

# Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease

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In Canada, primary care physicians provide care for 80%–90% of patients with asthma and chronic obstructive pulmonary disease (COPD).<sup>1,2</sup> Among these patients is a largely undetected and vulnerable minority who are genetically predisposed to rapidly and prematurely lose lung function because of the near absence of a protective glycoprotein, alpha-1 antitrypsin (also known as alpha<sub>1</sub>,  $\alpha$ -1 and  $\alpha_1$  antitrypsin). In North America, the prevalence of alpha-1 antitrypsin deficiency is about 1 per 3000 to 5000 people,<sup>3,4</sup> similar to that of cystic fibrosis.<sup>5</sup> Up to 5% of people with COPD are thought to have alpha-1 antitrypsin deficiency, yet only 4%–5% of those with a deficiency have been identified.<sup>6,7</sup> Even when the deficiency is diagnosed, there has typically been a delay of 5 to 10 years.<sup>8</sup>

In this review, we highlight the pathogenesis, clinical features, diagnosis and treatment of alpha-1 antitrypsin deficiency. The evidence used in this review is derived from a search of the available research literature and current guidelines (Box 1). Some management suggestions in this review are extrapolated from the literature on COPD, because the treatments have not been specifically studied for patients with alpha-1 antitrypsin deficiency.

## How does alpha-1 antitrypsin deficiency cause lung and liver disease?

Alpha-1 antitrypsin is a protease inhibitor encoded by the *SERPINA1* gene on chromosome 14.<sup>9</sup> This glycoprotein is synthesized mainly in the liver and is secreted into the blood, with serum concentrations of 1.5–3.0 g/L (20–52  $\mu$ mol/L) in healthy adults.<sup>15</sup> It diffuses into the lung interstitium and alveolar lining fluid, where it inactivates neutrophil elastase, thereby protecting the lung tissue from protease-mediated damage.<sup>15</sup>

Alpha-1 antitrypsin deficiency is inherited in an autosomal codominant fashion. Over 100 genetic variants of the *SERPINA1* gene have

been described, but not all are associated with disease.<sup>9</sup> The alphabetic designation of these variants is based on their speed of migration on gel electrophoresis. The most common variant is the M (medium mobility) allele, and the 2 most frequent deficiency alleles are Pi S and Pi Z (the latter having the slowest rate of migration). Several mutations have been described that produce no measurable serum protein; these are referred to as “null” alleles.<sup>9</sup>

The most common genotype is MM, which produces normal serum levels of alpha-1 antitrypsin. Most people with severe deficiency are homozygous for the Z allele (ZZ). The Z protein misfolds and polymerizes during its production in the endoplasmic reticulum of hepatocytes; these abnormal polymers are trapped in the liver, greatly reducing the serum levels of alpha-1 antitrypsin. The liver disease seen in patients with alpha-1 antitrypsin deficiency is caused by the accumulation of abnormal alpha-1 antitrypsin protein in hepatocytes and the consequent cellular responses, including autophagy, the endoplasmic reticulum stress response and apoptosis.<sup>16</sup> Figure 1 shows the most common genotypes and the respective serum levels of alpha-1 antitrypsin.<sup>9,17</sup>

Reduced circulating levels of alpha-1 antitrypsin lead to increased neutrophil elastase activity in the lungs; this imbalance of protease and antiprotease results in the lung disease associated with this condition. The risk of lung disease

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### KEY POINTS

- All adults with chronic obstructive pulmonary disease, asthma with incompletely reversible airway obstruction or necrotizing panniculitis, as well as people of any age with unexplained liver disease, should be screened for alpha-1 antitrypsin deficiency.
- Screening involves testing the serum alpha-1 antitrypsin level; the diagnosis must be confirmed by genotyping or phenotyping.
- People with diagnosed alpha-1 antitrypsin deficiency should undergo full pulmonary function testing, chest radiography and liver enzyme and function testing.
- Treatment of alpha-1 antitrypsin lung disease includes general treatment for chronic obstructive pulmonary disease and consideration of augmentation therapy.

