Pulmonary Vascular Complications of Chronic Liver Disease

A multidisciplinary team of Mayo Clinic specialists cares for patients with chronic liver disease, which occurs most commonly secondary to cirrhosis, including pulmonologists with expertise in the management of lung conditions commonly encountered in this population.

Portopulmonary hypertension
Portopulmonary hypertension (POPH) refers to the presence of pulmonary arterial hypertension (PAH) in patients with portal hypertension with or without cirrhosis. Pulmonary hypertension in patients with liver disease or portal hypertension can be due to multiple mechanisms, including hyperdynamic (high-flow) state, increased pulmonary venous congestion (pulmonary venous hypertension), and vascular constriction or obstruction of the pulmonary arterial bed (Figure 1).

Vascular obstruction to pulmonary arterial flow, reflected by increased pulmonary vascular resistance, is an important parameter that defines POPH. Among patients with portal hypertension, reported incidence rates of POPH range from 2 to 9 percent. The predominant presenting symptom of POPH is dyspnea on exertion or at rest. Transthoracic echocardiography has been the most practical screening method to detect POPH by estimating right ventricular systolic pressure (RSVP). This screening method has been found to have 97 percent sensitivity and 77 percent specificity to detect moderate to severe PAH. Patients with right ventricular systolic pressure > 50 mm Hg or right ventricular dysfunction or both should undergo right heart catheterization in order to obtain a definitive diagnosis. In the presence of portal hypertension, POPH is defined as a mean pulmonary artery pressure ≥ 25 mm Hg associated with pulmonary vascular resistance (PVR) ≥ 240 dynes/sec/cm-5 and pulmonary capillary wedge pressure < 15 mm Hg based upon right heart catheterization.

Long-term survival in POPH is poor. The management of POPH includes an emerging number of different therapeutic agents. The immediate goal of PAH-specific treatment for POPH is to improve pulmonary hemodynamics by reducing the obstruction to pulmonary arterial flow. This can be accomplished by medications that selectively or in combination result in vasodilation, anti-platelet aggregation.
and anti-proliferation. These goals may be attained by targeting pulmonary endothelial prostacyclin synthase deficiency (prostacyclin infusion), blocking circulating endothelin-1 effects (endothelin receptor antagonists) and enhancing local nitric oxide vasodilatation effects (phosphodiesterase inhibitors).

Favorable responses to PAH-specific therapy have been observed, but prospective, randomized trials are lacking. Severe POPH with right ventricular failure despite PAH-specific therapy is associated with adverse outcomes in the setting of liver transplantation (LT) and is therefore considered a contraindication to LT unless PAH-specific therapy is able to lower the pulmonary vascular resistance to safe levels.

Currently, the United Network for Organ Sharing (UNOS) has approved automatic higher priority for LT (exception points via the Model for End Stage Liver Disease, or MELD) if treatment can improve pulmonary hemodynamics (reduce mean pulmonary artery pressure to less than 35 mm Hg). The post-LT course of patients with treated moderate to severe POPH is unpredictable, but selected patients can be weaned from PAH-specific therapy over time, especially when right ventricular size and function can be normalized prior to transplant.

**Hepatopulmonary syndrome**

Hepatopulmonary syndrome (HPS) is a distinct pulmonary complication of end-stage liver disease (ESLD), occurring in between 5 to 32 percent of patients with cirrhosis or portal hypertension or both. HPS is independently associated with worsened survival in patients with ESLD, and this forms the basis for granting MELD exception points in these patients (discussed later).

