Paradigm Shift in the Management of ANCA-Associated Vasculitis: Pathogenetic Concepts Lead to Targeted Therapy

Three systemic autoimmune small vessel vasculitis syndromes are associated with antineutrophil cytoplasmic autoantibodies (ANCAs); collectively, they're called ANCA-associated vasculitis (AAV). AAV include:
• Microscopic polyangiitis (MPA)
• Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis
• Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome

The respiratory system is commonly involved in all three syndromes, which share certain histopathologic and clinical features. Other features are unique and disease-defining (Table 1).

Diffuse alveolar hemorrhage (Figure 1, A1, see page 2) is a potentially life-threatening complication of each of these syndromes. Patients with diffuse alveolar hemorrhage often require ICU care. Caused by pulmonary capillaritis, diffuse alveolar hemorrhage affects 20 to 30 percent of patients with MPA and GPA, but less than 5 percent of patients with EGPA. Other clinical manifestations caused by necrotizing small vessel vasculitis and capillaritis, such as glomerulonephritis, palpable purpura, scleritis, or sensory and motor mononeuropathies, also can occur in all three syndromes.

Granulomatous inflammation, which predominantly affects the respiratory tract, causes characteristic clinical features setting GPA and EGPA apart from MPA. The granulomatous inflammation is necrotizing and neutrophilic in GPA, but eosinophilic in EGPA. The necrotizing granulomatous inflammation of GPA can cause pulmonary nodules or mass lesions (Figure 1, B1, *see page 2*) and affect the large airways leading to subglottic and endobronchial stenoses (Figure 2, *see page 3*). Asthma and peripheral blood eosinophilia, the defining characteristics of EGPA, are not features of GPA or MPA.

The type of ANCA also seems to affect the disease phenotype of ANCA-associated vasculitis. Two types of ANCAs are of clinical significance in patients with vasculitis:
• ANCAs causing a cytoplasmic immunofluorescence pattern (C-ANCAs) on ethanol-

Table 1. Features of ANCA-Associated Vasculitis

	GPA	MPA	EGPA
Upper airway disease	90-95%	No	50-60%
Pulmonary parenchymal disease	54-85%	20%	30%
Alveolar hemorrhage	5-15%	10-50%	< 3%
Glomerulonephritis	51-80%	60-90%	10%-25%
Gastrointestinal tract	< 5%	30%	30-50%
Eyes	35-52%	< 5%	< 5%
Nervous system	20-50%	60-70%	70%-80%
Heart	8-16%	10-15%	10-15%
Skin	33-46%	62%	50-60%
Eosinophilia	Rare	Rare	Yes
Asthma	No*	No*	Yes
Granulomatous inflammation	Yes	No	Yes
PR3-ANCA	70-90%	10-30%	< 2%
MPO-ANCA	5-10%	70-90%	30-70%

No more than the general population

fixed neutrophils that react with proteinase 3 (PR3-ANCAs)

- ANCAs causing a perinuclear immunofluorescence pattern (P-ANCAs) on ethanol-fixed neutrophils that react with myeloperoxidase (MPO-ANCAs)

PR3-ANCAs occur in the vast majority of patients with GPA, while MPO-ANCAs occur far less frequently. In contrast, MPO-ANCAs are the predominant type of ANCAs in patients with both MPA and EGPA.

Recent advances in pathogenesis

Significant progress has been made over the last two decades in understanding the pathogenesis of AAV. Research conducted at Mayo Clinic and elsewhere has paved the way for novel and individually targeted therapeutic approaches. Clinical and experimental evidence supports the concept that a genetic predisposition for autoimmunity, epigenetic factors and environmental triggers are necessary for the loss of tolerance and development of an inflammatory milieu that supports the production of ANCAs. In the context of an inflammatory milieu, ANCAs can cause specific tissue inflammation and vascular injury by a variety of different mechanisms that involve direct interactions with the respective ANCAs' target antigens PR3 or MPO.

