American Society of Pediatric Otolaryngology Members’ Experience With Recurrent Respiratory Papillomatosis and the Use of Adjuvant Therapy

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Objective: To evaluate how evolving treatment technologies have affected our management of recurrent respiratory papilloma (RRP) since the last comprehensive survey of pediatric otolaryngologists in 1998.

Design: Web-based survey of all American Society of Pediatric Otolaryngology members residing in the United States, Canada, Europe, and Australia.

Results: Evaluable survey results were tabulated from 74 practitioners in 62 separate practices managing 700 current children with RRP. A total of 150 (21%) of these patients presently receive adjuvant medical therapies with cidofovir and interferon, accounting for more than two thirds of the total. Sixty-one percent of patients treated with cidofovir have experienced a beneficial response. Distal spread of RRP has occurred in 94 (13%) of the 700 patients. Half of the practices surveyed have experienced a death from RRP, with 89% of deaths directly related to RRP. The laryngeal microdebrider (53%) has supplanted the carbon dioxide laser (42%) as the preferred means of surgically removing papilloma from the larynx in children. Spontaneous, apneic, and jet ventilation (88%) anesthesia techniques have replaced the use of laser-safe endotracheal tubes (10%) as the preferred anesthetic management. Routine human papillomavirus subtyping is practiced by 45% of respondents while 15% treat all their patients with antireflux medications. Half of respondents send lesions for histologic examination only if there is a change in growth pattern while one third send lesions with every surgery.

Conclusions: Recurrent respiratory papilloma continues to be a frustrating disease to treat and is associated with significant morbidity and mortality. There has been an evolution in the past decade toward the increased use of antiviral adjuvant therapy and the use of microdebrider techniques for surgical management.

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Although recurrent respiratory papillomatosis (RRP) is the most common benign airway neoplasm in children, it continues to be a frustrating disease to treat. Recurrent respiratory papilloma is a chronic disease with a variable course most commonly caused by human papillomavirus types 6 and 11. The incidence of RRP in children is estimated at 4.3 per 100000, with 75% of children diagnosed by age 5 years. Firstborn children who are vaginally delivered to a teenaged mother appear to have an increased risk for RRP. The larynx is the most commonly affected site, with frequent recurrences causing voice changes and sometimes airway compromise. Patients with RRP often require numerous surgical procedures in their first year of diagnosis (and often longer) to maintain an adequate airway and voice, with the mean number of surgical procedures estimated at 4.4. It is estimated that children with RRP in the United States undergo more than 10000 surgical procedures a year. As a result, RRP is a burden emotionally for families and economically for society, with an estimated annual cost of $109 million.

In 1994, members of the American Society of Pediatric Otolaryngology (ASPO), the American Academy of Otolaryngology–Head and Neck Surgery, and the American Bronchoesophagological Association were surveyed regarding treatment of RRP. As a result of this survey, a multidisciplinary task force was established under the auspices of the Centers for Disease Control and Prevention (CDC) to establish a national registry of children with RRP in an attempt to better understand the natural history of this difficult disease. From 1996 to 2001, the registry tracked the clinical histories of more than 600 children with RRP, encompassing the clinical practices of 22 pediatric otolaryngological groups. Analysis of these registry data has revealed, among other findings, that children diagnosed before the age of 3 years were more likely to experience aggressive disease that required more surgical procedures and had a higher likelihood of spread outside the
larynx and a higher incidence of tracheotomy compared with children older than 3 years. The registry has provided a platform for further clinical research regarding RRP, including genetic analysis of papilloma specimens and the updating of RRP scoring systems.

Despite extensive research during the past 10 years, no cure has been found and treatment continues to be palliative. However, both medical and surgical treatments of RRP have continued to evolve. To better characterize current medical and surgical management, we conducted a Web-based survey of ASPO members regarding their approaches to RRP.

METHODS

A Web-based survey regarding experience with patients with RRP was administered to ASPO members from July to September 2002. Duplicate responses were excluded from analysis and values included in partners’ responses were adjusted to reflect the experience of physicians within the same practice. Frequencies and relative frequencies were tabulated.

