

**TITLE: Recurrent Respiratory Papillomatosis**

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**RESIDENT PHYSICIAN: Frederick S. Rosen, MD**

**FACULTY PHYSICIAN: Anna M. Pou, MD**

**SERIES EDITORS: Francis B. Quinn, Jr., MD and Matthew W. Ryan, MD**

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## **Introduction**

Recurrent respiratory papillomatosis (RRP) is a disease process characterized by exophytic lesions of the aerodigestive tract that display a tendency to recur and to spread throughout the entire respiratory tree. Though the lesions are benign, disease outcomes can be disastrous as a result of airway obstruction, distal airway spread, and malignant transformation, necessitating aggressive treatment and close clinical followup.

RRP has been classified in two categories based on age: juvenile onset (JORRP) and adult onset (AORRP). By definition, any case of RRP diagnosed before 12 years of age represents JORRP; this age cutoff was arbitrarily established. JORRP tends to be more aggressive than its adult counterpart. In addition, JORRP can be seen in both adults and children. Because various levels of disease severity have been noted in both children and adults, others have also described "aggressive" and "nonaggressive" forms of RRP. (2)

## **Epidemiology**

RRP occurs at essentially any age, with a reported range of 1 day old to 84 years old. RRP has a bimodal age distribution with peaks at 2-4 years and 20-40 years.

RRP represents the most common benign neoplasm of the larynx among children, and the second most common cause of childhood hoarseness. JORRP is typically diagnosed between 2 and 4 years of age, with an average delay of 1 year from the time of symptom onset to the time of diagnosis. 75% of children are diagnosed before age 5. 63% of patients are white. 1500-2500 new cases of JORRP are diagnosed in the United States every year with an incidence of 4.3 per 100,000 children. Children diagnosed at an earlier age tend to have more severe disease, with those diagnosed before age 3 more likely to have shorter intervals between surgery as well as more disseminated lesions.

75% of children with RRP are first born. The triad of a first-born child, a vaginal delivery, and a teenage mother is a known risk factor for JORRP but NOT AORRP, suggesting the adult form has a different mode of acquisition.

Approximately 3600 new cases of AORRP are reported per year in the United States with an incidence of 1.8 per 100,000 adults. While in children the incidence among boys and girls is equal, adult men tend to be more commonly affected than women (3:2 ratio). JORRP tends to be both more common and more aggressive than AORRP. According to the National RRP Registry, affected children undergo an average of 4.4 surgical procedures per year, or 19.7 procedures over their lifetime. (6) In contrast, ½ of affected adults undergo less than 5 procedures over a lifetime.

## **Etiology and Transmission**

Human Papilloma Virus (HPV) has been implicated as the cause of RRP, most commonly types 6 and 11; these are the same viral subtypes associated with 80-90% of cases of genital warts (*condyloma acuminata*).

HPV is a small, nonenveloped icosahedral (20-sided) capsid virus with double-stranded circular DNA. At least 90 different types of HPV have been identified, though only 6, 11, and rarely 16 have been strongly associated with RRP. HPV targets epithelial cells; the virus can exist within its host in an active or latent form.

HPV Types 6 and 11 account for most RRP cases. Type 11 appears to be the more virulent of the two types, associated with more airway obstruction early in the disease, a greater need for tracheotomy, and a greater tendency for pulmonary spread in children.

A history of active or prior genital HPV infection can be obtained in approximately 50% of mothers of affected children. While the association between cervical HPV infection in the mother and JORRP has been well established, the precise mode of disease transmission is unclear. Most is likely secondary to direct contact with papillomas in an infected birth canal. For example, first-born children are more prone to develop RRP, likely because primigravid mothers experience a longer second stage of labor. However, while 30%-50% of infants exposed to HPV in the birth canal become colonized with HPV in the nasopharynx, only a small fraction progress to RRP; furthermore, as many as 28% of pregnant women are infected with HPV. The risk of a child contracting RRP following vaginal delivery from a mother with active genital lesions has been estimated to range from 0.25 to 3%. Cesarean section is thought to protect against RRP, though 1 of 109 children delivered via Cesarean section to mothers with *condyloma acuminata* still developed RRP in one study. (17) This suggests that in utero, hematogenous spread of HPV is likely to occur, and HPV has been demonstrated in cord blood. Furthermore, post-natal contact with an infected mother is also a possible mode of transmission. Thus, routine prophylactic Cesarean section is NOT recommended. 31,000 women with visible condylomata undergo vaginal deliveries each year, and most third party payers will not cover Cesarean section for this indication. The decision should be made between the individual mother and her obstetrician. It should be strongly considered in young, primiparous women with recently acquired HPV.