A genome-wide association study found major histocompatibility complex (MHC) and non-MHC associations with AAV and genetic distinctions between GPA and MPO, and even more clearly between PR3- and MPO-ANCA-associated diseases, providing support for the concept that they are genetically distinct autoimmune disorders. The documented higher relapse rate of patients with PR3-ANCAs compared with MPO-ANCAs may have a genetic basis.

A large body of experimental work supports that B lymphocytes are essential for the development of ANCAs and disease activity, whereas T lymphocyte abnormalities seem to persist, particularly in patients with GPA, even during remission. The presence of ANCAs alone does not inevitably cause disease, but ANCAs seem necessary for the development of disease manifestations caused by capillaritis, such as alveolar hemorrhage, glomerulonephritis, scleritis or mononeuritis multiplex.

For all of these reasons, interventions aimed at B lymphocytes, T lymphocytes and ANCA have made inroads into the therapeutic arsenal for AAV.

Recent advances in therapy

About four decades ago, the introduction of cyclophosphamide (Cytoxan) changed the invariably fatal outcome of severe GPA and MPA. Remission could be successfully induced with the combination of glucocorticoids and cyclophosphamide, and the syndromes became manageable chronic conditions. Unfortunately, the relapsing nature of GPA and MPA often requires repeated and sometimes prolonged exposure to cyclophosphamide, causing significant cumulative toxicity. Infertility in both women and men is induced after only a few months of exposure, and solid as well as hematologic malignancies are dreaded late complications of cyclophosphamide exposure. Moreover, some patients could not achieve stable remission with maximal tolerated cyclophosphamide doses.

For these reasons, better tolerated alternatives were desperately needed. Randomized controlled trials and prospective observational cohort studies first showed that methotrexate could replace cyclophosphamide in patients with limited or nonsevere disease GPA. For patients with MPA and mild renal disease, mycophenolate mofetil (CellCept) might be the alternative.

Biologic response modifiers allowing mechanism-based treatment approaches have become available over the last decade. Targeting specific molecules, these agents can block immune pathways thought to cause maladaptive inflammation in autoimmune diseases by inhibiting pro-inflammatory cytokines, elimi-
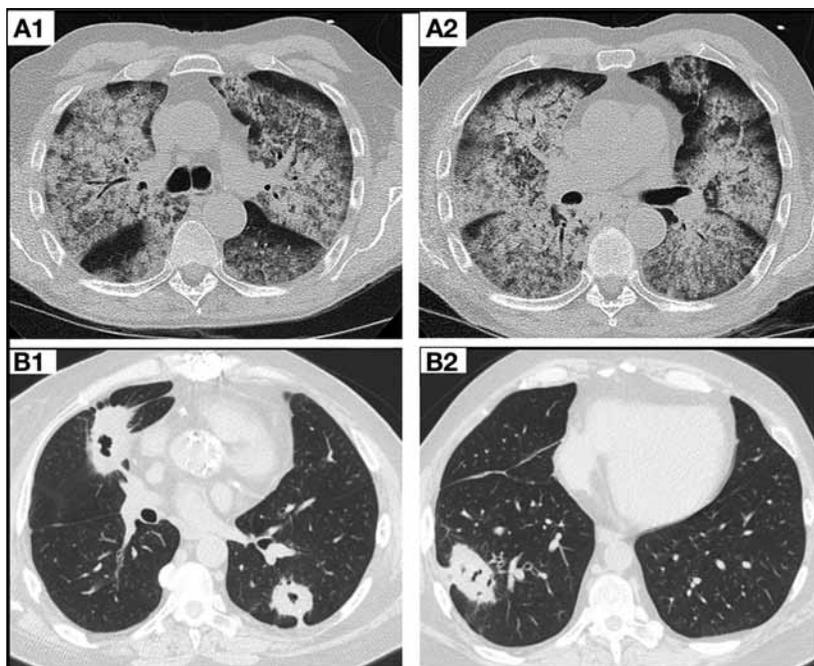

Figure 1. A1 and A2. *Diffuse alveolar hemorrhage.* **B1 and B2.** *Pulmonary nodules and mass lesions caused by the necrotizing granulomatous inflammation of GPA.*

nating cells of defined lineage (B lymphocytes) or inhibiting their activation or recruitment (T lymphocytes, eosinophils).

