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# A Consensus Statement on the Administration of Systemic Bevacizumab in Patients with Recurrent Respiratory Papillomatosis

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**Objective:** To provide detailed guidance on the administration of systemic bevacizumab in patients with recurrent respiratory papillomatosis (RRP) based on a detailed review of the scientific literature and a consensus of experts with real-world clinical experience.

**Methods:** A bevacizumab consensus working group ($N = 10$) was composed of adult and pediatric otolaryngologists, adult and pediatric oncologists, and a representative from the RRP Foundation (RRPF), all with experience administering systemic bevacizumab in patients with RRP. After extensive review of the medical literature, a modified Delphi method-based survey series was utilized to establish consensus on the following key areas: clinical and patient characteristics ideal for treatment candidacy, patient perspective in treatment decisions, treatment access, initial dosing, monitoring, guidelines for tapering and discontinuation, and reintensifying therapy.

**Results:** Seventy-nine statements were identified across nine critical domains, and 45 reached consensus [clinical benefits of bevacizumab (3), patient and disease characteristics for treatment consideration (7), contraindications for treatment (3), shared decision-making (incorporating the patient perspective) (5), treatment access (3), initial dosing and administration (8), monitoring (7), tapering and discontinuation (6), and reintensification (3)].

**Conclusion:** This consensus statement provides the necessary guidance for clinicians to initiate systemic administration of bevacizumab and represents a potential paradigm shift toward nonsurgical treatment options for patients with RRP.

**Key Words:** administration, Avastin, consensus, systemic bevacizumab.

**Level of Evidence:** 5

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## INTRODUCTION

Recurrent Respiratory Papillomatosis (RRP) is a rare chronic disease caused by infection of the respiratory epithelium by human papillomavirus (HPV) types 6 and 11 resulting in the formation of squamous papillomas in the larynx, trachea, and lungs.[1] The estimated incidences in children and adults in the United States are 4.3 and 1.8 per 100,000, respectively.[2–4] In countries with robust vaccination efforts, the prevalence of juvenile-onset RRP (JORRP) is changing.[5,6] Age of onset for RRP displays a trimodal disease distribution with peaks at age 7, 35, and 64 years and is traditionally designated as either JORRP

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or adult-onset RRP (AORRP) based on age of symptom onset.[7] Due to growth of papillomas in the upper aerodigestive tract, patients with RRP can experience dysphonia and dyspnea, as well as serious complications like pneumonia, malignant transformation, and acute respiratory distress requiring tracheostomy in severe cases.[1] Variability in disease behavior and progression contributes to the challenges related to its management.

Traditional standard of care for patients with RRP is repeated debulking surgeries to remove the papillomas to relieve dysphonia and restore airway patency.[1] Subsequent activity or reactivation of latent HPV in remaining or adjacent tissues leads to papilloma recurrence. Patients can undergo hundreds of surgeries throughout their lifetime. These repeated surgeries, regardless of skillful execution, inevitably damage the anatomy of the underlying larynx leading to glottic scarring, webbing, or stenosis.[8,9] The trauma of repeated medical procedures can lead to long-term effects such as post-traumatic stress disorder, anxiety, and depression.[10] A recent study using data from the RRP Foundation (RRPF)/Coordination of Rare Diseases at Sanford (CoRDs) Patient Registry indicated high mental, social, and fiscal burden impacting the quality-of-life of patients.[11] In many cases, the surgical treatment for this disease also contributes to its morbidity.

The RRPF conducted a qualitative survey to capture individualized disease burden for patients and caregivers JORRP 18+ years [$n = 13$], caregivers of children with JORRP under 18 years [$n = 10$], and individuals with AORRP [$n = 38$] (*communication from Kim McClellan of the RRPF in August 2022*). When asked what an end to surgical treatment would mean to them, the impact was clear: any reduction in the number of surgeries would be impactful.