seems to be most clinically important when serum levels of alpha-1 antitrypsin are less than the “protective threshold” of 11  $\mu\text{mol/L}$  (50  $\text{mg/dL}$ ).<sup>18</sup> However, even in those with severe deficiency, the development of lung disease is variable; environmental exposures and other unidentified genetic modifiers are likely also involved. Cigarette smoking is the best described risk factor, and smokers with alpha-1 antitrypsin deficiency tend to develop emphysema earlier than nonsmokers with the deficiency.<sup>19</sup> Other risk factors, including occupational exposure,<sup>20</sup> asthma<sup>21</sup> and male sex,<sup>22</sup> have been described.

## What is the usual presentation?

Alpha-1 antitrypsin deficiency is most common in white people, and it most frequently affects the lungs and liver. In the lungs, the most common manifestation is early-onset (patients in their 30s and 40s) panacinar emphysema most pronounced in the lung bases. However, diffuse or upper lobe emphysema can occur,<sup>9</sup> as can bronchiectasis.<sup>23</sup> The most frequently described symptoms include dyspnea, wheezing and cough.<sup>24</sup> Pulmonary function testing shows findings consistent with COPD; however, bronchodilator responsiveness may be seen and may be labelled as asthma.<sup>21</sup>

Liver disease caused by the ZZ genotype manifests in various ways. Affected infants may present in the newborn period with cholestatic jaundice, sometimes with acholic stools (pale or clay-coloured) and hepatomegaly. Conjugated bilirubin, transaminases and gamma-glutamyl transferase levels in blood are elevated.<sup>25</sup> Liver disease in older children and adults may present with an incidental finding of elevated transaminases or with signs of established cirrhosis,

including variceal hemorrhage or ascites.<sup>26</sup> Alpha-1 antitrypsin deficiency also predisposes patients to hepatocellular carcinoma.<sup>26</sup>

Although the homozygous ZZ genotype is necessary for liver disease to develop, a heterozygous Z mutation may act as a genetic modifier for other diseases by conferring a greater risk of more severe liver disease, such as in hepatitis C infection and cystic fibrosis liver disease.<sup>27,28</sup>

## Who should be screened?

The American Thoracic Society and European Respiratory Society’s recommendations for screening are presented in Box 2.<sup>9</sup> Some COPD guidelines recommend more selected screening, targeting testing to patients who develop COPD at a young age or who have a family history.<sup>11,13</sup> The most recent statement by the Canadian Thoracic Society offered recommendations similar to those in the joint statement by the European Respiratory Society and the American Thoracic Society, but the former group capped the age of screening in patients with COPD at 65 years, based on a review of available screening studies (weak recommendation, lower quality evidence).<sup>10,29</sup> All patients should be informed of the risks of testing for alpha-1 antitrypsin deficiency, including the risk of psychological burden and genetic discrimination.

## How is alpha-1 antitrypsin deficiency diagnosed?

The diagnosis of alpha-1 antitrypsin deficiency involves quantifying the serum protein level. If the level is low, confirmatory testing with alpha-1 antitrypsin genotyping or protein phenotyping should be performed. The initial screening test, a measurement of alpha-1 antitrypsin serum levels, is relatively inexpensive and can be done at most laboratories under provincial laboratory fee schedules. Because there are several assays used to measure protein levels, results may be reported in a variety of units (typically  $\mu\text{mol/L}$  or  $\text{mg/dL}$ ). The screening test may overestimate baseline serum alpha-1 antitrypsin levels (because the glycoprotein is an acute phase reactant) and may fail to detect people who are heterozygous for the Z allele, although it should not miss patients with a severe deficiency. If a patient’s alpha-1 antitrypsin level is below the lower limit of normal, confirmatory testing should be done. Most slightly reduced levels will belong to patients who are heterozygous carriers, who are thought to have only a minimally increased risk of lung or liver disease (Figure 1). Carriers are more com-

