7000 18–25-year-old women, the authors demonstrated no effect of the vaccine on viral clearance [30]. In an editorial published in the same issue of JAMA, Markowitz [31] discusses the implications of this study with respect to the need for continued Papanicolaou (Pap) screening, postlicensure safety monitoring and the potential for the vaccine to still benefit women with existing HPV infection with one vaccine type by boosting the antibody response and increased protection from infection by other HPV vaccine types.

Preliminary research into the development of therapeutic HPV vaccines is focusing on utilizing early viral proteins such as E6 and E7 as the target antigen. These have included peptide/protein-based vaccines, live vector vaccines, dendritic and tumor cell-based vaccines, and nucleic acid-based vaccines involving both naked DNA and RNA replicons [32•].

Head and neck surgeons are also curious regarding the implications of universal HPV vaccination on the development of future cases of head and neck tumors. There is a large body of evidence surrounding the role of HPV infection in the development of head and neck squamous cell carcinoma (SCC) with an overall HPV prevalence estimated at 26% with higher prevalence in oropharyngeal SCC (36%) than oral (24%) or laryngeal (24%) SCC. Tonsillar SCC has the highest rate of HPV detection (51%), which makes this anatomic location the highest of any extragenital malignancy [33•]. D'Souza *et al.* [34•] performed a case-controlled epidemiological study that showed a strong association of oropharyngeal cancer and HPV. They found HPV 16 DNA in 72% of the tumor specimens from their enrolled oropharyngeal cancer patients. Nearly 30 000 new cases of oral and oropharyngeal SCCs are reported annually in the United States. If a third are related to HPV infection then potentially

10 000 cases could be annually prevented. With a 55% 5 year overall survival and an increased incidence noted in younger, nonsmokers and nondrinkers, a vaccine that could confer long-term immunity could have a huge impact [35].

This brings us to the question as to whether the quadrivalent HPV vaccine may play a role in the prevention of RRP in children and newborns. Previous studies have shown that transplacentally acquired antibodies may be provided to the infant through vertical transmission [36]. This would bode well for prevention of RRP if a substantial percentage of the 12–26-year-old female population has received the three dose quadrivalent HPV vaccine. Schaffer *et al.* [37] proposes an alternative strategy of neonatal vaccination to boost HPV seropositivity in children citing the benefits of hepatitis B neonatal vaccination. This strategy would certainly require additional trials to assess the immunogenicity of HPV vaccines in infants and children and to assess the duration of immunity and is not likely to be widely adopted owing to cost and medico-legal considerations but could be selectively employed in high-risk neonates.

Role of host immune system

In a prospective study evaluating the immunologic status of 20 children with JORPP, Stern *et al.* [38••] looked at the immune system as a potential source of the haphazard transmission rates and unpredictable recurrence patterns of JORRP. When compared with healthy age-matched controls, they found that the CD4/CD8 ratio and the lymphocyte response to mitogen stimulation were significantly reduced. The reduction in lymphocyte response to mitogen stimulation as well as natural killer cell function was significantly correlated to a high number of papilloma sites or more frequent recurrences. This study suggests that cellular immune response may be compromised in children with JORRP. However, it remains unclear whether HPV causes this impaired response, or whether children with this impaired response develop JORRP. Future, larger studies will be necessary to investigate these findings further [38••].

Treatment: surgical

Currently, there are no medical or surgical cures for RRP. Goals of any therapeutic RRP regimen include eradication of disease from the airway, improvement in voice quality, control of disease spread and decrease in the number of trips to the operating room for surgical debridement. Surgical management remains the mainstay of therapy for RRP. A balance must be achieved between going to the operating room (OR) too often, risking stenosis, webbing, and anesthesia, and not going enough, allowing disease spread and tumor burden to increase. Our current surgical preference for debulking of RRP involves use of the microdebrider. Advantages of this device include minimal collateral laryngeal mucosal trauma, less thermal trauma, less procedure time, reduced risk to OR personnel (evacuated smoke), fewer personnel required in the OR, less expensive than laser, improved voice quality, and no increase in pain scores [39–42]. Patients with sessile lesions, disease involving the ventricle, and areas with significant scarring may benefit most from use of the carbon dioxide or pulsed dye laser (PDL).

The PDL is a nonablative laser that selectively targets the microvasculature of the lesion sparing the epithelium, a photoangiolytic effect. The PDL takes advantage of the chromophore in oxyhemoglobin, which has two peaks – one at 540 nm and one at 585 nm [43•] – with the wavelength of the PDL being 585 nm. Hartnick *et al.* [44••] demonstrated that the 585 nm PDL was safe and effective for use on JORRP in the pediatric population. In their small (23 patients), prospective, longitudinal study they noted no events of anterior commissure webbing or true vocal cord scarring on lesions treated with the PDL. Additionally, they found no evidence of damage to the normal epithelium during PDL therapy. This finding would allow bilateral anterior commissure therapy to be performed during one surgery and could potentially lead to improved voice outcomes. They also commented that the flexible fiberoptic delivery of PDL energy made it advantageous for lesions in hard-to-treat locations including the ventricles, infraglottic area, and trachea. Koufman *et al.* [45•] and Mouadeb and Belafsky [46•] promote the effectiveness of the PDL in the office setting. Using little to no topical anesthesia, Koufman's group performed 212 PDL procedures on 59 RRP patients with an average of 3.6 procedures per patient and a mean follow-up of 17 months. They noted no complications associated with the PDL procedures. Mouadeb and Belafsky performed office-based PDL therapy on 21 patients with RRP with similar findings of no anterior glottic webbing, vocal cord scarring, or significant complications. Additionally, they noted a statistically significant improvement in Voice Handicap Index (VHI) on the patients in their study.