In the case of AORRP, modes of disease transmission have not been well established or supported. Both a large number of sex partners and frequent oral sex have been established as risk factors for AORRP. Possible mechanisms include activation of a latent virus present since birth, or infection acquired in adolescence or adult life most likely as a result of anogenital-to-oral contact. However, evidence for the latter mechanism is circumstantial at best.

For AORRP, JORRP, and condyloma acuminata, the transmission of HPV disease is ultimately determined by 3 factors: dose of the infecting agent, close and prolonged contact to HPV, and recipient susceptibility. Most importantly, HPV transmission by casual contact (e.g., sibling to sibling or in a hospital) is NOT a concern.

There are 1 million new cases of condyloma acuminata in the United States per year. HPV is present in the genital tract of approximately 25% of all females of childbearing age worldwide.

## **Histology/Gross Appearance**

RRP appears as pedunculated masses with finger-like projections of nonkeratinized stratified squamous epithelium overlying a core of highly vascularized connective tissue associated with parakeratosis (retention of nuclei in stratum corneum), koilocytosis (cytoplasmic vacuolization), and acanthosis (epidermal hyperplasia). Cellular differentiation appears abnormal, with an altered expression and production of keratin. The degree of atypia varies.

RRP occurs most often at a junction between ciliated (respiratory) epithelium and squamous epithelium. This likely explains why RRP lesions are a common occurrence at tracheotomy sites (iatrogenic squamo-ciliary junctions). In addition, trauma causes squamous metaplasia of respiratory epithelium, which may explain why RRP flourishes in the setting of uncontrolled GERD. The most common sites are the limen vestibuli (junction of the nasal vestibule and nasal cavity proper), nasopharyngeal surface of the soft palate, midline laryngeal surface of the epiglottis, upper and lower margins of the ventricle, undersurface of the true vocal cords, carina, and bronchial spurs.

Grossly, papillomas can be sessile or pedunculated. They often occur in irregular exophytic clusters.

## **Clinical Features**

RRP most often involves the larynx, but it may involve the entire aerodigestive tract. Extralaryngeal spread of RRP occurs in 30% of children and 16% of adults. Other commonly involved sites in children, in order of decreasing frequency, are the oral cavity, trachea, and bronchi. The oral cavity and oropharynx are also commonly involved in adults.

The hallmark triad of JORRP involves relentlessly progressive hoarseness, stridor, and respiratory distress. The stridor typically begins as inspiratory, then progresses to biphasic. RRP may also present as chronic cough, paroxysms of choking, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, and acute life threatening events. These signs and symptoms often lead to

mistaken diagnoses such as asthma, croup, allergy, laryngitis, vocal nodules, and bronchitis. Adults most commonly present with hoarseness, but may also present with globus pharyngeus.

RRP has a variable disease course that may result in spontaneous regression, no regression, recurrence after years of remission, or malignant transformation. More recent data suggests that there is NOT a tendency for regression during puberty. (17) Typically, one sees recurrent exophytic lesions requiring frequent debulking. In rare instances, chronic invasive papillomatosis can result in malignant transformation (2-3% of cases); approximately 20 cases involving children have been reported in the world literature. Malignant transformation is universally fatal. It typically occurs in adults and is usually associated with other risk factors such as tobacco, a prior history of radiation therapy, a history of bleomycin use, and infection with HPV type 16. However, there have been reports of malignant transformation in the absence of any of these risk factors. (15) In adults, malignant degeneration typically involves the larynx, while malignant degeneration is typically bronchopulmonary in children. Malignant degeneration is thought to occur because of transforming oncoproteins E6 and E7, which inactivate tumor suppressor proteins p53 and pRb among other tumorigenic effects.

Death usually occurs secondary to a complication of frequent surgical procedures or respiratory failure from distal disease progression. Distal disease always implies a poorer prognosis, and this is thought to be due, in large part, to the relative inaccessibility of such lesions to surgical removal.

Spread to the lower airway results in cavitary pulmonary lesions and can produce fever, sepsis, and atelectasis. 4-11% of children with long-standing disease will develop bronchopulmonary involvement.

## **Patient Assessment and Disease Staging**

Stridor present since birth more likely represents laryngomalacia, subglottic stenosis, TVC paralysis, or a vascular ring, but RRP is still a possibility. If the onset of stridor and dysphonia is gradual and progressive over weeks to months, then neoplastic growth such as RRP must be considered.

