

NEW YORK-PRESBYTERIAN EAR, NOSE, & THROAT

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

INSIDE FALL 2008

Pediatric Airway Disorder

2 Hospital creates new multi-disciplinary clinics to treat pediatric airway disorders.

SAVE THE DATE

Otolaryngology Update in NYC

October 16-17, 2008

For more information, visit:
www.ENTColumbia.org/cme

For more information on
Ear, Nose, & Throat services, visit
www.nyp.org/ent

RESOURCES FOR PROFESSIONALS

- Webcasts
- CME Activities
- Medical Presentations
- Specialty Briefings
- Newsletters

Visit nyp.org/pro

Head, Neck Cancer Cellular Pathways Revealed

Patients with Fanconi anemia (FA) are at increased risk for head and neck cancer compared with the general population. Using FA as a model to study the natural history of head and neck cancer, David I. Kutler, MD, and colleagues have made exciting discoveries about the underlying mechanisms of carcinogenesis, which may ultimately help produce more effective and safer treatments for patients with FA.

The increased risk for cancer among patients with FA is thought to be attributable to instability of the genome, as evidenced by cellular hypersensitivity to DNA crosslinking agents and failure of chromosomal repair mechanisms. “The response to the severe DNA damage caused by diepoxybutane and mitomycin, for instance, is impaired in FA, and cells fail to correct the excessive chromosomal breakage and DNA crosslinking that occur when exposed to these agents,” said Dr. Kutler. The loss of genomic integrity is believed to contribute to the elevated risk for cancer in these patients.

Currently, Dr. Kutler is studying the cellular pathways of head and neck cancer in patients with FA at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. He was first drawn to studying FA after collaborating with Arleen Auerbach, PhD, a researcher at the Laboratory of Human Genetics and Hematology at Rockefeller University, and Bhuvanesh Singh, MD, PhD, from Memorial Sloan-Kettering Cancer Center, both in New York City. Dr. Auerbach had established the International Fanconi Anemia Registry (IFAR) to track patients with this rare disease. “She had observed through the registry that a relatively large number of FA patients developed head and neck cancers at a young age—20 to 30



Photo courtesy of David I. Kutler, MD.

Chromosomal instability: Cells with chromosomal breaks are seen as a major genetic risk factor for development of head and neck squamous cell carcinoma.

years old—despite an absence of traditional risk factors for this malignancy, such as cigarette smoking or excessive use of alcohol,” said Dr. Kutler.

Dr. Auerbach asked Dr. Kutler to help her explore a possible relationship between the genetics of FA and the etiology of head and neck cancer. “Using FA as a model to study the natural history of head and neck cancer was a unique opportunity,” said Dr. Kutler, “because there are no other known head and neck cancer-predisposing syndromes that might offer insights into the pathogenetic etiology of this disease.”

Patients with FA are at especially increased risk for leukemias and squamous cell carcinomas (SCCs), usually in the upper aerodigestive, gastrointestinal, and anogenital tracts. FA is an autosomal recessive genetic disorder characterized by progressive bone marrow failure, various phenotypic malformations, and a predisposition to development of

see **Fanconi Anemia**, page 2

Sublingual Immunotherapy Gains Popularity

For the 40 to 50 million Americans who suffer from allergic diseases, there may be good news as the use of sublingual immunotherapy (SLIT) becomes more widespread. According to William Reisacher, MD, this technique “has been widely used in Europe since the 1980s, with a high success rate, but is now beginning to gain traction in the United States.”