The pathophysiology of HPS is related to the development of intrapulmonary vascular dilatations (IPVDs), which are abnormally dilated precapillary and capillary vessels between 15 to 100 μm in diameter. These abnormal vascular channels are often present diffusely through the lung and result in intrapulmonary shunting and consequent hypoxemia. In contrast to POPH, intrapulmonary vasoconstriction, in situ thrombosis and plexiform lesions are not part of the

### Differentiating Characteristics of POPH and HPS

<table>
<thead>
<tr>
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<th>POPH</th>
<th>HPS</th>
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<tr>
<td><strong>Pathophysiology</strong></td>
<td>Pulmonary arterial hypertension (PAH)</td>
<td>Intrapulmonary shunting</td>
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<tr>
<td><strong>Pathology</strong></td>
<td>PAH due to plexiform lesions, thrombosis, obliteratorive pulmonary arteriopathy</td>
<td>Intrapulmonary vascular dilatations (IPVDs) causing intrapulmonary shunting and hypoxemia</td>
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<tr>
<td><strong>Severity of hypoxemia</strong></td>
<td>Typically mild</td>
<td>Mild to very severe, depending on degree of shunting</td>
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<tr>
<td><strong>Right ventricle (RV)</strong></td>
<td>Significantly elevated right ventricular systolic pressure (RSVP) with RV dilatation, impaired systolic function and low cardiac output</td>
<td>Normal or mildly elevated RVSP (due to high-flow state) with normal RV size and function</td>
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<tr>
<td><strong>Clinical findings</strong></td>
<td>Loud second heart sound, systolic murmur, RV heave, lower extremity edema</td>
<td>Clubbing, cyanosis, systolic flow murmur, platypnea, orthodeoxia</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Pulmonary hypertension (PH) therapy (for example, ambrisentan, sildenafil, epoprostenol, others)</td>
<td>Supportive care until liver transplantation, which is curative for HPS</td>
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<tr>
<td><strong>Is liver transplantation recommended/feasible?</strong></td>
<td>Only in patients where PH is adequately controlled prior to transplantation</td>
<td>Recommended/feasible in all patients — even in severe hypoxemia</td>
</tr>
<tr>
<td><strong>MELD exception points available?</strong></td>
<td>Yes</td>
<td>Yes</td>
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Table. Differentiating characteristics of portopulmonary hypertension (POPH) and hepatopulmonary syndrome (HPS) are identified.
pathophysiology of HPS (Table). Patients with HPS typically present with dyspnea and hypoxemia that is often worse in the upright position (platypnea and orthodeoxia, respectively). Clubbing may be seen. The degree of hypoxemia can range from mild to very severe, and patients may present with resting cyanosis. Pulmonary function tests typically show a low diffusing capacity. The room air resting PaO2 is used to grade severity of HPS:

- Mild: ≥ 80 mm Hg
- Moderate: ≥ 60 to < 80 mm Hg
- Severe: ≥ 50 to < 60 mm Hg
- Very severe: < 50 mm Hg

Diagnosis of HPS requires the demonstration of intrapulmonary shunting in the setting of hypoxemia. Contrast transthoracic echocardiography (bubble study) is a simple, sensitive and noninvasive test for the diagnosis of HPS and is recommended for both diagnosis and screening. The test involves the injection of agitated saline (microbubble diameter approximately 8 to 15 μm) via a peripheral vein (Figure 2). The appearance of bubbles in the left atrium 3 to 6 cardiac cycles after their initial appearance in the right atrium indicates intrapulmonary shunting. A quantitative measure of shunting can also be obtained by the brain shunt index using 99m-labeled macroaggregated albumin. Neither test distinguishes IPVDs from discrete pleural or pulmonary arteriovenous malformations, which can occasionally be seen in HPS and may be amenable to percutaneous embolization, coil or both. Other causes of hypoxemia such as POPH, COPD, ascites, pulmonary embolism (PE), interstitial lung disease and hepatic hydrothorax need to be excluded during the evaluation process.

Liver transplantation is currently the only proven treatment for HPS and results in resolution of hypoxemia and shunting in almost all patients within the first year of transplant. Overall, post liver transplant survival in patients with HPS is similar to outcomes in ESLD patients without HPS. Even patients with severe hypoxemia have excellent survival and outcomes post-transplant. Therefore, the severity of hypoxemia alone should not be a barrier to liver transplantation in otherwise suitable candidates, according to an article by Vivek N. Iyer, M.D., of Mayo Clinic in Rochester, Minnesota, and others in the June 2013 issue of Hepatology.