The ability to specifically target B lymphocytes with rituximab (Rituxan), a chimeric monoclonal antibody against the B lymphocyte specific cell surface receptor CD20, has fundamentally changed the therapy of severe AAV. Following the first report of its use in AAV in 2001, experience with rituximab in AAV has rapidly expanded. The Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial showed that rituximab was not inferior to cyclophosphamide for remission induction in severe GPA and MPA. In fact, for patients with relapsing disease, rituximab was found to be superior to cyclophosphamide. Based on the primary endpoint results of RAVE, the Food and Drug Administration (FDA) approved rituximab in combination with glucocorticoids for remission induction in newly diagnosed and relapsing severe GPA and MPA.

The 18-month follow-up study of RAVE, led by researchers at Mayo Clinic, showed that a single course of four once-weekly infusions of rituximab is as effective for remission induction and maintenance as 18 months of continuous immunosuppressant therapy with cyclophosphamide followed by azathioprine (Imuran). Long-term single-center cohort studies indicated that rituximab is also effective and safe for remission maintenance, particularly in chronically relapsing GPA. In 2013, most patients with GPA and MPA can be managed without exposure to cyclophosphamide and its dreaded long-term toxicities.

A role for biologic response modifiers is also emerging for EGPA. Glucocorticoids have long been the mainstay of treatment, and cyclophosphamide is used for disease activity that threatens the function of vital organs. Side effects of glucocorticoids represent the biggest challenge in the long-term management of this disease. The exact mechanisms of tissue injury in EGPA remain unclear, but blood and tissue eosinophilia appear to be responsible for tissue damage.

Interleukin-5 (IL-5) mediates bone marrow release, tissue survival, maturation and activation of eosinophils. Furthermore, IL-5 levels are
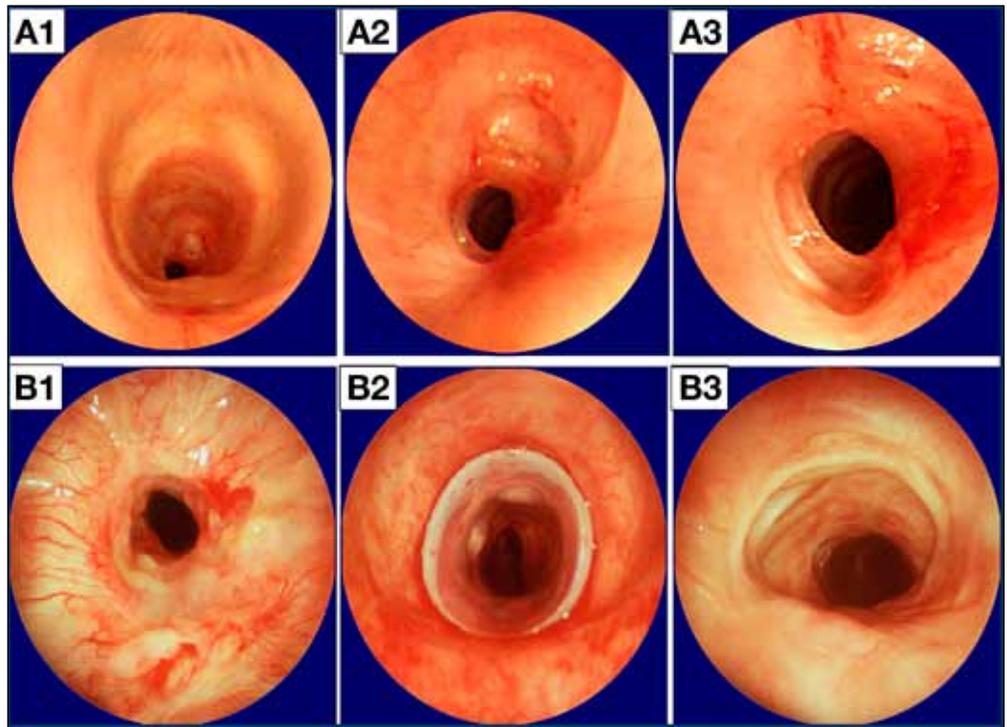

