

REVIEW

Recurrent respiratory papillomatosis: A 2020 perspective

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Abstract

Objective: Despite recent advancement recurrent respiratory papillomatosis (RRP) remains a rare but challenging benign airway neoplasm. In recent years there has been significant shifts in incidence of this disease due to changes in vaccination and prevention for human papilloma virus (HPV) and its related pathology. This review will highlight the epidemiology, prevention and treatment of RRP.

Methods: The PubMed database was searched using relevant MeSH terms including “recurrent respiratory papillomatosis.” The titles and abstracts were reviewed to assess relevance and unrelated articles were excluded. A full-text review for select articles was performed, the data and discussions were interpreted and synthesized to create a concise update on the management of RRP.

Results: With the increasing utilization of the 9-valent and quadrivalent HPV vaccine in Australia, we have seen a significant decrease in the incidence of RRP. Preliminary data in the US shows a similar trend of decreased incidence after implementation of vaccination. Single dose Gardasil in developing countries has shown sustained immunization for at least 7 years. Preliminary clinical trials and retrospective studies have shown the HPV vaccine may have benefit as a treatment method in addition to prevention for HPV related diseases. Bevacizumab (Avastin), a VEGF monoclonal antibody, has shown promise as a systemic treatment for RRP. The Corona Virus Disease 2019 (COVID-19) pandemic has affected perioperative management of RRP.

Conclusion: RRP continues to decline in incidence since the implementation of HPV vaccination. Advancement in the medical management including Bevacizumab show promise as an additional option for the management of RRP.

KEYWORDS

Bevacizumab, Bevacizumab, HPV vaccine, human papilloma virus (HPV), recurrent respiratory papillomatosis

1 | INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a rare benign neoplasm of the larynx that affects both the pediatric and adult population. RRP is caused by a local infection with HPV and presents with wart like

growths in the airway that affect voice and airway patency.¹⁻⁸ Despite recent advancement in vaccination and treatment, RRP remains a challenge to treat with high recurrence rate, risk of local airway involvement, and significant reduction in quality of life.⁹ With the advent of vaccinations for HPV initially intended to reduce the

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morbidity and mortality of cervical cancer and genital warts, the incidence of RRP is rapidly changing but has previously been estimated to be 4.3 per 100 000 children and 1.8 per 100 000 adults.¹ The initial 2 year direct cost of treating RRP can be as high as \$76 000 and the annual cost of all RRP patients has been estimated to be between \$40-123 million, which highlights the importance of prevention.^{10,11} The most substantial improvements to our understanding of RRP have been made in prevention and adjuvant therapies which will be highlighted in this review.

Since the identification of the infectious etiology of RRP, extensive research has been performed on HPV. The two primary HPV subtypes in RRP are HPV 6 and 11, but high-risk subtypes 16, 18, 31, 33 and 39 have all been identified.^{12,13} HPV is a ubiquitous virus with 75% to 80% of non-vaccinated adults having immunologic evidence of primary infection. HPV most commonly affects the skin, genitourinary tract, anus, and oropharynx. We do not understand why 90% of these patients go on to clear the disease and some individuals are affected by sequela of the infection, though it has been postulated to be due to complex immunologic interactions.^{14,15}

RRP has a variable course and predicting the timing and severity of recurrence has remained a challenge. RRP is generally classified as adult onset RRP (AORRP) and juvenile onset RRP (JORRP) due to the bimodal distribution of presentation and its relative natural history. JORRP is generally more aggressive form with higher recurrence rates while AORRP is thought to be more indolent, although adults can have aggressive variation of the disease. The variability in disease severity and recurrence highlights the challenge of simple surgical excision as single modality treatment. JORRP is thought to be obtained via vertical transmission of HPV during delivery via infected genital tract although exact mechanism is not clear. AORRP is thought to be obtained via sexual transmission.¹⁶ Early onset appears to be a risk factor for disease severity in JORRP, with age of onset <5 years of age being an independent risk factor.^{14,17} Laryngo-pharyngeal reflux (LPR) has also been identified as a risk factor, although no study has yet identified any reduction in disease recurrence or severity with treatment of LPR.^{18,19} Previously HPV subtypes, especially HPV 11, was thought to be an independent risk factor but recent data does not definitively correlate subtype with disease severity.^{14,20} The larynx is the most common site of RRP, specifically the membranous vocal fold.¹⁹ Recurrence rate also appears to be linked to primary location with higher rates of recurrence near the primary site of infection.