Given the significant negative effect of repeated surgeries on patient quality of life, there is a need for non-surgical treatments for RRP. Historically, local adjuvant therapies, including intralesional cidofovir and bevacizumab,[12,13] as well as systemic interferon[14,15] have had inconsistent clinical benefit in RRP. There is ongoing evaluation of the potential efficacy in the adjuvant setting of the HPV vaccine and two other therapeutic vaccines.[16–18] Vascular endothelial growth factor (VEGF) plays a critical role in angiogenesis.[19] Bevacizumab is a monoclonal antibody against VEGF that is FDA-approved for the treatment of multiple cancer types. Bevacizumab blockade of VEGF signaling disrupts existing tumor vasculature and prevents the formation of new blood vessels.[20] The potential utility of bevacizumab in reducing the growth or regrowth of papillomas is based on the vascular nature of the lesions.[21] Laryngeal tissues from patients with RRP express higher levels of VEGF as compared with normal tissue making them a potential target for this therapy.[22,23] Treatment with systemic bevacizumab demonstrated efficacy in patients with RRP in terms of a reduction in surgeries.[13,23–29] Previously, Sidell and colleagues issued an International Consensus Statement on key points supporting the use of systemic bevacizumab for the treatment of RRP and providing preliminary guidance surrounding treatment modality.[30] This initial statement was not intended to provide guidance regarding specific dosing, evaluation, or management of patients in the setting of remission or recurrence. Instead, it sought to provide guidance around patient selection and the setting of administration. Since that time, use of systemic bevacizumab has expanded, and clinical experience has increased. With use of systemic bevacizumab in more patients and with longer treatment durations, a group of expert clinicians sought to expand the recommendations of the previous consensus statement.

The objective of this consensus statement is to provide specific guidance to clinicians treating patients with RRP regarding the decision to initiate treatment with systemic bevacizumab, details of its administration, and monitoring. It is the authors' opinion that this non-surgical treatment option is under-utilized, and this statement provides an important opportunity for quality improvement in the care of patients with RRP.

## MATERIALS AND METHODS

### *Study Participants*

A consensus working group was established during the inaugural RRP Roundtable meeting in November 2022. Although many members were authors on the original consensus statement, the group felt it was imperative to include oncologists with the necessary expertise to advise on administration and monitoring. The group was composed of adult otolaryngologists ($n = 4$ [note: one member treats both adult and pediatric patients]), pediatric otolaryngologists ($n = 3$ [note: one member serves both adult and pediatric patients]), adult oncologist ($n = 1$), pediatric oncologists ($n = 2$), and one representative from the RRPF (head and neck surgeon and caregiver for a patient with RRP), all experienced with the use of systemic bevacizumab in patients with RRP. One additional pediatric otolaryngologist served as a methodologist and did not participate in the consensus survey voting. To ensure that the patient perspective was captured, one caregiver from the RRPF participated in the first round of the surveys.

### *Literature Review*

A literature review was completed before study initiation and distributed to group members. It was conducted using PubMed between January 30, 2023 and March 1, 2023 and included case studies/series, reviews, retrospective studies, letters, and expert consensus statements regarding treatment of patients with RRP with systemic bevacizumab (no date restrictions) (Material S1). The review was comprehensive in terms of pregnancy (all time periods) and pediatric safety profiles, including studies in other patient populations treated with systemic bevacizumab pediatric patients with hereditary hemorrhagic telangiectasia (HHT), neurofibromatosis (NF2), low-grade glioma, and refractory/recurrent pediatric solid tumors (search date range: 2018–2023). The results of this literature review are available in Material S2.

### *Modified Delphi Process*

The methodology applied for this study was consistent with the modified Delphi method outlined in the Consensus Statement Development Manual published by the American Academy

of Otolaryngology-Head and Neck Surgery (AAO-HNS).[31] The Delphi methodology aims to seek consensus on a series of statements through a systematic and iterative approach.[32]

The scope defined at initiation included critical topics for clinicians to successfully administer bevacizumab: patient perspective in treatment decisions, clinical and patient characteristics ideal for treatment candidacy, treatment access, initial dosing, guidelines for tapering and reintensifying therapy, and monitoring. Each member submitted topic questions within scope, and following priority ranking of collated topics, the initial survey was drafted. A 9-point Likert scale was used to measure agreement, with the following anchors: strongly disagree (1), disagree (3), neutral (5), agree (7), and strongly agree (9). Consistent with the AAO-HNS manual, statements were categorized based on mean score and number of outliers (any rating ≥2 Likert points from the mean in either direction) with the following criteria: Consensus = ≥7.00 mean score and ≤1 outlier, Near Consensus = ≥6.50 mean score and ≤2 outliers, No Consensus = <6.50 mean score or ≥3 outliers. Efforts were made to ensure that language in each statement was clear and unambiguous. To this end, two additional iterations of the survey were issued to determine agreement on final revised language.