Dr. Reisacher and colleagues in the Department

of Otorhinolaryngology at NewYork-Presbyterian Hospital/Weill Cornell Medical Center are prescribing SLIT for the oral delivery of safe and effective allergen-specific immunotherapy, traditionally given by subcutaneous (SC) injection. Hector Rodriguez, MD, and colleagues at NewYork-Presbyterian/Columbia University Medical Center are exploring the use of SLIT as well.

see **SLIT**, page 3

Multidisciplinary Clinic Treats Pediatric Airway Disorders

The multidisciplinary pediatric airway clinic is a relatively new concept in medicine. A paradigm based on the diverse challenges associated with congenital or acquired airway problems in children, the clinics at NewYork-Presbyterian Hospital/Columbia University Medical Center and Weill Cornell Medical Center are staffed by a variety of upper airway specialists, all with special skill in working within the smaller spaces of the pediatric airway.

According to Robert Ward, MD, children with serious acquired or congenital airway

defects are best managed in a specialized setting that caters to the pediatric patient. "With a multidisciplinary staff," he advised, "the clinic offers the expertise of a variety of pediatric specialties, from general pediatrics, otolaryngology, and pulmonology to pediatric gastroenterologists, neurosurgeons, and/or speech therapists when needed, thus addressing all of the problems of pediatric airway disorders at a single location and in a coordinated fashion."

Eli Grunstein, MD, added: "Congenital conditions such as laryngeal cleft or laryngomalacia may not be life-threatening but

can cause difficulty swallowing and speech and voice dysfunctions that demand the skills of pediatricians, surgeons, and speech specialists at the same time." Similarly, patients with airway scarring, with or without a tracheotomy tube in place, often require attention from a myriad of specialists. Furthermore, Dr. Grunstein noted, more serious problems can arise when children are born with tumors such as airway hemangiomas, which are typically benign but, based on location, may be life-threatening if they interfere with the patient's

see **Pediatrics**, page 3

continued from **Fanconi Anemia**, page 1

malignancies. Most patients with FA die by age 50, often as a result of these inevitable and aggressive malignancies.

Dr. Kutler and colleagues decided to examine the relationship between FA genotype and the development of head and neck malignancy by conducting a review of records from the IFAR database (*Arch Otolaryngol Head Neck Surg* 2003;129[1]:106-112). The sample included 754 patients with confirmed FA.

"In the group of patients with FA, we observed a 500-fold increase in the cumulative incidence of head and neck squamous cell carcinoma [HNSCC] compared with the general population," he noted. "We observed a 3% rate of HNSCC in people with FA, whereas the expected incidence for buccal and pharyngeal cancer based on Surveillance Epidemiology End Result data would be 0.038%." Additionally, patients in the study exhibited a statistically significant increase in risk for early-onset HNSCC with a 14% incidence of HNSCC before age 40 years ($P < 0.001$).

The high rates of cancers of the oral and genital mucosa, common entry points for oncogenic viral infections, next led Dr. Kutler and colleagues to investigate the possibility that human papillomavirus (HPV) may contribute to the onset of SCC in patients with FA (*J Natl Cancer Inst* 2003;95[22]:1718-1721). Using polymerase chain reaction screening to determine the presence of HPV DNA, the researchers found "a significant increase in HPV DNA in SCC specimens from patients with FA compared with control subjects, at 84% versus 36%, respectively, yet an absence of *p53* mutations, a marker commonly found in non-FA subjects with head and neck cancer," said Dr. Kutler. This finding suggested that HPV-induced carcinogenesis might

indeed contribute to the development of SCC in these individuals.

Furthermore, the HPV-linked oncoprotein E6, previously reported to inactivate the *p53* tumor suppressor gene, "may play a role in the development of these cancers in FA patients," added Dr. Kutler. Because of this unique pathway, "in which HPV inactivation of *p53* has been linked to increased cancer risk," he noted, "FA has proven to be an excellent model in which to study potential preventive strategies for HPV-induced carcinogenesis, as well."

Dr. Kutler emphasized that better understanding of the mechanisms of cancer formation in this patient population may improve quality of life for patients with FA. "These patients are at high risk for chromosomal damage if given chemotherapy or radiation to treat cancer," he explained, "but the more we understand about underlying mechanisms

of carcinogenesis, the better we can formulate effective yet safe treatments that will not in themselves cause harm."