2 | PREVENTION

HPV vaccination has had a profound effect on the incidence of RRP. Initial HPV vaccine development began with the discovery of the ability to isolate virus-like particles (VLP) which could stimulate a similar humoral response to L1 viral proteins.²¹ The initial quadrivalent vaccine (Gardasil, Merck) developed from the HPV L1 viral capsid was FDA approved in June of 2006 and included both high risk strains 16 and 18 and low risk 6 and 11. An additional vaccine Cervarix,

manufactured by GlaxoSmithKline, included L1 protein of HPV 16 and 18, and was approved in 2007 in Australia and Europe. Cervarix was eventually approved in the US in 2009. Gardasil has since been approved for females and males from ages 9 to 26 years of age with initial dosing recommended at 11 to 12 years of age. A 9-valent HPV vaccine was developed (Gardasil-9, Merck) which included additional strains 31, 33, 45, 52, and 58.²² As more data surrounding HPV and its sequelae including oropharyngeal carcinoma the age range has been expanded to ages 9 to 45 and labeling now includes prevention of head and neck cancers caused by HPV.^{23,24} The original Advisory Committee on Immunization Practices (ACiP) recommendation of a 3 dose protocol for all individuals has been scaled down to 2 doses given 6-months apart when initiated at 9 to 14 years of age and is also supported by the World Health Organization and the European Union Center for Disease Control. Those who initiate after age 15 or who are immune-compromised should still receive 3 doses.

Nokavic et al published a 5-year report based upon surveys of 28 pediatric otolaryngologists regarding new cases of RRP diagnosed after the implementation of HPV vaccination in Australia. Incidence of RRP decreased from 0.16 to 0.02 per 100 000 children totaling only 15 new cases on the Continent. The vaccination rate in Australia was high at >80% uptake in girls and >75% uptake in boys.² This is the first study to identify the decreased incidence of RRP after implementation of vaccination. Additional publications using the Australian Pediatric Surveillance Unit (ASPU) data have also shown significant decline with no reported new cases in 2019.²⁵ Currently, a Center for Disease Controlled (CDC) funded research study is evaluating the incidence of RRP in the United States. Patients were enrolled from 26 US pediatric otolaryngology centers and grouped by year of birth. The US census data was then used to calculate the incidence of RRP in 2004 to 2005, pre-vaccination era, and 2012 to 2013, post-vaccination era. Preliminary data shows a significant decline in the incidence of RRP over this time period. Similar studies are being performed in Canada with preliminary results showing a similar dramatic downward trend.

The limiting factor for prevention appears to be compliance with and acceptance of vaccination recommendations around the world. In 2018 in the US, only 68% of children ages 11 to 17 received one dose of the HPV vaccination and only 51% actually completed the vaccination schedule.²⁶ Although this shows some improvement from previous years, the rate is still low compared to other developed countries and other adolescent vaccines in the US. There is a continued effort by organizations such as the American Academy of Pediatrics (AAP) and the CDC to improve vaccination rates in the US. Provider recommendation remains the most important factor in acceptance of vaccination.^{27,28} In more recent years social media has become a more significant contributor to the US population's view on vaccinations. Many studies have shown that anti-vaccine messages and content receive more attention and views than pro-vaccination messages.^{29,30} Social media "influencers," users that are more influential within their social media network, have been shown to have the most substantial effect on consumer behavior and views.³¹ Focusing HPV vaccination as an anti-cancer vaccine using social media and "influencers" may be an effective way to reach more Americans.³² Additional resources,

including both audiovisual and printable information pamphlets, have shown some improvement in vaccine acceptance as well.³³ Insurance status and proximity to metropolitan statistical area (MSA) appear to have an effect on vaccination rates. It is hoped that improved national access to vaccinations may help solve this disparity.

