



Recurrent Respiratory Papillomatosis

Carla Giannoni, MD
Associate Professor
Pediatric Otolaryngology
Baylor College of Medicine
Texas Children's Hospital

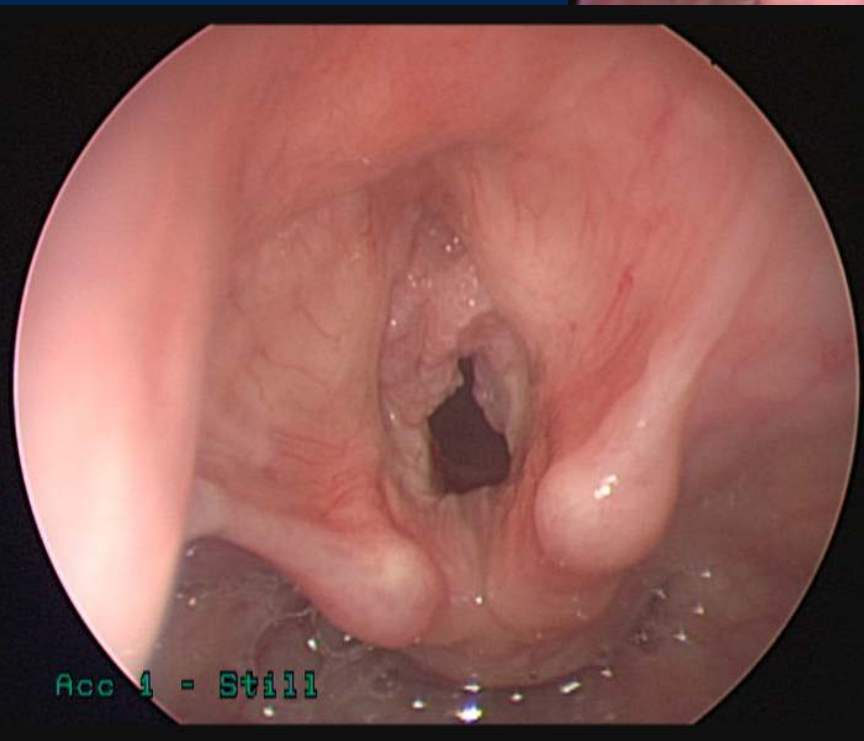
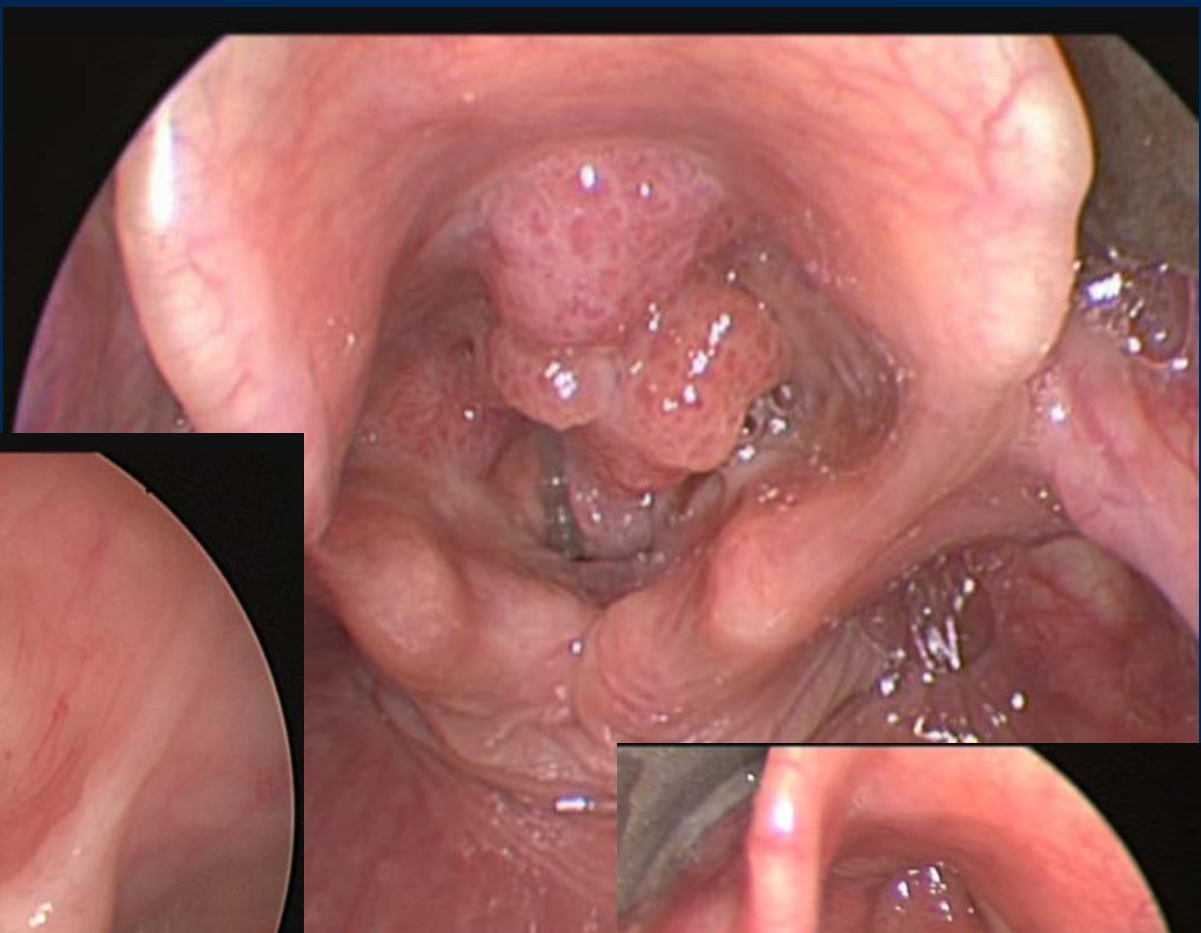