Technological advances in fiberoptic carbon dioxide laser delivery and endoscopic scopes utilizing distal-chip advancements have made office-based therapy of papilloma a viable, cost-effective option. Patient comfort with the office-based procedure has been documented as well, with one study reporting 87% of patients preferring it to similar OR-based upper aerodigestive tract PDL procedures [47]. For the most part, pediatric patients still need to be treated under general anesthesia given cooperation issues and a smaller airway, but the PDL promises to be a part of our expanding armamentarium for JORRP. With current third-party reimbursement rates, there are perverse financial disincentives preventing the

proliferation of office-based PDL therapy for RRP. Rees *et al.* [48••] found a potential $5000 per case savings when PDL therapy was performed in the office instead of under general anesthesia yet the existing reimbursement scheme does not cover the cost for the surgeon of using the laser in the office. Until there is reconciliation of the cost–payment issues, this office-based technology and its benefits will be largely unavailable to those with RRP.

Another laser that can be delivered via a flexible fiberoptic medium for treatment of RRP is the pulsed potassium-titanyl-phosphate (KTP) laser. This laser uses a 532 nm wavelength to treat papillomatous lesions in a similar, photoangiolytic, fashion to the PDL in the office or OR setting. This wavelength is close to one of the two peak absorption wavelengths of oxyhemoglobin. In a prospective pilot study on 55 adult patients with RRP with the end point of disease regression using the KTP laser, Burns *et al.* [43•] found 90% or greater disease regression was achieved in 80% of those patients for whom they had available near-term follow-up. Despite having 93% of their cases with anterior commissure disease, they reported no new webbing. The authors make the argument for the KTP laser over the PDL based on its extended pulse width giving it enhanced clinical efficacy as well as using a wavelength closer to an absorption peak of oxyhemoglobin. No study yet has determined the optimum energy delivery necessary to affect tissue coagulation and/or effectively cause photoangiolysis [49•]. Additionally, hard data for clinical outcomes are difficult to establish with patients with RRP because of the inherent variability that characterizes the course of RRP and the nature of the tertiary referral pattern of patients with RRP, who sometimes travel great distances for treatment, making outcome data difficult to analyze [45•].

Treatment: medical

The most commonly utilized adjuvant medical therapy for RRP utilizes intralesional cidofovir (Vistide, Pharmacia & Upjohn, Erlangen, Germany) [50]. Cidofovir is a nucleoside analog of deoxycytidine monophosphate. Once converted into its active form, this prodrug becomes incorporated into DNA and produces toxicity against the herpesvirus family. It is FDA approved only for intravenous use in the treatment of cytomegalovirus retinitis in patients with HIV. However, laboratory and clinical studies have demonstrated its effectiveness in the intralesional treatment of RRP in adults and children [51–53], and it is relatively widely used 'off label' for this disease in severely affected patients [50]. Donne *et al.* [54] demonstrated that cidofovir was effective against HPV 16-infected cells but had only marginal effectiveness against HPV 6-infected cells. This study was done in an isogenic system in which low-risk and high-risk viral proteins are expressed in the same genetic background. The authors concluded that cidofovir may have little selectivity for low-risk HPV (type 6)-related disease. These results may provide one explanation as to why clinical studies looking at cidofovir in RRP have only partial success.

Chadha and James [55•] performed a 10-year systematic review of the literature regarding RRP treated with intralesional cidofovir and reported complete resolution in 57% of all patients and partial response in 35% of patients. Despite these promising numbers, the authors note a tremendous variability in dosage, interval of administration and number of injections. They also point out the need for a well designed, placebo-controlled, double-blinded, randomized trial to better study this adjunct. McMurray *et al.* [56•] found no statistical difference between cidofovir and placebo when looking at Derkay severity score, VHI, and a quality of life survey with both arms of the study showing statistically significant improvement in all the above measures. Limitations of the study included small sample size ($n = 19$), low dose of cidofovir (0.3–5 mg/ml), and short follow-up period. Despite its weaknesses, this study points out the importance of the placebo group in demonstrating the effectiveness of surgical debridement in the successful treatment of aggressive RRP.

Based on animal toxicity studies and case reports, there are concerns regarding the side effect profile of cidofovir including the possibility of malignant degeneration of papilloma lesions following intralesional injection [57]. Lindsay *et al.* [58] reported on a retrospective review of pediatric operative biopsy specimens from patients with JORRP treated with cidofovir and found no cases of dysplasia identified in those specimens.

Recent research into the molecular biology of RRP, specifically the signaling cascades leading to regulation of cyclooxygenase-2 (COX-2), has revealed that HPV-infected cells behave differently. The individual elements of these unique signaling cascades may present themselves as new targets for therapeutic regimens in the treatment of RRP and other HPV-induced diseases [59]. Favorable anecdotal results with the use of Celebrex have resulted in the announcement of NIH funding of a multiinstitutional study of COX-2 inhibitors in the treatment of adults and children with RRP.

Conclusion

Despite new techniques to manage RRP, treatment remains a challenge. Preventive quadrivalent HPV vaccination holds great promise regarding protecting future populations from RRP; however, it will likely take decades before we will see an effect on disease prevalence. In the meantime, development of therapeutic vaccines is

ongoing and may one day help those afflicted with RRP. Photoangiolytic lasers promise an effective approach to anterior commissure/sessile disease and provide an office-based application for adults. The literature supporting adjuvant use of cidofovir is equivocal and further research needs to be done before its efficacy can be firmly established. On the horizon, we look forward to research into therapeutic regimens that can target the signaling mechanisms of RRP.

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