Implementation of HPV vaccination programs in countries within the developing world may have the most profound effect on RRP eradication due to a higher incidence of JO RRP in low resource nations.³⁴ Despite the higher incidence of disease burden, many low income and middle-income countries have not introduced the HPV vaccine as part of their national routine vaccination schedule.³⁵ This may be in part be due to cost and supply availability. A recent study from India, intending to evaluate a two vs three dose Gardasil vaccination schedule, inadvertently investigated the efficacy of a single dose schedule. Due to suspension of the vaccine use in India during the study, a large cohort of patients received only a single dose of Gardasil vaccine. This group showed detectable concentration of neutralizing antibodies with sustained response for at least 7 years. This may represent an alternative schedule for developing countries who have been unable to implement HPV vaccination due to cost or supply.³

3 | VACCINATION AS TREATMENT

In addition to prevention, HPV vaccination may have some role in treatment of RRP. In the last few years, several case series of 9-valent Gardasil being utilized as an adjunct to primary surgical debridement have been published with promising results. Initial case reports suggested benefit in increasing the inter-surgical intervals especially in recalcitrant disease for JORRP.³⁶⁻⁴⁰ A recent systematic review and meta-analysis by Rosenfield and colleagues evaluated 12 publications and included 63 patients with RRP who underwent treatment with Gardasil-9. A meta-analysis of this data showed statistically significant reduction of surgeries per month after HPV vaccination. The mean intersurgical interval increased from 7.02 month prior to vaccination to 34.45 months after vaccination which translates to a substantial improvement in quality of life and cost of RRP treatment for patients.⁷ The meta-analysis was limited due to variability in serologic and HPV DNA collection and outcome measurement but still suggests a role for patients with active disease. HPV vaccination has been studied as an adjunct for treatment of other HPV diseases including anogenital warts and cervical cancer with no statistically significant benefit seen for secondary prevention.^{4,41}

The exact mechanism for a therapeutic effect of the HPV-9 vaccine as a therapeutic is unknown but is postulated to be due to a vaccine-mediated humoral response inhibiting latent HPV infection near or within the surgical site decreasing the risk and rate of recurrence.⁴² Additionally, there is evidence that patients with RRP have a more robust immunologic response to HPV vaccination compared to their response to their indolent HPV infection which may explain the vaccines' efficacy as a treatment option.⁴³

In addition to the currently available Gardasil-9 vaccine there has been significant breakthroughs in HPV DNA vaccines. Gardasil-9 targets the L-1 protein of the viral capsid to create neutralizing antibodies while the novel DNA vaccines target E6 and E7 oncoproteins.⁴⁴ E6 and E7 have been shown to have high expression in HPV related tumors and associated diseases increasing potential therapeutic efficacy.⁴⁵ The potential benefit of DNA vaccines for treatment of HPV related disease stems from the ability to create more robust T cell immunologic response. The novel vaccine INO-3016 has shown both in vitro and in vivo immunologic response and clinically significant reduction in frequency of operative intervention.^{44,45} Additionally there are two ongoing trials for HPV-DNA vaccines, Inovio trial INO-3107 (NCT04398433) and an NIH funded trial being performed by Clint Allen et al.⁴⁶ These DNA vaccines may be a better option for future therapeutic vaccination treatment.⁴⁷ It is worth noting that all of these experimental trials have been completed in the adult population which represents a different patient population and disease severity from pediatric cohort.

4 | ADVANCEMENT IN MEDICAL THERAPY

In addition to primary prevention with vaccination, the last few years have seen a significant expansion in adjuvant medical treatment options for patients with severe RRP. A variety of targeted therapies via immune modulation, checkpoint inhibition and VEGF inhibition have been under investigation and have shown some promise as adjuncts to the surgical treatment of RRP.

With the advent of monoclonal antibodies, targeted therapy has become a mainstay of new drug development and application. RRP has several pathologic pathways that can be targeted for therapeutic benefit. Bevacizumab (Avastin, Genentech) utilizes one such pathway via vascular endothelial growth factor (VEGF) which has been identified to have strong expression in papilloma epithelium and underlying endothelial cells in RRP patients.⁴⁸ Avastin, FDA approved in 2004, is a monoclonal antibody that binds to VEGF and inhibits interaction with receptors. There have been several studies that have evaluated intra-lesional injection of Avastin in patients with both JORRP and AORRP at the time of surgical treatment.⁴⁹⁻⁵¹ An increased time between surgical interventions, decreased disease severity and improvement in voice related quality of life outcomes were noted in a small cohort of JORRP patients.⁵² There have been some documented complications of intra-lesional injection including pyogenic granuloma formation.⁵³