**Texas Children's
Hospital**[®]

BCM

Baylor College of Medicine

RRP (JORRP)



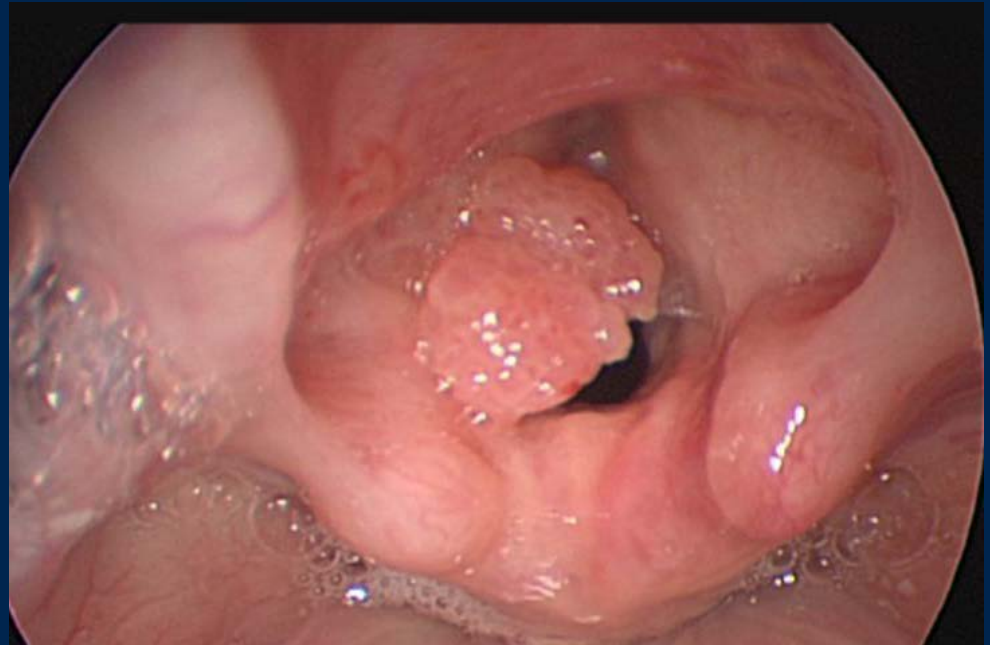
Acc 1 - Still



Presentation

- Symptoms:

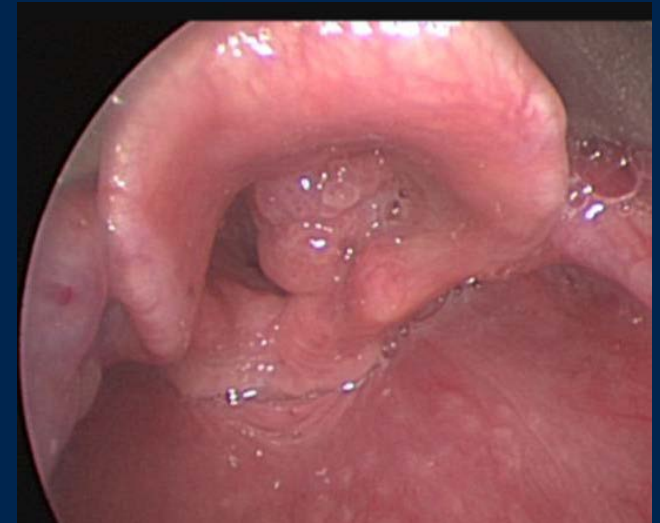
- Hoarseness
- Aponia
- Airway distress
- Cough



- May be misdiagnosed as asthma, recurrent croup, or bronchitis (stridor mistaken for wheezing)
- Younger children present with worse airway sx
- Average time of sx onset to diagnosis: 13 mo

Histopathology

- Epithelial projections around a fibrovascular core
- Epithelial hyperplasia, normal epithelial maturation is absent
- Junctional sites: ciliated resp and squamous epithelia
 - Larynx (ventricle, vocal folds, laryngeal epiglottis),
 - Trachea (carina),
 - Also: Soft palate, Nasal vestibule
- Normal epithelium harbors HPV
- Malignant degeneration to SCCa



Case Report

- Presentation: 4.5 mo old
- First procedure: 5 mo old
- To date: 12.6 yrs old, 60 procedures



Recurrent Respiratory Papillomatosis

- Bimodal age distribution

- <5 yo (75% of cases, 25% present in infancy); M=F (JORRP)

- 20 - 30 yo (STD); more common in males

- Average lifetime cost per patient = \$200,000

- (range, US \$60,000–US \$470,000).

Age, y	Total (Privately insured)			Total (Publically insured)		
	n	Incidence	Prevalence	n	Incidence	Prevalence
0–4	416,025	0.65 (0.12–2.00)	1.02 (0.29–2.55)	482,928	1.68 (0.73–3.29)	2.97 (1.64–4.95)
5–9	555,926	0.61 (0.14–1.68)	1.92 (0.94–2.55)	516,443	0.85 (0.25–2.09)	2.86 (1.59–4.74)
10–14	589,096	0.46 (0.08–1.41)	1.34 (0.58–2.65)	446,225	0.98 (0.29–2.42)	3.78 (2.20–6.06)
15–17	374,505	0.27 (0.01–1.49)	1.38 (0.46–3.18)	253,916	0.27 (0.01–1.97)	1.49 (0.39–3.91)
0–17	1,935,552	0.51 (0.24–0.94)	1.45 (0.96–2.09)	1,699,512	1.03 (0.61–1.64)	2.93 (2.17–3.86)