Figure 2. (A and B). *Large airway disease in two patients with mid-tracheal stenosis resulting from granulomatosis with polyangiitis. Because of severity of stenosis* **(B1)**, *dilatation and stent placement was performed* **(B2)** *with good airway patency after stent removal* **(B3)**.

increased in patients with EGPA and are associated with disease activity. Consequently, reducing the number of eosinophils and preventing their activation by inhibiting IL-5 appears to be a rational novel approach for EGPA. Mepolizumab, a monoclonal antibody targeting IL-5, has shown promise in EGPA. Small pilot trials demonstrated prompt and prolonged reduction of peripheral eosinophils, clinical improvement and reduction in glucocorticoid use. A large multicenter randomized controlled trial of this agent in EGPA is underway. Small case series and a pilot trial suggest that rituximab may represent an alternative to cyclophosphamide in severe EGPA, particularly if it's MPO-ANCA-associated.

Multidisciplinary approach to management

At Mayo Clinic, a multidisciplinary team of experts collaborates to provide optimal care to patients with this complex multisystem disorder. This team will often include pulmonologists, nephrologists, rheumatologists, otolaryngologists, neurologists, and sometimes dermatologists or endocrinologists.

The role of otolaryngologists is particularly important for patients with GPA, many of whom suffer from conductive or sensorineural hearing loss, chronic rhinosinusitis and subglottic stenosis. Surgical interventions to address these disease complications need to

be carefully coordinated and appropriately timed in consideration of each patient's status of disease activity. Most surgical procedures aimed at restoring airway patency, such as reconstruction of a saddle nose deformity or dilatation of a subglottic stenosis with intralesional injection of long-acting glucocorticoids and mitomycin C, should be performed when systemic disease activity is well-controlled. Tracheal and bronchial stenoses often benefit from care by interventional bronchoscopists experienced with GPA.

As for the management of subglottic stenosis, dilatation procedures and stent placement (Figure 1B, see page 2) decisions need to be individualized and coordinated in the context of overall disease activity control.

Ongoing and imminent clinical trials enrolling patients at Mayo Clinic

Plasma exchange has been advocated for use in patients with severe alveolar hemorrhage leading to respiratory failure and for severe renal disease. The rationale for this approach is that the rapid removal of pathogenic ANCAs might be beneficial in rapidly progressive disease. The data supporting this practice, however, are inconclusive. The FDA and multiple international agencies have joined forces to cooperatively fund an ongoing global randomized trial (PEXIVAS) to evaluate the efficacy and safety of plasma-exchange for patients with ANCA-associated renal disease or diffuse alveolar hemorrhage or both.

The biggest remaining challenge in the management of these relapsing conditions is the long-term maintenance of remission with minimum cumulative drug toxicities. The relapse risk is not the same for all patients. For these reasons, the focus of phase III randomized controlled trials has shifted from remission induction trials to remission maintenance trials.

While rituximab may be effective for remission maintenance in GPA and MPA, the best dosing and timing of re-treatment as well as efficacy and safety of long-term B lymphocyte depletion compared with traditional agents remains to be clarified by larger randomized controlled trials. Currently, an international, open-label, randomized trial comparing rituximab versus azathioprine for maintenance of remission following induction with rituximab in relapsing GPA and MPA patients (RITAZAREM) is open for enrollment. Other biologic agents may also be of interest for remission maintenance.

Belimumab (Benlysta) is a human IgG1λ monoclonal antibody that neutralizes soluble B cell activating factor (BAFF), also called B lymphocyte stimulator (BLyS). BAFF is essential for B lymphocyte development and survival as well as immunoglobulin production. Targeting BAFF with belimumab is effective and safe in systemic lupus erythematosus. As B lymphocytes appear crucial for AAV disease activity, the Belimumab in Remission of Vasculitis (BREVAS) trial is designed to evaluate the efficacy and safety of belimumab in combination with azathioprine for remission maintenance in GPA or MPA following standard remission induction.