### Box 1: Evidence used in this review

We identified studies by searching Medline (2003 to October 2011) with the search term “alpha-1 antitrypsin deficiency”; the search was limited to English-language original research studies involving humans. This search yielded 411 articles; we screened the titles and abstracts. Two of the authors (S.B. and K.C.) independently performed full-text reviews of the clinical features, evaluation or therapy of lung disease related to alpha-1 antitrypsin deficiency ( $n = 37$ ). We also reviewed published guidelines on alpha-1 antitrypsin deficiency, including the American Thoracic Society/European Respiratory Society’s 2003 guidelines<sup>9</sup> and the Canadian Thoracic Society’s 2012 guidelines.<sup>10</sup> We reviewed published guidelines on chronic obstructive pulmonary disease, including the American Thoracic Society’s 2004 guidelines,<sup>11</sup> the Canadian Thoracic Society’s 2008 guidelines<sup>12</sup> and the 2011 update of the Global Initiative for Chronic Obstructive Lung Disease guidelines.<sup>13</sup> We searched the bibliographies of each set of guidelines for relevant articles.

We assessed the quality of randomized trials using the Jadad scale.<sup>14</sup> Some management suggestions presented in this article are extrapolated from studies of typical chronic obstructive pulmonary disease and have not been specifically studied in patients with alpha-1 antitrypsin deficiency.

mon than people with “full” or clinically important deficiency and will account for most of the abnormal alpha-1 antitrypsin serum levels reported to physicians. Most results just below the lower limit of normal (i.e., levels between 50 and 89 mg/dL) will be from carriers at low risk of lung or liver disease.

Genotyping is typically performed on blood samples and can detect the most common deficiency alleles (Z and S). However, genotyping will miss many of the more rare alleles; if genotyping is inconclusive, patients should undergo protein phenotyping. Phenotyping involves identifying the alpha-1 antitrypsin variants based on isoelectric point, by means of thin-layer isoelectric focusing, which is usually performed using plasma or serum samples. Methods of obtaining genotyping and phenotyping in Canada are provided in Box 3.

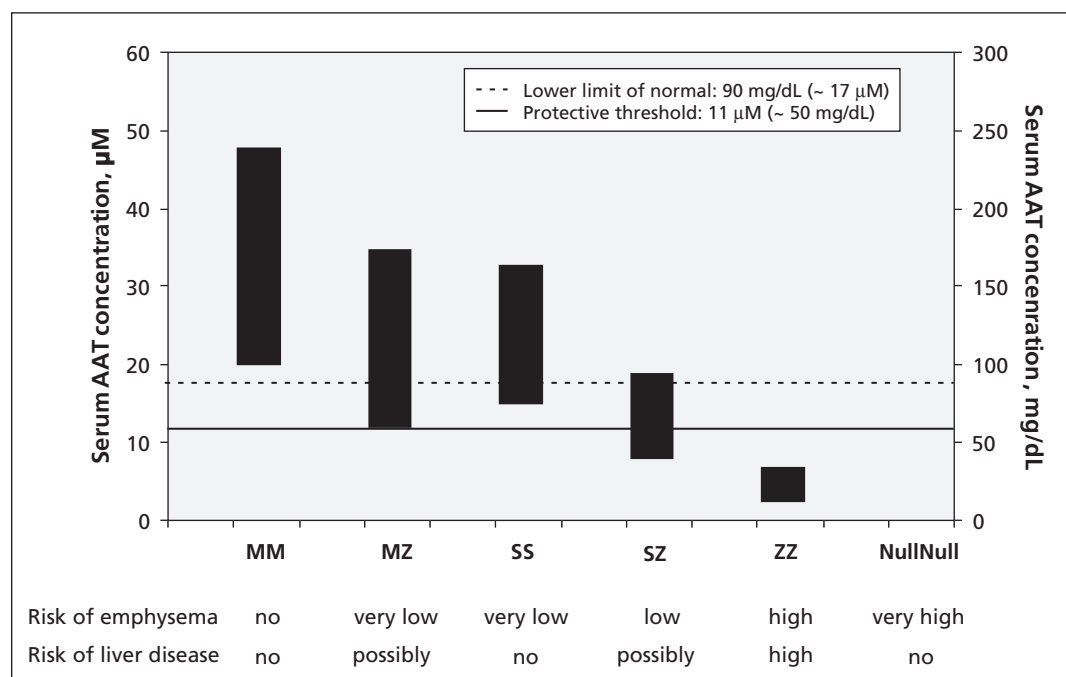
A similar diagnostic pathway is used to look for alpha-1 antitrypsin deficiency as a cause of liver disease in patients who present with symptoms or signs of liver disease or with incidental findings of liver abnormalities on blood work or imaging. A liver biopsy is not essential to confirm the diagnosis but can be used in some clinical situations in which it is important to achieve a rapid diagnosis, including the exclusion of other liver diseases and to stage the severity of liver fibrosis. The characteristic histopathology