Per 100,000 persons. Estimates are based on the proportion of electronic claims-based cases that were confirmed by medical chart review
 © 2015 Ovid Technologies, Inc. All rights reserved. OvidSP_UI03.15.01.102, SourceID 66680

Sexually Transmitted Diseases. Issue: Volume 41(5), May 2014, p 300–305

RRP and HPV

- RRP caused by infectious agent
 - Ullman, ACTA Otolaryngologica V:317, 1923
- Child with maternal history of active first trimester HPV condylomata identified, 1956
- HPV (+) confirmed by Southern blotting
 - Quick, Ann Otol 89:467, 1980
 - Genital condylomata also HPV (+)
- HPV Types 6, 11 and rarely 16 implicated in RRP
 - Type 11
 - Younger children
 - More aggressive disease
 - Type 16 – least common
 - Malignant degeneration to SCCa

RRP: Vertical transmission

- Transmission: Prenatal, Intrapartum or Perinatal transmission
 - HPV has been identified in amniotic fluid & cord blood
 - RRP has occurred in children born by C-section
 - 13 of 220 cases in database maintained by RRP Foundation
 - Case report of C-section before rupture of amniotic membranes
- Risk triad:
 - First-born children, vaginally delivered, teenage mother

Age, y	Total (Privately insured)			Total (Publically insured)		
	n	Incidence	Prevalence	n	Incidence	Prevalence
0-4	416,025	0.65 (0.12-2.00)	1.02 (0.29-2.55)	482,928	1.68 (0.73-3.29)	2.97 (1.64-4.95)
5-9	555,926	0.61 (0.14-1.68)	1.92 (0.94-2.55)	516,443	0.85 (0.25-2.09)	2.86 (1.59-4.74)
10-14	589,096	0.46 (0.08-1.41)	1.34 (0.58-2.65)	446,225	0.98 (0.29-2.42)	3.78 (2.20-6.06)
15-17	374,505	0.27 (0.01-1.49)	1.38 (0.46-3.18)	253,916	0.27 (0.01-1.97)	1.49 (0.39-3.91)
0-17	1,935,552	0.51 (0.24-0.94)	1.45 (0.96-2.09)	1,699,512	1.03 (0.61-1.64)	2.93 (2.17-3.86)

Per 100,000 persons. Estimates are based on the proportion of electronic claims-based cases that were confirmed by medical chart review

© 2015 Ovid Technologies, Inc. All rights reserved. OvidSP_UI03.15.01.102, SourceID 66680

Vertical transmission: Yes, but....

- 26.8% of woman of childbearing age (14–49 years) are infected with HPV
 - 2.8% and 0.3% with HPV types 6 and 11, respectively
- Genital condylomata (HPV-GC) in ~2% of US women
 - 7 in 1000 children born to HPV-GC mothers develop JORRP
 - 50 - 67% of moms of RRP children have HPV-GC
 - Risk of JORRP is 231 times higher for babies born to mothers with HPV-GC than those born to mothers without HPV-GC
 - C-section is controversial: does not clearly reduce risk of transmission and carries risk to the mother – appears most likely to be beneficial if done before membrane rupture
- Only 1 in 400 “at risk” infants develop RRP
 - Much lower than risk of contracting other STDs
- MULTIFACTORIAL process: Host factors
 - Immune dysfunction
 - Mucosal membrane disruption
 - Certain HLA haplotypes
 - Viral co-infection (HSV, EBV)