Today, Dr. Kutler is working with scientists in the new cancer center, led by Andrew J. Dannenberg, MD, at NewYork-Presbyterian/Weill Cornell, where they are developing cell lines from patients with FA to further study the cellular pathways for HNSCC in this population. He is also involved in a study with Dr. Singh, studying children with FA to determine rates of HPV infection in this young population.

"With continued research into HNSCC pathways and prevention in FA," he concluded, "we hope to continue to improve the lives and outcomes for people with this challenging disease."

Contributing faculty for this article:
David I. Kutler, MD

Correction

The article on vocal cord paralysis that appeared on page 3 of the Spring 2008 issue of this newsletter contained inaccurate images. The editors have reprinted the corrected images below:



Figure 1. The right vocal fold of a 39-year-old female patient is paralyzed and hypotonic, causing the patient to aspirate liquids and have a profoundly hoarse voice.

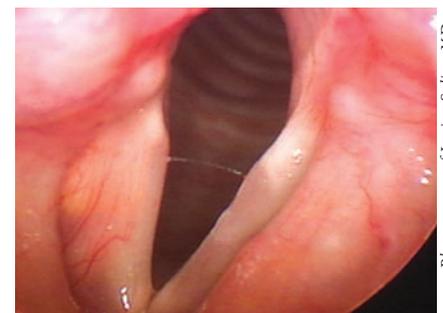


Figure 2. One week after an injection of calcium hydroxylapatite paste to the right vocal fold, the vocal fold remains paralyzed but has good closure and both aspiration and hoarseness have resolved.

Photos courtesy of Lucian Sultica, MD.

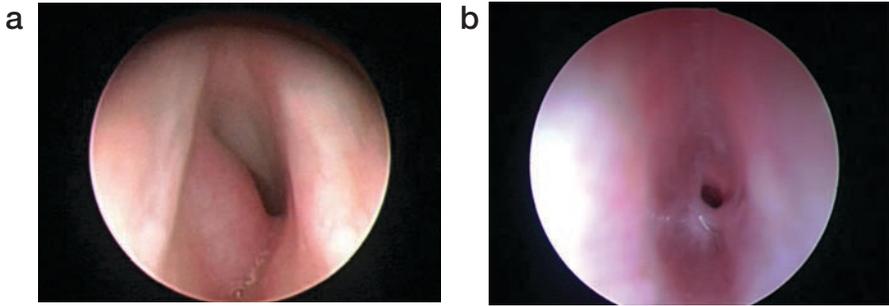


Photo courtesy of Eli Grunstein, MD.

Figure. a. Image depicts pediatric patient with a subglottic hemangioma. **b.** Laryngoscopy of a 1-year-old female patient with a history of prematurity, chronic lung disease, and prolonged intubation at birth reveals severe laryngeal stenosis. In preparation for laryngotracheal reconstruction, she was seen by pediatric pulmonologists and pediatric gastroenterologists. She underwent ph probe placement and upper endoscopy with biopsies. After confirming stable lung function and controlled reflux, she was scheduled for laryngotracheal reconstruction using a rib cartilage graft.

continued from **Pediatrics**, page 2

ability to breathe adequately (Figure). “In the clinic we tend to see the most severe cases, often referred from the intensive care unit or community otolaryngologists.”

Craniofacial anomalies are another frequent presentation at the pediatric airway clinic. “Infants born with small mandibles,” Dr. Ward said, “often have severe breathing problems, and children with cleft palates may need to see ENT surgeons as well as the plastic surgeon, dentist, and/or orthodontist.” In addition, acquired airway disorders, or iatrogenic problems such as vocal cord paralysis or tracheal stenosis related to frequent or long-term intubation, are a particular interest of Dr. Ward’s.