The most common presentation of RRP is hoarseness. Slowly progressive hoarseness or hoarseness associated with respiratory distress, tachypnea, decreased air entry, tachycardia, cyanosis, dysphagia, chronic cough, failure to thrive, or recurrent pneumonia, if present, necessitate visualization of the larynx.

At the time of physical examination, the first order of business is to determine if the child is in respiratory distress. Indications include flaring of the nasal alae, use of accessory neck and chest muscles, cyanosis, and hyperextension of the neck. If respiratory distress is identified, the child must be transported immediately to the OR (preferable), ICU, or ER, where resuscitation equipment is available. A safe airway must then be established.

If the child is stable, one should auscultate over the nose, open mouth, neck, and chest with a stethoscope to localize the site of obstruction. Keep in mind that the stridor associated with RRP does NOT change with a change in position. Finally, a flexible laryngoscopic

examination should be performed in the stable patient. In children between 1 and 6 years of age, this can be particularly challenging. If an adequate flexible examination is not possible, then the child should be taken to the OR.

Coltrera and Derkay have established a staging system based upon area of involvement, severity of involvement, and observational data such as the patient's voice quality and/or extent of respiratory distress. (6) The primary purpose of this system has been to standardize the evaluation of RRP patients so that established and emerging treatment modalities may be evaluated. A national registry of patients with JORRP was established in 1997.

## **Surgical Treatment**

The standard of care for RRP is surgery with the goals of eradicating disease, assuring an adequate airway, improving voice, and facilitating disease remission while limiting morbidity. The treating surgeon should remove as much disease as possible without causing complications such as subglottic and glottic stenosis, web formation, or diminished airway. The most commonly used techniques are the carbon dioxide laser, cold instrumentation, and the microdebrider.

The carbon dioxide laser has, by far, been the most popular tool in the treatment of RRP. The CO<sub>2</sub> laser has a wavelength of 10,600 nm. It vaporizes water and cauterizes tissue surfaces, resulting in minimal bleeding. The KTP and argon laser may also be used, but these are not nearly as popular as the CO<sub>2</sub> laser. The KTP laser can be extremely useful in treating distal tracheobronchial lesions when used together with a ventilating bronchoscope.

Common complications of the CO<sub>2</sub> laser include scarring, webbing, and alteration of the mucosal wave. Uncommon complications of the CO<sub>2</sub> laser include airway stenosis, airway perforation, and airway fire.

Cold instrumentation techniques, such as laryngeal microflaps, may also be useful, particularly in adults. Vocal cord stripping is inappropriate for most cases of RRP. Cold instrumentation does not burn tissue, nor does it result in a laser plume. However, it does result in more bleeding.

Before the patient enters the OR, all equipment should be checked. In addition, the surgeon and anesthesiologist must communicate about the patient's airway and the logistics of the procedure. The smallest possible laser-safe endotracheal tube should be used that allows for adequate ventilation. If a cuff is used, it should be filled with saline rather than air to decrease the risk of an airway fire. Furthermore, the tube should not be overtaped, so that it can be removed rapidly in the event of an airway fire. All members of the operating room staff should wear micropore laser filtration masks for protection from the laser plume and eye protection. It is also important to use suction to minimize exposure of patient and staff to the laser plume. Derkay routinely administers dexamethasone and cefazolin intraoperatively. (6)

No muscle relaxants should be given until the airway is secured. The Lindholm laryngoscope is a good choice, and should be suspended. The operative field should then be draped with moist towels, and the patient's eyes protected with moist eye pads. Cup forceps

should be used to obtain a specimen for surgical pathology from the site of bulkiest disease. The laser should not be used until the oxygen concentration has decreased to 26-30%. A good initial setting for the laser is 4W. The beam can be defocused for bulky papillomas. If the endotracheal tube obstructs the operative field, apneic technique may be used. One should avoid lasing both TVC's in the area of the anterior commissure. At some point during the procedure, the tracheobronchial airway should be examined either with a rigid endoscope or a bronchoscope.