of liver disease from alpha-1 antitrypsin deficiency is the presence of intrahepatocellular globules that stain positively with Periodic Acid Schiff stain and remain positive following treatment of the pathology slide with diastase (PAS-D positive staining). Biopsy findings may vary considerably among affected individuals, such that differentiating alpha-1 antitrypsin deficiency from other causes of liver disease may be very difficult based on liver biopsy alone.

### After diagnosis, which tests and monitoring should be performed?

Patients being evaluated for alpha-1 antitrypsin deficiency should be assessed for the presence and extent of lung and liver damage, which will help guide treatment. Typical investigations include the measurement of liver enzymes and liver function tests, as well as full pulmonary function testing (including spirometry, measurement of static lung volumes and diffusing capacity) and chest radiography.

After the diagnosis of alpha-1 antitrypsin deficiency is made, patients should be referred to lung or liver specialists who have experience managing this disease. All patients, including those without lung disease, should be counselled about smoking cessation, because smoking is associated with



**Figure 1:** Typical ranges of serum alpha-1 antitrypsin levels for different genotypes (normal, heterozygous carriers of alpha-1 antitrypsin deficiency and homozygous deficiency). The left axis is expressed in  $\mu\text{M}$  because this unit is common in the literature. The right axis shows an approximate conversion into mg/dL because this unit is commonly reported by clinical laboratories and by different measurement technology (nephelometry or radial immunodiffusion). Adapted from Brantly and colleagues<sup>17</sup> and the American Thoracic Society/European Respiratory Society statement.<sup>9</sup> Note: AAT = alpha-1 antitrypsin.

early development of emphysema in patients with alpha-1 antitrypsin deficiency.<sup>18</sup> Additionally, patients should be counselled about testing for their family members. The diagnosis of alpha-1 antitrypsin deficiency in asymptomatic family members may be beneficial for prompting lifestyle modifications such as smoking cessation, but the adverse effects of testing (e.g., issues of insurability) should also be considered. Testing is recommended for siblings of patients with alpha-1 antitrypsin deficiency, because siblings have a 25% probability of having severe deficiency; the risk among children of patients with alpha-1 deficiency is about 1%.<sup>9</sup>

Guidelines recommend that patients with alpha-1 antitrypsin deficiency undergo annual spirometry, either to monitor for the development of COPD or to follow its progression.<sup>9</sup> Patients with alpha-1 antitrypsin deficiency should also have their liver enzymes and function checked regularly; we recommend yearly testing. Given the gaps in our knowledge of this condition, patients should be encouraged to join the Canadian Alpha<sub>1</sub> Antitrypsin Deficiency Registry ([www.alpha1canadianregistry.com](http://www.alpha1canadianregistry.com)), and useful support materials are available from Alpha<sub>1</sub> Canada ([www.alpha1canada.ca](http://www.alpha1canada.ca)).