Given the significant adverse impact of HPS on survival, patients with a resting room air PaO2 < 60 mm Hg receive additional MELD points to facilitate early transplantation. Thus HPS should be a diagnostic consideration in all ESLD patients with dyspnea or hypoxemia or both.

Mayo Clinic has developed an organization-wide diagnosis and treatment algorithm for POPH and HPS. The Division of Pulmonary and Critical Care Medicine participates in interventional trials, including Sorafenib for Hepatopulmonary Syndrome (SHPS) and Ambrisentan in Patients With Porto-pulmonary Hypertension: A Multicenter Open Label Trial (Portopulm), as well as prospective cohort studies. An ongoing Mayo Clinic prospective cohort study of POPH patients (over 250 patients enrolled to date) provides a foundation to facilitate further clinical research in these disorders.

For more information


Alpha-1-antitrypsin (AAt) is a serine protease inhibitor produced primarily in the liver. This disorder, which affects males and females equally, is inherited in an autosomal codominant fashion and primarily results in liver disease, lung disease or both. The skin is rarely affected, resulting in panniculitis. During the first two to three decades of life, AAt deficiency is primarily a liver disorder that can present as neonatal cholestasis, hepatitis and cirrhosis. Lung disease presents typically after the third decade of life with accelerated panacinar emphysema predominantly affecting the lung bases. Bronchiectasis and asthma also have been linked to AAt deficiency.

AAt deficiency occurs when a single point mutation in the AAt gene results in misfolding and polymerization of the mutated AAt protein within the hepatocytes, according to an article published by Michael J. Krowka, M.D., and others in the Journal of Hepatology in 2013. About 80 to 90 percent of this misfolded-polymerized AAt protein is retained within the rough endoplasmic reticulum of the hepatocyte, resulting in two problems:

- Cellular injury (hepatitis) and eventual cirrhosis due to the toxic effects of the retained AAt protein
- Significantly reduced AAt serum levels due to this hepatocyte retention and lack of secretion

This circulating serum AAt deficiency results in unopposed neutrophil elastase activity, progressive lung destruction and emphysema (Figures 1 and 2). Such lung destruction is dramatically accelerated in individuals with AAt deficiency who are smokers. Normal AAt levels can be achieved by exogenous AAt supplementation and can maintain the delicate balance between protease (neutrophil elastase) and anti-protease (AAt) activity in the lung.

**Evaluation**

Mayo Clinic is recognized as a Clinical Resource Center by the Alpha-1 Foundation (www.alpha1portal.org/). Patients suspected of having AAt deficiency should be referred to such centers for evaluation and management recommendations. Such patients would include those individuals with liver dysfunction and early-stage chronic obstructive lung disease or asthma that does not respond to treatment. Family members also may request consultation to check on their AAt status and to assess end-organ disease.

The laboratory evaluation includes serum alpha-1-antitrypsin level measurement (normal 100 to 190 mg/dl). It is thought that levels < 57 mg/dl predispose to accelerated lung damage. Routine Mayo testing includes state-of-the-art AAt proteotype assessment by liquid chromatography-tandem mass spectrometry to discern normal protein variants (M variant) from specific AAt disease variants such as Z and S variants. Same day consultation, state-of-the-art pulmonary function testing and imaging studies (chest CT scan with 3-D reconstruction), liver ultrasound, and a noninvasive MRI-based technique to detect liver fibrosis (MR elastography) are available to guide clinical management decisions and recommendations.

**AAt-related treatment options**

The lung manifestations may be slowed by correcting the serum deficiency with intravenous replacement of the AAt protein from human pooled plasma (augmentation therapy). Currently, there are four commercial Food and Drug Administration-approved products available. The infusions are accomplished weekly or biweekly and conducted either at infusion centers or at the patient’s home. Specific guidelines exist as to which patients should receive and will benefit most from these expensive therapies (over $75,000 a year).