The use of the microdebrider represents a major shift in the treatment of RRP over the last few years. The 3.5 or 4-mm skimmer angled tip is most appropriate for this use. Advocates say that it is safer and more accurate than the laser and prevents thermal injury with minimal postoperative edema. Used with a rigid endoscope, it is relatively easy to remove subglottic and even tracheal lesions. In a retrospective study, complications following surgical treatment of RRP were rare (anterior glottic web in 11%, severe glottic edema in 6%, and posterior glottic scarring in 6%), but occurred only with the laser and NOT the microdebrider. (7) However, the same study also found that more operative procedures were required in children treated with the microdebrider as compared to the laser. One prospective study comparing the microdebrider to the laser found no statistically significant difference in post-operative pain scores or voice. However, operative time was shorter, and the cost of the procedure was less using the microdebrider. (11)

Once in the recovery room, the patient should receive humidification. Additional steroid doses may be given at 6-hour intervals.

Jet ventilation represents another possible method of administering anesthesia with improved airway visualization, but has not met with the popularity of a laser-safe tube for several reasons: increased risk of distal airway spread, risk of pneumothorax (especially in the case of inadequate muscle relaxation or ball-valve type lesions), excessive mucosal drying, and gastric distention.

Up to 14% of children with JORRP require tracheotomy. Most authors agree that tracheotomy is a procedure to be avoided unless absolutely necessary. Furthermore, when a tracheotomy is unavoidable to maintain a safe airway, the patient should be decannulated as soon as the disease process is under adequate control. Prolonged tracheotomy and subglottic papilloma present at the time of tracheotomy have been associated with an increased risk of distal tracheal spread. Approximately 1/2 of tracheotomized patients will develop peristomal and/or tracheal lesions. Even so, the reported decannulation rate following tracheotomy has only been 36%. Of note, simple endotracheal intubation has also been linked to an increased risk of mechanical dissemination of RRP

## **Adjuvant Treatment, Prevention, and Other Therapeutic Considerations**

Up to 10% of patients with RRP require adjuvant medical therapy. The most common criteria for adjuvant treatment include 1) more than 4 surgical procedures required per year, 2) distal multisite spread, and 3) rapid regrowth of disease with airway compromise. However, many patients receive adjuvant therapy without meeting any of these criteria.

Alpha-interferon has been the most commonly employed form of adjuvant treatment, used to treat RRP in the United States since the 1980's. The exact mechanism of action is unknown, but alpha-interferon is thought to have an antiproliferative action, an immunomodulatory action enhancing the killing of infected cells, and it makes cell membranes less susceptible to viral penetration. Side effects are common and may be broken down into acute and chronic categories. Acute reactions include fever, flu-like symptoms, chills, headache, myalgia, anorexia, parasthesia, and nausea. Severity of these symptoms may be decreased by nighttime administration until tolerance develops (usually requires about 2 weeks). Chronic reactions include neutropenia, decreased growth rate, elevated liver transaminases, spastic diplegia, febrile seizures, thrombocytopenia, rashes, dry skin, alopecia, pruritis, renal insufficiency, and fatigue. Dosing typically starts at 5 million Units/meter-squared QD X 28 days, then 3 days/week X 6 months given IV, IM, or subcutaneously. In children with an excellent response and severe side effects, the dose can be decreased to 3 million units/meter-squared 3 days/week, then weaned as tolerated. Complete resolution of clinical disease occurs in 30-50%, with partial resolution in 20-42%. However, results may not be sustained over the long term, and a recurrence rate of approximately 50% has been reported. On the bright side, most patients who respond initially will respond to repeat treatment. (6,9,17)

Photodynamic therapy was popularized at Long Island Jewish Hospital. This involves the administration of a photosensitizing medication (dihematoporphyrin) that is preferentially taken up by papillomas. The argon pump dye laser is then used on the lesions. A small but statistically significant decrease in growth of papillomas has been noted. The downside is that patients tend to become very light sensitive for a period of 2-8 weeks. A relatively new drug (Foscan) results in less photosensitivity and may increase the popularity of this technique. (6)

Indole-3-Carbinol is an FDA-approved dietary supplement found in high concentrations in cruciferous vegetables. It is well tolerated with few side effects. The mechanism of action involves estrogen metabolism, with a shift to production of antiproliferative estrogen. However, I3C may not maintain its effectiveness when taken with antacids or H2-blockers. A new drug available as capsules or flavored sprinkles (Indoplex) is thought to overcome this limitation. Preliminary results have shown a complete response in 1/3 of patients, a partial response in 1/3 of patients, and no response in 1/3 of patients. (6,17)

Retinoic acid modulates epithelial differentiation. It has shown a variable response when used as a single agent in RRP. However, it may have a synergistic effect when used in conjunction with alpha-interferon, particularly in the treatment of distal airway involvement. It should not be given to females of childbearing age. Side effects include dry skin, cheilitis, arthralgia, and birth defects. (6)