RESULTS

A total of 74 pediatric otolaryngologists from 62 practices responded to the survey. Not all physicians responded to all of the questions in the survey; however, question non-response rates were less than 10% per practice. It should be noted that the questionnaire did not extract practice demographic information. Thus, it is impossible to draw conclusions regarding trends among groups or physicians who failed to respond to particular questions. Physicians were practice members within both adult hospitals and free-standing children’s hospitals in 27 of the United States, as well as France, Canada, and Australia.

Approximately 700 active patients with RRP are served by these practices, with a median of 9 patients per practice (minimum = 1, 25th percentile = 5, 75th percentile = 15, maximum = 50). There were 12 practices in which 2 physicians from the same practice responded to survey. In these cases, the number of children with RRP within the practice was tabulated as an average of the 2 physician responses. Thirty-five (56.3%) of the 62 practices have a total of 150 (21%) patients of 700 currently receiving adjuvant medical therapy. The most common adjuvant therapies used are cidofovir (n=72), interferon (n=25), indole-3-carbinol (n=15), and heat shock protein (HSP)-E7 (n=11).

Cidofovir has been tried in 34 (97%) of 35 practices using adjuvant therapy. The median age at first cidofovir injection is 5.5 years (interquartile range [IQR], 3-9 years). For these patients, there is a median of 5 IQR, 3-9) cidofovir injections with 61% of children reported as much improved or free of disease, 35% as not improved, and 4% as reportedly worse. Prior to cidofovir, the median number of lifetime RRP operations for these patients was 14.5 (IQR, 8-30) with surgical interval ranging from weekly to yearly with most treated monthly. The Figure depicts a subjective physician rating of cidofovir efficacy with most practitioners who have used it rating it between 2 and 4 on a scale of 1 to 5, where 1 signifies “doesn’t work” and 5 signifies “a miracle drug.”

Respondents were questioned regarding distal spread of papilloma disease among their cidofovir-treated patients. Of 31 practices that responded, distal spread was reported in 20 (64.5%). The actual percentage of patients taking cidofovir with distal spread was not reported. Ten (13.9%) of these patients were reported to have tracheotomies.

Overall, 94 children from 33 practices have developed distal spread of their RRP into the trachea, bronchi, or pulmonary parenchyma. Of these 94 children, 53 have disease in the trachea only; 20 have disease in the trachea and bronchi; 19 have disseminated disease in the trachea, bronchi, and pulmonary parenchyma; and 2 have disease in the lung only.

The microdebrider and carbon dioxide (CO2) laser were the preferred means for surgical removal of laryngeal RRP, with 39 (52.7%) preferring the microdebrider and 31 (41.9%) the CO2 laser. Other methods reported include phonomicrosurgery (n=1), other laser types (n=1), or a combination of techniques. Regarding anesthesia management during laryngeal papilloma surgery, 47 (63.5%) prefer spontaneous or apneic ventilation techniques, 18 (24.3%) prefer jet ventilation, and 7 (9.6%) prefer using a laser-safe endotracheal tube.

Thirty-one (50.0%) of the 62 practices reported that a patient from that practice with RRP has died under their care. The most common cause of death reported was progressive pulmonary failure (pneumonia or cavitary pulmonary disease) (n=15), followed by anesthesia-related complications (n=7) and malignant transformation to squamous cell carcinoma (n=3).

Physicians were questioned regarding their use of computed tomographic (CT) scanning to monitor distal disease spread. Eleven (36.7%) of 30 physicians who responded to this question recommended a CT scan every 6 months, 17 (56.7%) recommended once yearly, and 2 (6.7%) recommended a scan only on an as-needed basis.

Human papillomavirus (HPV) subtyping, reflex management, and physicians’ protocol for performing biopsy and repeated biopsy (rebiopsy) of papilloma lesions were also queried. Eleven (15.3%) of the respondents routinely (virtually every time) prescribe reflex medications or reflex precautions for their patients with RRP, while 32 (45%) routinely obtain HPV typing. After initially establishing the diagnosis, half of respondents send lesions for repeat histologic examination if there is a change in growth pattern, while 22 (31%) perform a rebiopsy with every surgery, 9

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(13%) do a rebiopsy once a year, and 5 (7%) do a rebiopsy by some other method.