The airway clinic at NewYork-Presbyterian Hospital/Weill Cornell evolved over time, said Dr. Ward, “as a place where the necessary specialists can concentrate resources and provide comprehensive office care.” The success of the program is evident in the expansion of the clinic and its move to a new 4,000-square-foot space on East 72nd Street, complete with dedicated offices, nursing staff, equipment and toys, all in a child-centered setting.

The multidisciplinary pediatric airway clinic at NewYork-Presbyterian/Columbia is “imminent,” said Dr. Grunstein, “with concept approval from the Departments of Pediatrics, Pediatric Pulmonology, and Pediatric Otolaryngology, and architecture assigned specifically for the purpose of pediatric outpatient and operative ENT care.” There are operating rooms designated for the pediatric clinic cases, an endoscopy suite with new equipment for pediatric upper aerodigestive tract endoscopy, and staffing by full-time pediatric anesthesiologists. It is hoped that the clinic will be ready and opened within the year.

Dr. Ward hopes to continue to build the concept of the specialty airway clinic and provide a learning opportunity that will benefit ENT specialists. “As we move into our new facility and the uptown clinic nears completion, our ongoing camaraderie, discussion, and cross-pollination of ideas should continue to further the growth of the pediatric airway clinic model.”

Contributing faculty for this article:
Eli Grunstein, MD, and Robert F. Ward, MD

NewYork-Presbyterian Ear, Nose, & Throat Editorial Board

Lanny Garth Close, MD

Director of Service, Department of Otolaryngology/Head and Neck Surgery
NewYork-Presbyterian Hospital/Columbia University Medical Center
Chairman and Howard W. Smith Professor of Otolaryngology
Columbia University College of Physicians and Surgeons
E-mail: lgc6@columbia.edu

Michael G. Stewart, MD, MPH

Otorhinolaryngologist-in-Chief
NewYork-Presbyterian Hospital/Weill Cornell Medical Center
Chairman, Department of Otorhinolaryngology and Professor of Otorhinolaryngology and Public Health
Weill Cornell Medical College
E-mail: mgs2002@med.cornell.edu

Related Links:

www.ENTColumbia.org • www.CornellENT.org

continued from **SLIT**, page 1

“After attempts at avoidance therapy and pharmacotherapy with antihistamines, decongestants, and nasal steroid sprays, people who do not achieve adequate symptom relief are good candidates for immunotherapy, and SLIT represents a promising advance over the SC injection approach,” advised Dr. Rodriguez.

Most of the literature to date on SLIT is based on European research, although large U.S. trials are under way, including a Weill Cornell Medical College study. “With about a 30% dropout with SC administration,” Dr. Reisacher said, “our first study is examining whether the dropout rate is improved among SLIT-treated patients.” A second trial, assessing whether preseason preventive therapy with SLIT can reduce symptoms of seasonal allergies, is being considered. “Patients with seasonal allergies to only 1 or 2 allergens generally are not offered SC immunotherapy, but this is a population who might benefit from the convenient and safe SLIT method,” emphasized Dr. Reisacher.

SLIT provokes the immune system with increasing amounts of allergen stimulus, thereby increasing tolerance to the antigen and reducing symptoms of seasonal or perennial inhalant allergies. Although it uses the same allergen extract and works by a mechanism similar to SC immunotherapy, the oral method is considered more convenient and safe. SLIT is administered via 3 daily drops of allergen extract solution under the tongue; the antigen is held for 1 to 2 minutes and then swallowed or spit out.

“Pharmacokinetic studies show that while the allergen remains in the oral mucosa for up to 40 hours, there is no evidence of systemic distribution,” said Dr. Reisacher, making this approach what he called a “full-body surveillance system,” wherein the immune system reacts systemically to a local stimulus (*Clin Exp Allergy* 2001;31[1]:54-60). The simplicity and safety of the oral administration, Dr. Rodriguez said, “allows for home-based self-medication, although the first dose is given in the doctor’s office.” It may also be a preferred option for children, particularly those with needle phobia.