### *Statistical Analysis*

Statistical analysis was performed using Excel for Microsoft 365 (Microsoft Corp, Redmond, Washington). Web-based surveys were generated and distributed via email using Survey Monkey (San Mateo, California).[33]

### *Definitions and Assumptions*

Disease severity was defined by rate of progression beyond the larynx, requirement for emergent airway management more than one time prior to performing operative treatment to remove papillomas, and the number of events of respiratory distress. High disease severity was defined as rapid progression of disease beyond the larynx, requirement for emergent airway management more than one time prior to performing operative treatment to remove papillomas, or recurrent or multiple documented events of respiratory distress. A patient with highly recurrent, high frequency, or frequent disease should meet the following criteria: disease requiring ≥2 surgeries within a 12-month period. Quality-of-life impact was defined as patient-reported negative impact on academic/work participation and/or performance, or on ability to participate in social activities. For the purpose of this study, pre-infusion workup was previously defined by Sidell and colleagues.[30]

## RESULTS

The group identified nine critical domains needed for clinicians to select candidates for and successfully administer systemic bevacizumab: (1) Clinical benefits of bevacizumab, (2) Patient and disease characteristics for treatment consideration, (3) Contraindications for treatment, (4) Shared decision-making (incorporating the patient perspective), (5) Treatment access, (6) Initial dosing and administration, (7) Monitoring, (8) Tapering and discontinuation, and (9) Reintensification. Within the nine domains identified, 79 statements were drafted and included in the first survey. Following revisions and two additional iterations to clarify and refine, 45 statements met consensus criteria and 13 statements met near-consensus criteria (Table S1). Twenty-one statements that did not meet consensus criteria and one statement that met consensus criteria were eliminated (Table S2).

Domain 1 described the clinical benefits of bevacizumab based on the accumulated real-world evidence and the clinical experience of group members. Importantly, the group reached consensus on the ability of systemic bevacizumab to reduce or eliminate surgical debridement in patients with RRP.

Domain 2 focused on an expansion of the initial patient and disease criteria outlined out by Sidell and colleagues.[30] All patients with RRP, juvenile- and adult-onset, should be evaluated for candidacy regardless of disease severity, surgical frequency, anatomic location of papillomas, or HPV subtype. Correspondingly, statements that restricted the candidacy of patients for treatment reached no consensus.

Domain 3 addressed contraindications for the use of systemic bevacizumab which align with the United States package insert warnings and precautions. Based on safety data with the use of bevacizumab during pregnancy, the group suggests that pregnancy tests be conducted prior to administration. Consensus was reached on the need to make timing adjustments to administration around planned surgical or invasive procedures.

Domain 4 focused on the importance of gathering the patient perspective when making treatment decisions, particularly due to the heterogeneous disease course. Consensus was reached on statements promoting shared decision-making, education, and quality-of-life conversations, including the negative impact of recurrent surgeries.

Domain 5 focused on treatment access logistics and the challenges associated with insurance coverage for an off-label therapy. Guidance is provided regarding supplemental evidence submission to support positive coverage decisions. To mitigate the geographical barriers preventing treatment access, the group reached consensus on care coordination among otolaryngologists and qualified oncologists administering systemic bevacizumab at any infusion setting.

Domain 6 outlined the procedures for initial administration of bevacizumab including coordination with medical oncologists, pre-infusion workup and assessments, initial dose, and dosing interval. The prior workup was initially outlined by Sidell and colleagues[30] and the following considerations were added: monitor renal function and blood pressure with each dose, and obtain a chest CT to evaluate for pulmonary involvement. The standard initial dose and interval is 10 mg/kg administered every 3–4 weeks.

Domains 7–9 provided guidance on monitoring for treatment response, discontinuation/tapering, and reintensification of therapy. Because bevacizumab should be administered with a frequency as low as possible to maintain disease control, outcomes for each individual patient should be reviewed to monitor trends and identify the minimal effective dose. A holistic approach to monitoring treatment response is optimal, as opposed to single-outcome criteria. Specifically, response should be monitored by periodic, objective, anatomical assessment