**COMMENT**

This survey was intended to gain further understanding of the current treatment of pediatric RRP among ASPO members. This survey also relied on accurate documentation by surveyed physicians regarding the aspects of care for children with RRP in their practice. Our survey had obvious limitations and there is potential for bias and sampling errors in any survey-based data collection. In addition, some questions relied on subjective evaluation of patient response to treatment. For instance, there were no objective parameters used to define “response,” “improved,” or “disease-free” regarding the efficacy of cidofovir. While many surveys were filled out in their entirety, some were incomplete; however, question nonresponse rates for each responding practice was less than 10%. No trends among practices with nonresponse questions could be deduced because practice demographic information (private vs academic) was not obtained. This information may have been useful to determine practice trends among ASPO members. Some practitioners only gave best estimates of actual practice numbers while some practices returned multiple surveys. In 12 practices, 2 physicians from the same practice responded to the survey. As a result, we took the average number of RRP patients within the practice based on the numbers provided by each respondent. No response and “best estimate” bias can affect mean calculations; however, the overall response rate was high with 62 (51%) of 122 ASPO practices responding to the survey. We believe this survey is a good representation of the current clinical practice trends among ASPO members. The 1994 survey on RRP had an 81% return rate by ASPO members though the membership was quite a bit smaller at that time.

Although many of the results obtained from our survey are consistent with prior studies, there are some interesting changes noted since the last survey in 1994, including dramatic changes in anesthesia and surgical management of RRP. The goal of surgery in RRP has been to remove disease while preserving normal anatomic structure and function. It has and continues to be the mainstay of treatment for RRP. In the 1970s, the CO₂ laser replaced the cup forceps as a precise means of removing papilloma. In 1994, the preferred surgical tool for papilloma removal was overwhelmingly the CO₂ laser with more than 90% of respondents using the laser and almost 50% using a laser-safe endotracheal tube. In our survey, the microdebrider has replaced the laser as the most preferred instrument with 53% of ASPO members using it as the main modality, followed by the CO₂ laser (42%). There may be numerous reasons for this evolution. Use of the CO₂ laser can be more time-consuming, expensive, and potentially risky. Airway fires, collateral damage to local tissue, and laser injuries to the surgeon are potential hazards. In addition, it has been shown that HPV DNA particles may be aerosolized during the procedure with the potential risk for inhalation by operating room staff. El-Bitar and Zalzal compared the microdebrider with the CO₂ laser and concluded that the microdebrider was just as precise, easier to use, and reduced operative time. They also found that surgeons, anesthesiologists, and parents preferred the microdebrider. Pasquale et al noted no difference in pain, better voice quality, reduced costs, and shorter procedure times when comparing the microdebrider with the CO₂ laser. As a possible result of this change in surgical technique, spontaneous and apneic ventilation techniques (63.5%) and jet ventilation (24.3%) have supplanted the laser-safe endotracheal tube (9.6%) as the primary means of anesthesia.

While surgical and anesthetic management continues to evolve, the tracheotomy rate, at least among severely affected children, has remained fairly constant. Our survey indicated a 14% tracheotomy rate among children being treated with cidofovir, which is consistent with prior literature, although the actual percentage is most likely lower for the total population of patients with RRP. A reason for this may be that patients receiving adjuvant therapy tend to have worse or disseminated disease. Other studies have reported a tracheotomy rate of 5% to 60%. Results from the National Registry revealed that 11% of patients with RRP had tracheotomies with a 36% decannulation rate. Our survey suggests a similar rate of extralaryngeal spread compared with that of prior studies. Approximately 13% (94/700) of the total number of children with RRP were reported to have distal spread of disease compared with 31% reported in 1994 and 48% in 1998. Interpretation of these data are complicated by individual practitioner interpretation of what constitutes extralaryngeal spread (ie, subglottic vs tracheal). Cole et al reported a distal spread rate of approximately 50%, while Lindeberg and Elbrond noted a rate of 21%.