Abnormalities of T lymphocyte activation seem to hold the key to chronic relapses in AAV. Full activation of T lymphocytes can be prevented by inhibiting the costimulatory signaling required for full T lymphocyte activation. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) down regulates T lymphocyte costimulation under physiologic conditions. Abatacept (CTLA-4-IgG1) is a recombinant fusion protein consisting of the ligand binding portion of CTLA-4 and a modified Fc portion of human IgG1 that acts therapeutically by blocking T lymphocyte costimulation. This agent is approved for the use in rheumatoid arthritis, and a pilot trial with abatacept in nonsevere GPA has yielded promising results. A phase III study of abatacept (ABROGATE) will clarify the potential role of this agent in the treatment of relapsing, nonsevere GPA.

Points to remember

- Treatment for GPA and MPA consists of a multidisciplinary individualized approach based on disease severity and specific organ involvement.

- Rituximab has emerged as an alternative to cyclophosphamide for most patients and is the preferred agent for severe disease relapses.

- The different ANCA types, PR3-ANCAs versus MPO-ANCAs, have a different genetic background and portend a different prognosis and risk of relapse.

- Plasma exchange and biologic agents targeting B lymphocytes and T lymphocyte activation are under investigation for GPA and MPA, and anti-IL-5 therapy targeting eosinophils with mepolizumab is under investigation for EGPA.

Mayo Clinic: Hereditary Hemorrhagic Telangiectasia Center of Excellence

Hereditary hemorrhagic telangiectasia (HHT) is a heterogeneous autosomal dominant vascular disorder characterized by recurrent epistaxis, mucocutaneous telangiectases and visceral involvement represented by arteriovenous malformations. The disease, which affects approximately 1 in 5,000 to 8,000 individuals, is also known as Osler-Weber-Rendu disease.

The main pulmonary complication of HHT is pulmonary arteriovenous malformations (PAVMs). These low-resistance, high-flow abnormal vascular structures most often connect a pulmonary artery to a pulmonary vein, bypassing the normal pulmonary capillary bed and resulting in an intrapulmonary right to left shunt. Physiological consequences of PAVMs depend on the degree of right to left shunt and include hypoxemia, dyspnea and cyanosis. Because the pulmonary capillary bed is an 8 to 10 µm diameter sieve that normally filters blood coming from the pulmonary arteries, PAVMs predispose patients to complications of paradoxical systemic embolization, including stroke and brain abscess. (Other clinical features of HHT, complications and therapeutic options are described in Table 1.)

The mainstay of diagnosis of HHT remains the Curaçao Criteria, an international consensus statement. A definite HHT diagnosis is recognized if at least three of the following conditions are present:
• Spontaneous, recurrent epistaxis
• Multiple telangiectases at characteristic sites (lips, oral cavity, fingers, nose)
• Visceral lesions, including but not limited to gastrointestinal telangiectasia (with or without bleeding) and pulmonary, hepatic, cerebral or spinal AVMs
• Family history of a first-degree relative with HHT. The disease is possible or suspected if two criteria are present and unlikely if one or none of the criteria is present.

Mutations in three genes have been identified in HHT affecting TGF-β superfamily signaling in vascular endothelial cells. The majority of HHT patients will have HHT1 due to mutations in the ENG gene encoding endoglin or HHT2 due to mutations in ACVRL1 encoding activin receptor-like kinase (ALK-1). A small percentage of cases (1 to 2 percent) have mutations in SMAD4 that can cause gastrointestinal epithelial precancerous state of juvenile polyposis, and approximately 25 percent of mutations in SMAD4 appear to