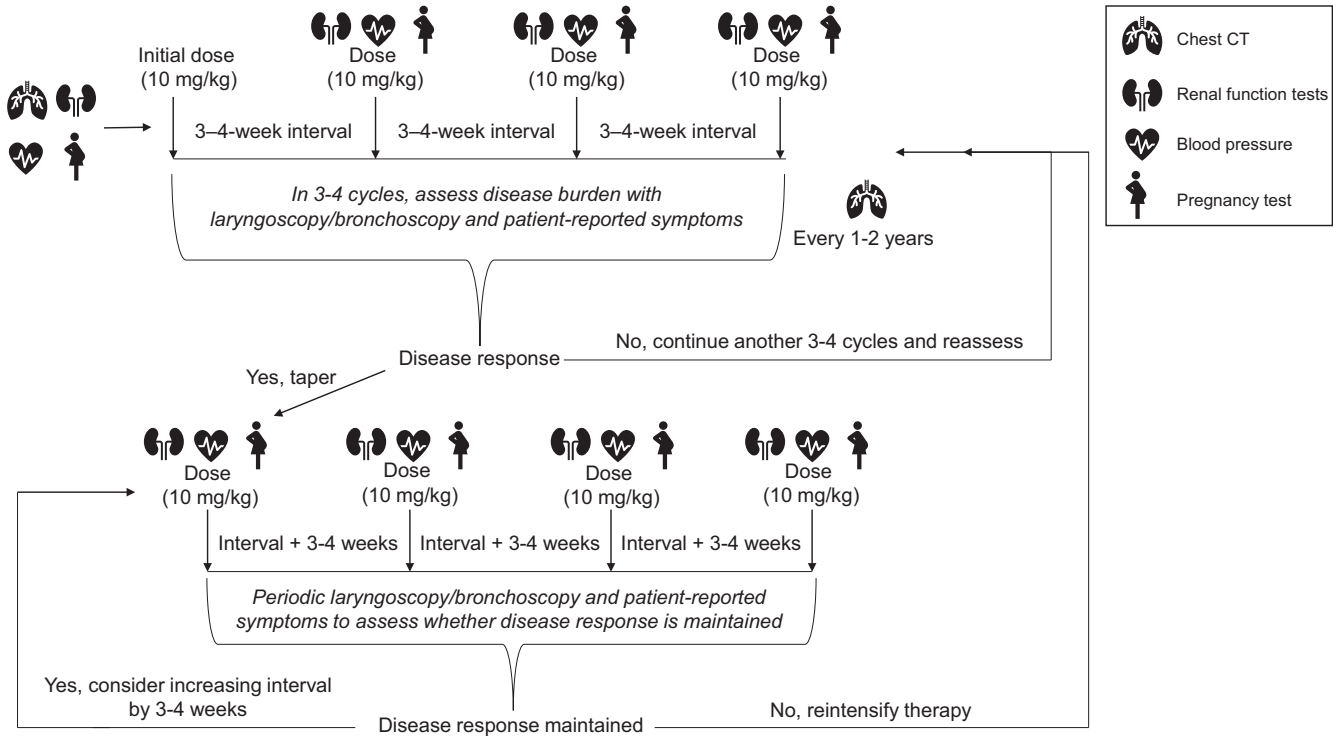


Fig. 1. Consensus dosing regimen outlining initial dose, interval, tapering, monitoring, and reintensification.

of affected disease sites by laryngoscopy or bronchoscopy, patient-reported symptoms, symptom severity scores, surgical frequency, and annual or biannual chest CT in patients with pulmonary disease. These treatment responses and any observed adverse reactions should be rigorously and systematically recorded, preferably through an international patient registry. An overview of dosing and monitoring considerations is provided in Figure 1.

## DISCUSSION

### *Non-surgical Treatment of Patients with RRP*

This consensus statement serves as a milestone in the paradigm shift toward the early use of bevacizumab as a non-surgical treatment for patients with RRP. Systemic bevacizumab could be considered a potential first-line therapy as this group of experts encourages the evaluation of all patients with RRP for treatment candidacy, as the HPV-driven etiology and pathophysiology in pediatric and adult patients is indistinguishable. All published series show an almost universal clinical response to bevacizumab that eliminates or greatly reduces the need for surgical management of RRP.[13,23–29,34] By reducing the need for surgery, there is a substantial impact on patient quality of life and a significant reduction in the risk of iatrogenic laryngeal injury. With the accumulation of additional real-world evidence since its publication, this guidance expands on the patient candidacy criteria originally outlined by Sidell et al.[30] Because of the variable disease course and quality-of-life impact, the group encourages clinicians to make individualized treatment decisions with their patients, supported by education and risk–benefit discussions.

### *Treatment Access*

Use of systemic bevacizumab requires a coordinated multidisciplinary approach, and the group encourages otolaryngologists to work closely with their medical oncology colleagues on patient selection, treatment, and monitoring. By the treating provider collaborating with more accessible local infusion centers, some of the geographic restrictions to treatment access may be safely circumvented. Bevacizumab and biosimilars are off-label therapies for the treatment of patients with RRP. There are currently five FDA-approved biosimilars for bevacizumab, including Avzivi (bevacizumab-tnjn; Bio-Thera Solutions), Vegzelma (bevacizumab-adcd; Celltrion, Inc), Alymsys (bevacizumab-maly; Amneak Pharmaceuticals), Zirabev (bevacizumab-bvzr; Pfizer), Mvasi (bevacizumab-awwb; Amgen).[35] Without randomized controlled trial data, providers can leverage available case studies, expert consensus statements, and retrospective data to support appeals for insurance coverage.