Although surgery is the mainstay of treatment, we found that 22% of children are being treated with adjuvant medical therapies. This is a significant increase from the 10% previously reported in the literature. The criteria most practitioners have used for initiation of adjuvant treatment are (1) patient underwent more than 4 surgical procedures per year, (2) distal spread of disease, or (3) rapid regrowth with airway compromise. Until recently, the most common drug in the adjuvant therapy arsenal has been interferon, although other therapies have included acyclovir, ribavirin, isotretinoin, indole-3-carbinol, and photodynamic therapy. Interferon was the most popular form of adjuvant therapy in 1994 with 9% of RRP children overall receiving the drug; however, it has now declined to less than 4%. The decrease in use of interferon may be due to its unfavorable side-effect profile, which includes hepatic and renal dysfunction as well as spastic diplegia. It also has had mixed clinical success with a 30% to 60% complete response rate. The decline in the use of interferon therapy has paralleled the emergence of other therapies, most notably cidofovir.

Cidofovir is a nucleotide analogue that has antiviral activity against the herpesvirus family and is approved by the Food and Drug Administration for the treatment of cytomegalovirus retinitis in patients with human immunodeficiency virus disease. It has also been shown to induce apoptosis in HPV-positive cells. Snoeck et al demonstrated a complete initial clinical response in 14 of 17 adult patients with laryngeal RRP locally injected with cidofovir, with 10 of 14 remaining disease free. While Pransky et al were unable to reproduce these results in terms of
complete responses, they were able to markedly improve the airway and increase the interval time between surgical procedures in 10 severely affected children with RRP. They also noted a marked improvement in voice quality. Over 75% of respondents in our survey believe cidofovir has moderate to good efficacy with 61% of patients much improved or free of disease while taking cidofovir. Only 4% reported that their patient’s disease worsened.

While deaths from RRP have been reported in the literature, to our knowledge there have been no previous attempts to quantify death rates or examine the cause of death in children who die with RRP. We found that 50% of responding ASPO practices have had at least 1 patient with RRP die. Our survey documents the death of 25 RRP patients with 89% dying from direct RRP-related causes such as progressive pulmonary disease, anesthesia-related complications, or malignant transformation of disease. The remaining 3 patients have died of causes possibly related to RRP. The survey did not inquire about the length of care for these children before death.

Other clinical management tools such as antireflux medications have also been used in the treatment of RRP. Cimetidine, a histamine₂-blocker histamine, has been shown to have immunomodulatory effects and recent case reports demonstrate a decrease in the rate of recurrence of RRP in patients taking antireflux medication. In addition, antireflux medications have been shown to reduce soft tissue complications, such as webbing and scarring, in patients with RRP. However, only 15% of responding physicians report routine use of reflux medications or precautions.

Once RRP has spread outside the larynx, CT scans can be used to monitor the development or worsening of pulmonary disease. However, fewer than 50% of ASPO members routinely use CT scans to monitor for progression. Of those that do use CT scans, 57% do so on a yearly basis and 37% every 6 months.

Although the evidence is not overwhelming, HPV subtyping may be useful in predicting the aggressiveness of RRP disease with some researchers finding that HPV-11 disease is more likely to result in the need for tracheotomy. In addition, antireflux medications have been shown to reduce soft tissue complications, such as webbing and scarring, in patients with RRP. However, only 15% of responding physicians report routine use of reflux medications or precautions.

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Once a diagnosis of RRP has been established, there remains controversy regarding the need to perform a rebiopsy of the papilloma at subsequent surgical interventions. About one third of respondents do a rebiopsy of the lesions at every surgery, presumably worried about the progression from squamous papilloma to papilloma with atypia and possibly to squamous cell carcinoma. In contrast, about half of respondents only perform a rebiopsy if there has been a change in the growth pattern and the remainder do a rebiopsy yearly or use some other criteria.

Recurrent respiratory papilloma has traditionally been and continues to be a difficult disease to treat. While benign in nature, it results in significant morbidity and when disseminated, the disease can be fatal. To date, we know of no randomized prospective trials using adjuvant therapy that have demonstrated convincing effectiveness in controlling or eradicating HPV. However, new therapies continue to be sought. From our survey data it appears that intralesional administration of cidofovir is the favored adjuvant therapy; however, at best, it may be effective in less than two thirds of those severely affected. Research efforts are under way to develop an effective HPV-6/11 vaccine or immunomodulator that can eradicate HPV and its latent state in surrounding tissues. However, until an effective medical therapy arises, surgical debulking will continue to be the primary treatment modality. Also, it is likely that with improvements in laryngeal microdebrider technology and phonomicrosurgical techniques, these modalities will continue to supplant the CO₂ laser in surgically managing this vexing disease.

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