Table 1. Hereditary hemorrhagic telangiectasia and associated clinical features, complications and management

| Clinical feature (estimated prevalence)	Associated complications	Treatment principles
Nasal telangiectasia (90%)	Epistaxis with possible iron deficiency anemia	- Iron supplementation and nasal humidification - Blood transfusion for more-severe cases - Laser therapy - Embolization for severe cases - Septodermoplasty - Oral estrogen-progesterone - Topical bevacizumab (Avastin)
Mucocutaneous telangiectasia (50-80%)	Cosmetic	- Usually not indicated unless cosmetic problems, which could be treated with laser therapy
Gastrointestinal telangiectasia (80%)	Iron deficiency anemia from chronic bleeding, occasionally acute bleeding	- Iron supplementation and blood transfusion for more-severe cases - Oral estrogen-progesterone - Endoscopic therapy with laser - Embolization or surgery for severe cases
Pulmonary AVM (50%)	Hypoxemia from right to left shunt, stroke, TIA, brain abscess, migraines, decompression illness, hemoptysis and hemothorax	- Transcatheter embolization or rarely surgery - Dental hygiene and prophylactic antibiotics - Extra care to avoid air embolism when using intravenous access - Caution against scuba diving
Cerebral AVM (10-15%)	Asymptomatic, headache, epilepsy, ischemia due to vascular steal, hemorrhage	- Evaluation in multidisciplinary experienced center - Microsurgical excision - Stereotactic radiotherapy - Transcatheter embolization
Hepatic AVM (32-78%)	Asymptomatic in most cases, possible increased cardiac output/high output failure due to left to right shunting. Portal hypertension, portosystemic encephalopathy and steal syndrome (intestinal ischemia) have also been described.	- Staged hepatic artery embolization carries high risk of liver necrosis and should be avoided - Possible liver transplantation for severe cases - Avoid performing liver biopsy - Intravenous bevacizumab
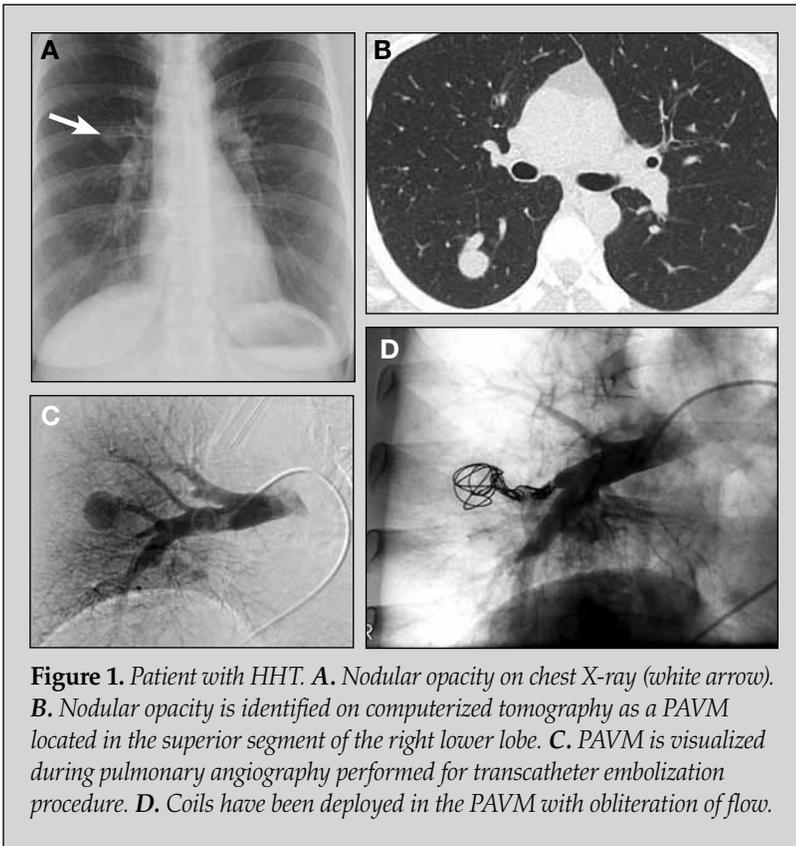
Figure 1. *Patient with HHT.* **A.** *Nodular opacity on chest X-ray (white arrow).* **B.** *Nodular opacity is identified on computerized tomography as a PAVM located in the superior segment of the right lower lobe.* **C.** *PAVM is visualized during pulmonary angiography performed for transcatheter embolization procedure.* **D.** *Coils have been deployed in the PAVM with obliteration of flow.*