HPV & Immune dysregulation

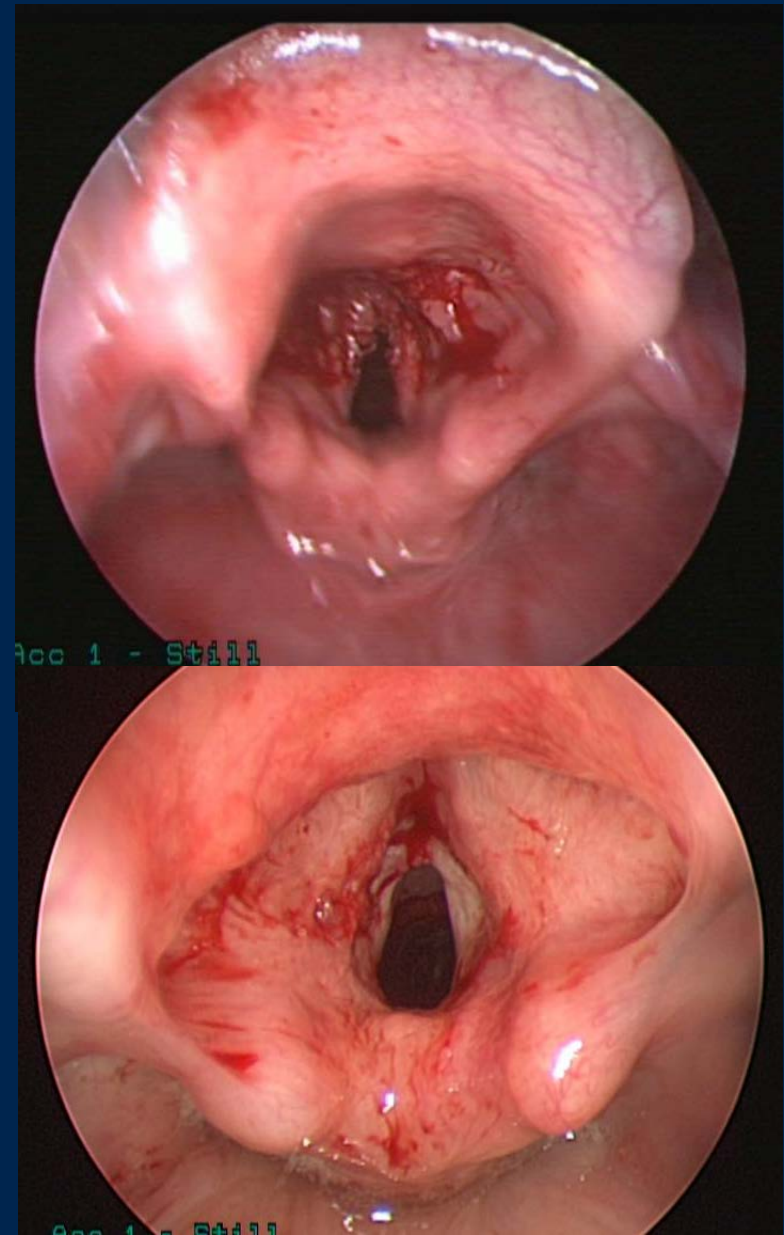
- Lucs AV et al. **Immune Dysregulation in Patients Persistently Infected with Human Papillomaviruses 6 and 11.** J Clin Med. 2015 Mar;4(3):375-388.
 - “HPV-induced diseases are likely the result of a complex and localized immune suppressive milieu ... Altered innate and adaptive immune responses contribute to the cellular and humoral microenvironment that supports HPV 6 and 11-induced disease.”
- Bonagura VR et al. **Recurrent respiratory papillomatosis: a complex defect in immune responsiveness to human papillomavirus-6 and -11.** APMIS. 2010 Jun;118(6-7):455-70.
 - Permissive adaptive and innate responses made by patients with RRP support chronic HPV infection and prevent immune clearance of these viruses. Taken together, RRP is a complex, multigene disease manifesting as a tissue and HPV-specific, immune deficiency that prevents effective clearance and/or control of HPV-6 and -11 infection.
 - T(H)2-like polarization in papillomas and blood of patients with RRP
 - Restricted CD4 and CD8 Vbeta repertoires
 - HPV-11 early protein E6 effect on T-cell alloreactivity
 - Enriched Langerhans cell presence
 - Dysfunctional natural killer cells