Severe AAt deficiency may lead to advanced emphysema causing hyperinflation and severe expiratory flow obstruction with or without

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**Figure 1.** Bilateral lower lobe bronchiectasis associated with ZZ genotype AAt deficiency in a patient with minimal emphysema
airway hyper-reactivity. In selected individuals, bullectomy or lung volume reduction surgery may be recommended. For others, bronchoscopically placed one-way endobronchial valves are designed to decrease air trapping and emphysema. Some patients may be candidates for lung transplantation, which can more than double survival rates in those with the ZZ genotype, as published by Hanan A. Tanash, M.D., and others in The Journal of Heart and Lung Transplantation in 2011.

The liver manifestations of AAt accumulation (and abnormal degradation) in hepatocytes may lead to cirrhosis and the need for liver transplantation. These individuals may or may not have coexisting lung manifestations of AAt deficiency. Mayo investigators recently published the largest series to date describing outcomes following liver transplantation in 73 patients with severe AAt deficiency and cirrhosis. The one-, three- and 10-year post-transplant survivals were 91 percent, 86 percent and 79 percent, respectively. Of interest, a subgroup of patients continued to experience accelerated lung function decline even after liver transplantation. Prospective studies are being planned to better understand the impact of liver transplantation (with resulting normalization of serum AAt levels) and subsequent lung function outcomes, according to an article published by Elizabeth J. Carey, M.D., of Mayo Clinic’s campus in Arizona, and others in Liver Transplantation in 2013.

For more information


Kamada Ltd. Phase II, Safety and ELF Study of “Kamada-API for Inhalation.” Clinical Trials.gov.

Ongoing research
Basic science and clinical research in AAt deficiency is ongoing and described on the Alpha-1 Foundation website at www.alpha1portal.org. In addition, The Alpha-1 Project (TAP), which is a subsidiary owned by the foundation, is designed to fund and facilitate the commercialization of lung and liver-related therapeutic discoveries. Mayo Clinic is active in screening studies and participating in multicenter treatment trials conducted for patients with AAt-related lung disease, liver disease or both. Mayo is currently facilitating participation in a multicenter inhaled alpha-1 protein research study.

Regarding AAt-related liver disease, Mayo is participating in a multicenter trial using carbachol as a medication to facilitate unfolding of the accumulated AAt protein within the hepatocytes, thus increasing the serum levels.
Cystic fibrosis (CF) is a multisystem disorder that remains the most common genetic disease of Caucasians. The clinical manifestations leading to chronic lung disease and malnutrition are a direct result of mutation of the CF transmembrane conductance regulator (CFTR) protein which is expressed predominantly in epithelial cells. Normal CFTR regulates and functions as the chloride channel as well as inhibiting activation of the epithelial sodium channel. These effects result in desiccated obstructing mucus due to enhanced water resorption in epithelial-lined ducts in all tissues affected in CF.

Fortunately, expected survival has increased from about 18 years in 1976 to 38-plus years in 2012, thanks to adherence to recommended therapeutic strategies such as aggressive management of chronic airway infection and nutritional deficiencies.

The Cystic Fibrosis Foundation guidelines have provided the cornerstone for the care principles employed to treat these patients. Mayo Clinic, designated as a CF care center by the Cystic Fibrosis Foundation, has a multidisciplinary care team committed to the overall health and care of these individuals.

Diagnosis

The diagnosis of CF is based on typical phenotypic findings and family history, accompanied by laboratory confirmation of CFTR dysfunction or identification of two CFTR mutations. Presenting signs and symptoms include the following (roughly in order of reason for diagnostic testing):

- Acute or chronic respiratory signs and symptoms
- Failure to thrive or malnutrition
- Steatorrhea, abnormal stools or malabsorption
- Meconium ileus or intestinal obstruction
- Electrolyte imbalance
- Rectal prolapse
- Nasal polyps or sinus disease
- Liver problems
- Edema

Signs and symptoms consistent with a diagnosis of CF differ by age; for example, male infertility presents in adulthood. Family history accounts for about 15 percent of the reasons for diagnostic testing.