Multidisciplinary management

As a Center of Excellence recognized by HHT Foundation International, Inc., Mayo Clinic specializes in multidisciplinary management of HHT. Patients with HHT should undergo a screening process for evaluation of visceral AVMs that might require intervention, such as those in the cerebral, pulmonary or hepatic circulatory beds. At Mayo, an initial screening process for PAVMs includes the use of transthoracic contrast echocardiography (bubble echocardiogram) with agitated saline. This test detects intrapulmonary shunting using noninvasive ultrasound to visualize delayed appearance of microbubbles in the left heart after three to four cardiac cycles.

Percutaneous transcatheter embolization is the most commonly used treatment for PAVM, because it is effective in reducing the risk of paradoxical embolism and other complications. Figure 1 describes a patient with HHT affected by a PAVM who was successfully treated with percutaneous transcatheter embolization of coils.

Recurrent epistaxis, which occurs in 95 percent of patients, is the most common sign of HHT. Laser treatment and septal dermoplasty remain the principal surgical options to control nasal bleeding. In patients with large nasal septal perforations complicating HHT, Mayo otolaryngologists have placed medical-grade Silastic prostheses, sized by a 3-D CT process, that close the perforation as well as protect adjacent septal mucosa against exposure to turbulent air currents (Figure 2). The use of topical vascular endothelial growth factor inhibitors and sclerotherapy show promise as future treatments to control epistaxis in HHT.

arise de novo. At least two further unidentified genes that can cause HHT have been described recently (HHT3 and HHT4).

Age-related penetrance occurs in HHT, so increasing manifestations of the disease develop with aging. In addition, there is profound variation in disease expression between different members of the same HHT family, suggesting that other genetic or environmental factors can modify the phenotype of the disease.
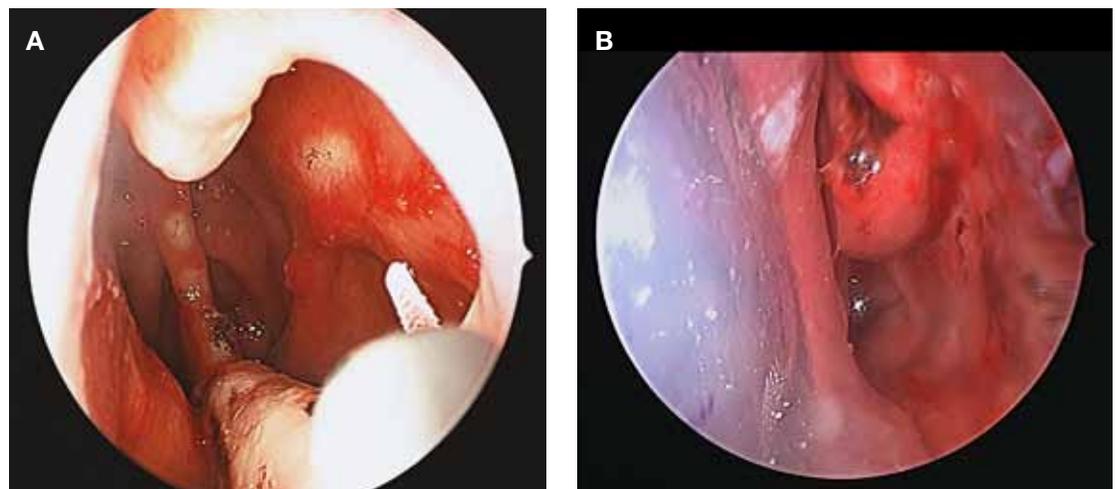

Figure 2. **A.** *Large nasal septal perforation. Telangiectases are visible on lateral wall. Laser treatment is in progress.* **B.** *Medical-grade Silastic prosthesis, sized by 3-D CT process for exact closure of the perforation and optimal comfort, also protects adjacent septal mucosa against exposure to turbulent air currents.*