### *Dosing Adjustments and Monitoring*

No consensus was reached on a statement indicating that the initial dosage should align with disease severity. Instead, the group suggests a standard starting dose of 10 mg/kg with flexibility to modify the dosing interval

based on disease severity. This guidance is paired with an approach of tapering and reintensifying therapy based on patient response. Reinstensification would be appropriate either in patients with recurrence who have either completely stopped therapy or extended their tapering interval. The group encourages a holistic approach to assessing treatment response by combining objective assessments with patient-reported symptoms. It is imperative to include objective anatomical visualization and imaging when monitoring progression. Because pulmonary involvement occurs in approximately 9% of patients and is associated with a 32% increased lifetime risk of malignancy compared with the overall RRP population,[36] it is important to evaluate all patients prior to initiation of treatment with bevacizumab. In addition, patients with pulmonary involvement at the start of treatment should be monitored periodically during treatment.

Treatment duration with bevacizumab is presumed to be indefinite and supported by a recent systematic literature review indicating universal rapid response (within days) upon resumption of therapy following recurrence with a mean time to recurrence of 5.4 months after treatment was ceased.[23] There is experience in other diseases regarding long-term treatment with bevacizumab, including NF2and HHT. A meta-analysis of 247 patients with NF2 treated with systemic bevacizumab (5–10 mg/kg every 2 weeks) for a median duration ranging from 6 to 75 months noted the following adverse events; menstrual disorders 44% [95% CI, 16%–73%], proteinuria 30% [95% CI, 18%–44%], hypertension 29% [95% CI, 23%–35%], hemorrhage 14% [95% CI, 4%–26%], and grade 3/4 events 12% [95% CI, 4%–22%] with 12% of these adverse events being grade 3/4.[37] A multicenter retrospective study of 238 patients with HHT treated with systemic bevacizumab for a median of 12 (range of 1–96) months noted the following treatment-emergent adverse events with ≥5% incidence: hypertension (18%), fatigue (10%), proteinuria (9%), and myalgia and/or arthralgia (6%).[38] Of the 41 patients with hypertension, 26 had new-onset hypertension whereas the remaining 15 had worsening hypertension from baseline. Of the 21 patients with proteinuria, one patient had baseline chronic kidney disease and three patients had baseline diabetes mellitus.

### *Biosimilars*

Because the group thought there was a need for additional systematic data, no consensus was reached on a specific statement regarding biosimilars. However, the group remained neutral regarding the use of biosimilars, neither discouraging nor endorsing their use. It is important to note that both the United States Food and Drug Administration and the European Union European Medicines Agency definitions and requirements for approval state that biosimilars are highly similar to the reference product and have no clinically meaningful differences in terms of safety, quality, and effectiveness from the reference product.[39–41]

### *Areas of Future Research*

The group emphasized the importance of data sharing to further bolster the evidence base for the efficacy and safety of systemic bevacizumab in the RRP patient population. Leveraging these data to assess effectiveness and safety of systemic bevacizumab aligns with the primary uses for patient registries outlined by the Agency for Healthcare Research and Quality.[42] These data will also aid in the identification of trends that will inform the minimal effective doses and ideal intervals in pediatric and adult patients. The existing Global RRPF/CoRDS RRP Patient Registry can be leveraged for the collection of these data.[43]

The consensus panel recognized a need to develop formal tools to collect patient-reported outcomes data. The following statement met criteria for consensus (mean score = 8.2; outliers = 1): *Patient-reported outcomes measures should be included when monitoring for treatment response*. Because of the lack of standardized patient-reported outcomes tools in this population, the group ultimately chose not to include this statement. However, it is important to note that other statements were included regarding shared decision-making and disease monitoring. The group strongly supports specific conversations with patients and caregivers regarding disease impacts on social, mental, financial, and emotional health. Regardless of the current deficit in tools, the group advocates for surveillance of patient-reported symptoms during treatment with bevacizumab.

## CONCLUSION

This consensus statement provides guidance for clinicians treating patients with RRP regarding the administration of systemic bevacizumab for clinicians treating patients with RRP. The statement highlights the importance of consultative discussions with patients and caregivers regarding bevacizumab as a possible nonsurgical treatment. This group has outlined specific considerations for the systemic administration of bevacizumab including the clinical and patient characteristics ideal for treatment candidacy, patient perspective in treatment decisions, treatment access, initial dosing, monitoring, guidelines for tapering and discontinuation, and reintensifying therapy. The authors urge clinicians to offer bevacizumab as an early non-surgical treatment option for patients with RRP.

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