Ribavirin is an antiviral drug normally used to treat respiratory syncytial virus pneumonia. Preliminary data has shown an increase in surgical interval with an initial IV loading dose followed by QID dosing. (6)

Acyclovir acts via thymidine kinase, an enzyme that is not produced by papillomavirus. However, HPV coinfection with HSV, CMV, and EBV has been demonstrated in adults and children. It is thought that acyclovir may help by treating viral coinfection. (6)

The latest development in the area of adjuvant therapy has been the use of cidofovir either intralesionally or intravenously in both children and adults. It is a cytosine analogue with potent activity against a broad spectrum of Herpes viruses by inhibiting viral DNA polymerase. With an intracellular half-life of up to 65 hours, it is able to continue efficacy with infrequent dosing. This drug is FDA approved for HIV positive patients with CMV retinitis. Though proteinuria, renal failure, and neutropenia have been noted with systemic use, no adverse effects have been noted with intralesional use in either children or adults. The maximum systemic dose according to the FDA is 5 mg/kg. Concentrations from 2.5-6.25 mg/ml have been used for intralesional injection. In one study in adults, 100% of subjects achieved remission with no visible papilloma after a mean of 6 injections at 1-month intervals without any surgical debulking. Treatment intervals of 2 weeks in conjunction with surgical debulking have been used in children, in whom complete remission is the exception rather than the rule with cidofovir. Anecdotal reports suggest that intralesional cidofovir may be more effective when the patient is pretreated with Indole-3-Carbinol. Intravenous cidofovir may be more effective when used with alpha-interferon. The optimal dose, dosage interval, duration of treatment, and drug combinations have yet to be determined. (13,14)

The primary safety concern with cidofovir is its possible tumorigenicity. Adenocarcinoma was noted to develop in female rats following subcutaneous injection, but the same findings were NOT seen in primates, nor has increased tumorigenicity been noted with intravenous cidofovir. And, thus far, no adults or children who have received intralesional cidofovir for RRP have developed new malignancy. However, intralesional use of cidofovir is a recent phenomenon, so no long-term followup is available to confirm a lack of tumorigenicity or to demonstrate long-term (>3 year) disease remission rates. Van Custem first introduced intralesional cidofovir for esophageal lesions in 1995, while Snoeck made the first report of laryngeal use for RRP in 1998. (3)

Infant home intercom-type monitors are often all that is recommended or required when the patient is at home. Apnea/bradycardia monitors, and pulse oximetry are not necessary at home. Early speech and language therapy is a good idea.

Children with RRP are generally encouraged to return to the office or to call as often as necessary, or whenever a parent believes the child may be in need because of the urgent nature of the disease.

Contributing medical conditions such as asthma and GERD should be controlled.

The future holds hope for a vaccine to protect against condyloma acuminata and RRP. Currently, the hepatitis B vaccine is the only licensed vaccine that targets a sexually transmitted disease. Phase 3 clinical trials are currently underway for a subunit/protein vaccine for HPV to prevent genital warts and cervical carcinoma. This vaccine uses E6 and E7 as protein antigens. However, optimism is guarded, since a similar attempt to vaccinate against HSV-2 has already failed. (8)

## Conclusion

RRP is a disease primarily caused by HPV types 6 and 11 that usually affects the larynx. Lesions typically occur at squamo-ciliary junctions of the aerodigestive tract. The younger the age at the time of diagnosis, the more severe the disease. RRP may or may not regress with time. The disease does NOT tend to regress with puberty. Malignant transformation, though rare, is universally fatal.

RRP most commonly presents with hoarseness.

Tracheotomy is important to maintain a safe airway, but is best avoided when possible, and tracheotomized patients should be decannulated as soon as the disease is under adequate control.

Prophylactic Cesarean section is not routinely recommended, but should be strongly considered in young, primiparous mothers with recent HPV infection and genital warts.

The present state of treatment for RRP involves palliative surgery – often requiring multiple trips to the OR – for debulking of papillomas while awaiting natural disease remission. Recent developments in the treatment of RRP have been the use of the microdebrider and intralesional cidofovir injection. Though not universally endorsed, the microdebrider has proven safer, cheaper, and faster than the CO2 laser according to the literature. Cidofovir has been highly effective in both adults and children, but data on long-term followup is not available with respect to tumorigenicity or prolonged disease remission.

The greatest promise for future management of HPV-associated disease rests with development of an HPV vaccine.

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