Clinical course

- Highly variable
- Typically requires extensive medical and surgical treatment
 - Average surgeries/year = 5
 - Average lifetime procedures = 20
- Causes intense physical, psychological, and financial strain on patients and their families
- Prognosis: Remission and Progression
- Cancer risk:

Surgical therapy

- NOT CURATIVE
- Goals of surgery:
 - Improve airway
 - Phonation, preserve or improve
 - Eradicate disease (and obtain biopsy)
 - Variety of tools (laser, microdebrider, etc)
- Complications
 - Stenosis, webbing, airway fires, pneumothorax



Tracheotomy

- Reserved for most aggressive cases
 - Protects airway!
 - Avg. age at trach 2.7 yr old
 - Avg. age at decannulation 6.3 yr old
- Creates new epithelial junctional zones
- Seeding lower airway
 - 13 Trachs - Pittsburg, 1996
 - 6/13 developed new ds @ trach site (confined to trach site)
 - 1/13 developed new ds @ carina (pt already had subglottic ds)
 - Similar distal extension rates in non-trach patients

Advuvent medical therapy

•Historical

- Cryotherapy
- Antibiotics
- Vaccines (BBG, mumps (intralesional))
- Podophyllin
- Cimetidine
- Chemotherapeutic agent that affects rapidly dividing cells
- Used in worst cases
- 13-cis-Retinoic acid
- Indole-3-carbinol

•Current

- Cidovifir, intralesional
- Interferon - $\alpha 2a$
- Bevacizumab
- HPV vaccine
- Celecoxib?

Adjuvant Therapy

- [Chadha NK1](#), [James A](#). Adjuvant antiviral therapy for recurrent respiratory papillomatosis. [Cochrane Database Syst Rev](#). 2012 Dec 12;12
- “There is insufficient evidence to support the efficacy of antiviral agents as adjuvant therapy in the management of recurrent respiratory papillomatosis in children or adults. The included randomised controlled trial showed no advantage of intralesional cidofovir over placebo at 12 months.”

HPV: goal = control rather than cure?

- [Forslund O](#), [Schwartz S](#), [Olofsson K](#), [Rydell R](#). Viral load and mRNA expression of HPV type 6 among cases with recurrent respiratory papillomatosis. [Laryngoscope](#). 2015 May 22.

	Papilloma	Healthy mucosa
HPV6 (copies/cell)	41 (min 5.4)	1.1 (50% cells HPV+)
HPV6-mRNA/HPV6-DNA transcription ratio (median)	1.5	3.8

- “The amount of HPV6-DNA was consistently higher in the papilloma than in healthy mucosa. The transcription level of HPV6 E7 mRNA was similar in the papilloma and in normal mucosa. We suggest that interfering with replication of HPV6 and suppression of HPV6 to fewer than five copies/cell may be curative.”

Patient Support and Research

- RRP Task force (, ASPO, ABEA)
- RRP Registry (CDC)



The screenshot displays the RRP Foundation website. On the left is a vertical navigation menu with icons for Home, About, Patient, Practitioner, and Contact pages. The main content area features the RRP Foundation logo (two stylized figures, one green and one orange, with the text 'rrpf.org') and a header with the text 'RRP Foundation Est. 1992'. Below the header is a section titled 'About the Foundation.' which provides a brief description of the organization's mission and a link to 'learn more...'. At the bottom of the main content area are two links: 'RRP Voice Page' and 'RRP Educational Video'.

rrpf.org

- HOME PAGE
- ABOUT the RRPF
- PATIENT PAGE
- PRACTITIONER PAGE
- CONTACT PAGE

RRP Foundation
Est. 1992

About the Foundation.
The Recurrent Respiratory Papillomatosis Foundation was created to provide patient/family support, serve as an information resource for patients and practitioners, promote public awareness, and aid in the prevention, cure and treatment of RRP by encouraging and participating in promising RRP research studies.
[learn more...](#)

[RRP Voice Page](#)

[RRP Educational Video](#)