Chronic Thromboembolic Pulmonary Hypertension — Surgical Therapy and New FDA-Approved Medical Treatment

Chronic thromboembolic pulmonary hypertension (CTEPH), an underappreciated cause of severe pulmonary artery hypertension (PAH), usually presents with progressive exertional dyspnea. Approximately 75 percent of patients with CTEPH have a documented history of acute pulmonary embolism; 50 percent have had a previous deep venous thrombosis. CTEPH is characterized by:

- Increased pulmonary vascular pressures determined by right heart catheterization (mean pulmonary artery pressure greater than 25 mm Hg and pulmonary vascular resistance (PVR) greater than 240 dynes/s/cm-5)
- Imaging evidence of obstruction within the pulmonary arterial bed by vascular webs, intimal irregularities and luminal narrowing, all arising as the thrombus gradually incorporates into the pulmonary endothelium.

These abnormalities may be detected using various imaging modalities, including nuclear ventilation-perfusion scanning, pulmonary angiography or CT angiography. Patients with CTEPH and these abnormalities are uniquely identified as Group 4 in the Dana Point classification of pulmonary hypertension (Table 1, see page 8). Untreated, CTEPH leads to increasing obstruction to pulmonary arterial flow and subsequent right heart failure.

Integrated approach to management

Mayo Clinic provides an integrated approach to the management of patients with pulmonary hypertension. The Pulmonary Hypertension Clinic at Mayo Clinic in Rochester, Minn., is staffed by cardiologists, pulmonologists, interventional radiologists and cardiothoracic surgeons with expertise in the diagnosis and treatment of CTEPH.

Conventional pulmonary angiography best discerns whether the obstruction is proximal enough for pulmonary thromboendarterectomy (PTE), a potentially curative procedure. Surgical selection depends on:

- Severity of pulmonary hemodynamic abnormality (usually PVR between 600 and 1,200 dynes/sec/cm-5)
- Degree of symptoms
- Lesion location
- Comorbidities

The procedure is conducted via median sternotomy and cardiopulmonary bypass hypothermic circulatory arrest and is a

Figure 1. *Preoperative: Coronal CT with chronic embolus, most prominent along the pulmonary artery to the right lower lobe (arrow).*

Figure 2. *Preoperative: 3-D reconstruction shows areas of peripheral pulmonary arterial narrowing.*

Figure 3. *Post-endarterectomy: Removal of chronic embolus from the right pulmonary artery.*

Figure 4. *Post-endarterectomy: Flow is restored to distal pulmonary arterial beds as seen on 3D image.*

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true endarterectomy (as opposed to an embolectomy). Although approximately 40 percent of CTEPH patients will not be operable, in those who undergo PTE, recent series have reported normalization of pulmonary hemodynamics in 25 to 35 percent. Lifelong anticoagulation is advised.

The Food and Drug Administration recently approved riociguat (Adempas), a pulmonary vasodilator that acts through the endogenous nitric-oxide cyclic GMP pathway, as the first medical alternative for CTEPH patients who are not operative candidates or who have persistent PAH following pulmonary endarterectomy. Recent trials of riociguat have shown improvements in exercise capacity and PVR, though improvements in RV function with this treatment haven't yet been demonstrated.

Table 1. Dana Point Classification of Pulmonary Hypertension (abridged)

1. Pulmonary arterial hypertension (PAH)
   - Idiopathic PAH/heritable
   - Drug- and toxin-induced
   - Associated with:
     - Connective tissue diseases
     - HIV infection
     - Portal hypertension
     - Congenital heart diseases
     - Schistosomiasis
     - Chronic hemolytic anemia
1′. Pulmonary venoocclusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH) or both
2. Pulmonary hypertension owing to left heart disease
3. Pulmonary hypertension owing to lung diseases or hypoxia or both
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
   - Includes HHT, sarcoid, lymphangioleiomyomatosis (LAM), histiocystosis-X, myeloprolifer

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MC2985-1213