Laboratory confirmation of CFTR dysfunction includes sweat testing, genetic mutation analysis and nasal potential difference. The sweat test remains the most available and clinically useful way to diagnose CF when done according to strict guidelines with pilocarpine iontophoresis and a quantitative determination of chloride concentration. A sweat chloride level of 60 mmol/L (normal is < 30 mmol/L) is considered a diagnostic criterion for CF. Several methods of CFTR detection are commercially available that can include specific mutations or full sequencing, which runs the risk of revealing novel mutations and polymorphisms of unknown importance. There are approximately 2,000 known mutations in CFTR. Measurement of transepithelial nasal potential difference is generally reserved for the more-difficult-to-diagnose patient. Patients with CF have a characteristic bioelectric abnormality in nasal epithelium in vivo.

Treatment

Since pulmonary manifestations of CF often relate to chronic airways infection, antibiotics are a mainstay of treatment for acute exacerbations of pulmonary CF. Specific antibiotic therapy is chosen based on organism identification and the antibiotic susceptibility profile of the last available sputum culture. Outpatient treatment, when possible, is preferred, but a lack of response to oral antibiotic therapy often necessitates hospital admission for provision of IV antibiotics and more intense adjunctive therapies.

Although dual IV antibiotics are often used in the treatment of an acute exacerbation presumed to be due to *Pseudomonas aeruginosa*, the question of monotherapy versus combination therapy is a relevant one. Use of a single antibiotic may result in reduced toxicity as well as cost in a patient who will be treated with antibiotics multiple times throughout life. On the other hand, single antibiotics will be more likely to select for resistant pathogens. Currently, use of a single antibiotic is considered an appropriate choice in patients with a milder stage of disease, but in more advanced stages of disease, combination therapy is favored. A recent advance is the use of once-daily dosing of aminoglycosides (as opposed to three times daily) to reduce the risk of nephrotoxicity.

Aerosolized antibiotics are often used on a regular basis for suppression of infection, particularly with pseudomonas. The most commonly used antibiotic is tobramycin, though more recently available inhaled drugs are likely to increase in use, including amikacin, aztreonam and, for staphylococcal infections,
vancomycin. Safety and efficacy have not been demonstrated in patients with a forced expiratory volume (FEV) less than 25 percent or more than 75 percent predicted. The Cystic Fibrosis Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and reduce the rate of exacerbations, but it has not been shown to be distinctly beneficial during acute exacerbations.

Airway clearance techniques and devices are mainstays for CF lung disease management. Hypertonic saline (3 percent or 7 percent) is an inexpensive and useful therapy to increase hydration of airway surface liquid, thereby improving mucociliary clearance. The Cystic Fibrosis Foundation recommends for patients 6 years of age and older the chronic use of inhaled hypertonic saline to improve lung function and reduce exacerbations. Dornase alpha (DNase) is an endonuclease that cleaves extracellular DNA and decreases the adhesiveness and viscoelasticity of CF mucus laden with DNA from white blood cells. Daily administration of dornase alpha is indicated to improve pulmonary function. In patients with a forced vital capacity (FVC) more than 40 percent of predicted, daily administration of dornase alpha has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

Recent drug development has resulted in a paradigm shift in the treatment of CF. In an effort to modulate CFTR function rather than targeting downstream effect, two classes of medications are available or in development:

• Potentiators: Drugs that open CFTR channels that already exist at the cell surface.
• Correctors: Drugs that seek to bring CFTR to the cell surface where none previously existed.