Intravenous (IV) administration of bevacizumab has developed into a promising adjuvant medical treatment for patients with advanced tracheal and pulmonary RRP.⁵⁴⁻⁵⁶ Early case studies utilizing systemic IV bevacizumab in severe JORRP refractory to surgical and other adjuvant medical treatments demonstrated significant regression in many cases and complete resolution of laryngeal and tracheal disease in others. Interestingly, no patient showed progression of pulmonary disease during therapy.⁵⁷ Best et al. surveyed the RRP task force and identified 8 patients who were treated with 5-10 mg/kg

every 2 to 4 weeks, all displaying at least partial response. A standardized treatment protocol is currently in development with patients often requiring repeated cycles every 2 to 3 months with endoscopy to reevaluate the lesions.⁵⁵ The current best practice recommendation is to collaborate with your oncology service to perform IV infusion after hospital approval for off-label use. Pretreatment labs should include evaluation of kidney function and echocardiogram as side effects can include bleeding, hypertension, thrombus formation, electrolyte abnormalities and renal injury. Patients should then undergo direct laryngoscopy and debridement in the operating room followed by IV bevacizumab 10 mg/kg for 1.5 hours.⁵⁴ A recent systematic review, evaluated the JORRP literature in regards to IV Avastin therapy, 20 distinct patients were identified. All patients had significant reduction in disease burden and need for operative intervention.⁵⁸ Additional case series in the adult population have shown similar benefit for patients with tracheobronchial RRP or patients with high disease burden (atleast >2 interventions per year).⁵⁹ Although initial data has been promising, it is important to highlight that IV Avastin is a maintenance therapy with no clear end point of treatment. An international consensus statement on systemic Avastin has been prepared by Doug Sidell and colleagues at Stanford University utilizing a Delphi method to address key point supporting the use of IV Avastin for treatment of RRP and provides preliminary guidance surrounding the use of this treatment modality.⁶⁰

Additional targeted therapies utilizing monoclonal antibodies have targeted the programmed death 1 pathway (PD-1). The PD-1 pathway has shown clinical activity in HPV-mediated head and neck cancer and PD-L1 inhibitors have been used successfully to treat these patients.⁶¹ A Phase II trial in 2019 treated 12 adult RRP patients with the anti-PD-L1 monoclonal antibody, Avelumab (Bavencio). All patients with laryngeal RRP showed some response, while 56% showed a partial response and patients with pulmonary RRP showed no response to their pulmonary lesions.⁸ PD-1 inhibitors may represent an additional alternative adjuvant therapy but currently is only used in preliminary research trials while Avastin has been utilized more in the clinical setting.

5 | RRP AND COVID-19

The COVID-19 pandemic has had a profound effect on public health, economics and social interaction worldwide. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified to be transmitted via large and small droplet aerosols, leading to challenges with containment and isolation.⁶² Initial data out of China and Iran identified aerosol-generating procedures (AGPs) as a high risk for spread putting Otolaryngologists at significant risk for infection and further spread of disease.⁶³ Patients with RRP often undergo frequent operative interventions putting them at particular risk for requiring surgery during the pandemic. Minimizing aerosolization via meticulous titrating of anesthetic agents, to avoid coughing and laryngospasm during their surgical intervention is recommended.⁶⁴ Preoperative PCR testing for COVID-19 is

recommended by American Academy of Otolaryngology/Head and Neck Surgery (AAO-HNS) and in some institutions two negative tests are required before proceeding with elective airway surgery. Even in the face of negative COVID-19 test results, use of N95 masks, face shields and minimizing exposure to additional OR staff during RRP surgery seems prudent. Due to the number of severe RRP patients who are tracheostomy-dependent, it is important to recognize the increased risk of aerosolizing spread of virus and encourage the donning of appropriate PPE for both the perioperative and intraoperative care of these individuals.

6 | CONCLUSION

Over the last several years, we have seen significant advancement in our ability to prevent and treat RRP. Current data suggests that there will be significant decrease in the incidence of RRP due to the increasing utilization of the HPV vaccine. Providers can help expedite this decline in RRP by encouraging HPV-9 vaccination which could eventually lead to eradication of this challenging disease. The addition of systemic medical treatment options including secondary vaccination, IV bevacizumab has expanded our arsenal to control the refractory cases of RRP. Ongoing research in DNA vaccines and PD-L1 blockade may offer additional treatment options in the future. The COVID-19 pandemic has added additional challenges to caring for RRP patients but with appropriate precautions and PPE quality care can still be performed.

CONFLICT OF INTEREST

The authors have no financial disclosures or conflict of interest.

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