In contrast, SC immunotherapy requires weekly office visits for injection of allergen, with dosage increases to achieve maximum efficacy. “Each visit for SC therapy includes a 20-minute wait after the injection, to be certain the patient does not have an anaphylactic reaction,” Dr. Reisacher said. Once a

see **SLIT**, page 4

continued from **SLIT**, page 3

maintenance dosage is reached, the schedule is decreased to every 2 weeks and monthly thereafter. "This is a huge time commitment that can interfere with follow-through by many patients with severe allergies," he added.

The SC method has been associated with some toxicity and deaths—principally caused by avoidable dosing errors, buildup of immunotherapy, administration during active asthma or allergy season, or first injection from a treatment vial. Although mishaps can be eliminated with careful administration, improved safety and convenience have driven the search for a noninjectable alternative.

Both Drs. Reisacher and Rodriguez will be participating in educational programs that address SLIT in the coming months. Dr. Reisacher will serve on a panel at the 2008 American Academy of Otolaryngology—Head and Neck Surgery conference in Chicago, to address issues such as optimizing SLIT dosing, assessing its role in patients with asthma, and seasonal preventive therapy. In addition, on October 16, Dr. Rodriguez is presenting a paper at a nationally attended symposium at NewYork-Presbyterian/Columbia, which will address the effects of allergy on nasal membranes and the role of surgical treatment of inferior turbinate hypertrophy. The program

Contributing Faculty

The following is a list of the doctors quoted in this issue of the *NewYork-Presbyterian Ear, Nose, & Throat* Newsletter. For more information on their work, please contact them at the e-mail addresses listed.

NewYork-Presbyterian Hospital

Columbia University College of Physicians and Surgeons

Eli Grunstein, MD

Assistant Director of Pediatric Otolaryngology
Assistant Professor of Otolaryngology/Head and Neck Surgery
E-mail: eg582@columbia.edu

Hector P. Rodriguez, MD

Director of Rhinology in the Department of Otolaryngology/Head and Neck Surgery
Assistant Professor of Clinical Otolaryngology/Head and Neck Surgery
E-mail: hpr1@columbia.edu

Weill Cornell Medical College

David I. Kutler, MD

Assistant Attending Otorhinolaryngologist
Anne Belcher, MD, Assistant Professor of Otorhinolaryngology
E-mail: dik2002@med.cornell.edu

William Reisacher, MD

Director of Allergy
Assistant Attending Physician in Otorhinolaryngology
Assistant Professor of Otorhinolaryngology
E-mail: wir2011@med.cornell.edu

Robert F. Ward, MD

Attending Otorhinolaryngologist
Professor of Otorhinolaryngology
Professor of Otorhinolaryngology in Pediatrics
E-mail: rfw2001@med.cornell.edu

also includes a presentation on SLIT by Bradley Marple, MD, from the American Academy of Otolaryngic Allergy.

Both Drs. Rodriguez and Reisacher are following the progress of additional allergy treatments in the pipeline, such as monoclonal antibodies (anti-immunoglobulin E), other forms of immunotherapy, and protein extracts

for improved efficacy or safety. As interest in SLIT grows and other new treatments gain a foothold in the United States, the Departments of Ear, Nose, and Throat at the Hospital will continue to research and clinically apply these exciting new strategies.

Contributing faculty for this article:
William Reisacher, MD, and Hector P. Rodriguez, MD



NEWYORK-PRESBYTERIAN EAR, NOSE, & THROAT

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

Important news from the Ear, Nose, and Throat Centers of NewYork-Presbyterian Hospital—current research projects, clinical trials, and advances in the diagnosis, treatment, and rehabilitation of ear, nose, and throat disorders.

NewYork-Presbyterian Hospital
525 East 68th Street
New York, NY 10065

NONPROFIT ORG.
U.S. Postage PAID
Permit No. 37
Utica, NY