Ivacaftor was approved by the Food and Drug Administration in 2012 (for ages 6 years and older) for the 4.4 percent of CF patients who have a specific class III G551D mutation. The drug binds to the nucleotide binding domain of CFTR and increases channel open probability (a potentiator). There is a near immediate benefit in FEV1, which increases approximately 8 percent within two weeks. In adults and children, these increases are sustained at 48 weeks (10.5 and 10 percent, respectively). The FDA recently granted approval in patients with an additional eight mutations. Importantly, ivacaftor also improves function of other organ systems affected by CF.

The most common CFTR mutation is deltaF508, which prevents translocation of CFTR to the cell surface, and for which ivacaftor alone is ineffective. Yet to be approved for use, lumacaftor is a new corrector that protects the abnormal deltaF508 CFTR from programmed degradation and allows it to move to the airway surface, resulting in about 25 percent more chloride transport. Combination therapy with agents such as lumacaftor is likely to become preferred therapy.

Short courses of systemic corticosteroids also have been utilized in the treatment of acute exacerbations, in a manner similar to the treatment of those patients with exacerbations of chronic obstructive pulmonary disease. Supplemental oxygen is often used in patients who are hypoxemic.

Mayo Clinic Cystic Fibrosis Center
The Mayo Clinic Cystic Fibrosis Center specializes in the care of pediatric and adult patients. The dedicated staff includes physicians, nurses, dietitians, genetic counselors, physical therapists, social workers and respiratory therapists. All patients are discussed at weekly joint pediatric and adult care team meetings, which provide a long-term perspective on the unique needs of each patient. Patient independence is fostered during early adolescence, a particularly difficult time for many patients with CF. The CF center staff works closely with the Transplant Center, and together, they have performed successful transplants in many patients with advanced CF lung disease.

Areas of active CF-related research at Mayo Clinic in Rochester, Minnesota, include:

• Exploration of the role of ATP in skeletal muscle vasodilation during exercise (Michael J. Joyner, M.D.)
• The role of Staphylococcus aureus toxin as a toxic agent of airway damage in individuals with cystic fibrosis (James R. Phillips, M.D.)
• Slc26 anion transporters interaction with CFTR in transepithelial chloride absorption and bicarbonate secretion (Michael F. Romero, Ph.D.)
Education Opportunities

For more information or to register for courses, visit www.mayo.edu/cme/pulmonary-medicine, call 800-323-2688 (toll-free) or email cme@mayo.edu.

TransFuse 2015: Transformative Fusion of Innovative Blood Management
Feb. 11-13, 2015, in Phoenix

2015 A Multidisciplinary Update in Pulmonary and Critical Care Medicine
April 23-26, 2015, in Scottsdale, Ariz.

Clinical Trials

Several National Institutes of Health (NIH)-funded trials are currently underway in the Division of Pulmonary and Critical Care Medicine at Mayo Clinic’s campus in Rochester, Minnesota.

NIH-supported multicenter trials, with Ulrich Specks, M.D., as the Mayo Clinic principal investigator, that are actively recruiting patients with ANCA associated vasculitis include:

- Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis (PEXIVAS), NCT00987389
- Rituximab Vasculitis Maintenance Study (RITAZAREM), NCT01697267
- A Study to Investigate Mepolizumab in the Treatment of Eosinophilic Granulomatosis With Polyangiitis, NCT02020889

NIH-funded trials exploring rehabilitative treatment for patients with chronic obstructive pulmonary disease and led by Roberto P. Benzo, M.D., principal investigator, include:

- Lung Rehabilitation in Treating Patients With Chronic Obstructive Pulmonary Disease Who Are Undergoing Surgery for Lung Cancer, NCT00363428
- Promoting Physical Activity in Chronic Obstructive Pulmonary Disease (COPD) Through New Technology and Health Coaching, NCT01217710
- Multicomponent Intervention to Decrease Chronic Obstructive Pulmonary Disease (COPD)-Related Hospitalizations, NCT01058486

For more information
See all Pulmonary and Critical Care Medicine Clinical Trials at Mayo Clinic at www.MayoClinic.org/departments -centers/pulmonary-critical-care-medicine/clinical-trials or access the studies at ClinicalTrials.gov.