The natural history and prognosis of alpha-1 antitrypsin deficiency is variable. Most people with this deficiency have a decreased life expectancy relative to those in the general population,<sup>30,31</sup> with the exception of people who have

never smoked but were identified through family or population screening.<sup>32</sup> A low forced expiratory volume in 1 second (FEV<sub>1</sub>) appears to be the major risk factor for death.<sup>30,33</sup> Emphysema is the most common cause of death (58%–72%), followed by cirrhosis (10%–12%).<sup>30,31</sup>

## What options are available to treat lung disease?

The management of lung disease secondary to alpha-1 antitrypsin deficiency includes the usual approaches used in more typical COPD without alpha-1 deficiency, as well as therapy specific to this deficiency. Key recommendations are summarized in Box 4. Influenza and pneumococcal vaccines are recommended.<sup>9</sup> Medical therapy, including the use of inhaled bronchodilators, inhaled corticosteroids and supplemental oxygen, should be provided according to published COPD guidelines,<sup>11</sup> although these therapies have not been independently studied in patients with alpha-1 antitrypsin deficiency.<sup>9</sup> Patients with exercise limitations may benefit from pulmonary rehabilitation.<sup>9</sup>

The usual treatment of acute exacerbations of COPD, including systemic corticosteroids and ventilatory support when necessary, should be provided for exacerbations.<sup>9</sup> Early antibiotic therapy is recommended for all purulent exacerbations,<sup>9</sup> with the hopes of decreasing neutrophil elastase release and preventing further lung destruction.

Surgery may also be an option for patients with severe COPD. Lung transplantation should be considered for patients with alpha-1 antitrypsin deficiency, severe airflow obstruction and severe functional impairment, because it may result in substantial improvements in quality of life.<sup>34</sup> Although the median survival after lung transplantation is currently 5.3 years, patients with alpha-1 antitrypsin deficiency may have better survival than patients with COPD.<sup>37</sup> Conversely, lung volume reduction surgery, which may be beneficial for COPD patients without alpha-1 deficiency, has shown less benefit in patients with alpha-1 antitrypsin deficiency.<sup>36,38</sup> The National Emphysema Treatment Trial<sup>35</sup> has shown that lung volume reduction surgery improves exercise capacity and FEV<sub>1</sub> in patients with COPD involving heterogeneous upper-lobe predominant emphysema. In patients with alpha-1 antitrypsin deficiency with a more homogenous pattern of emphysema, improvement is much less likely. In the National Emphysema Treatment Trial, patients with alpha-1 antitrypsin deficiency had smaller and shorter-lived improvements in exercise capacity and FEV<sub>1</sub> with lung

### Box 2: Who should be tested for alpha-1 antitrypsin deficiency<sup>9</sup>

- All symptomatic adults with chronic obstructive pulmonary disease or emphysema
- Adults with asthma whose airflow obstruction is incompletely reversed after treatment
- Asymptomatic people with persistent obstruction on pulmonary function tests and identifiable risk factors (e.g., cigarette smoking, occupational exposure)
- Individuals with unexplained liver disease
- Adults with necrotizing panniculitis (inflammation of the subcutaneous fatty and fibrous tissue layer)
- Siblings of people with alpha-1 antitrypsin deficiency

### Box 3: How to obtain confirmatory testing in Canada

- Sponsored genotyping testing kits can be obtained from 877-325-7421; patients submit their own dried blood spot samples to a testing laboratory in the United States with reports sent to their physicians.
- In Montréal, testing is available through the Royal Victoria Hospital (Dr. Brian Gilfix, MUHC-Royal Victoria Hospital; [brian.gilfix@mcgill.ca](mailto:brian.gilfix@mcgill.ca)).
- In Vancouver, testing is available through St. Paul's Hospital (Dr. Andre Mattman, St. Paul's Hospital; [AMattman@providencehealth.bc.ca](mailto:AMattman@providencehealth.bc.ca)).
- For more information, contact the Canadian Registry for Alpha<sub>1</sub> Antitrypsin Deficiency ([www.alpha1canadianregistry.com](http://www.alpha1canadianregistry.com) or 800-352-8186).

volume reduction surgery when compared with individuals with normal alpha-1 antitrypsin levels; others have had similar results.<sup>36</sup>

## What is the role of augmentation therapy?

Specific therapy for alpha-1 antitrypsin deficiency is currently available in the form of intravenous augmentation therapy with purified human alpha-1 antitrypsin. The goal of this therapy is to elevate the level of alpha-1 antitrypsin in the plasma and lung interstitium to prevent further lung destruction and stabilize the disease. This medication is given as a weekly intravenous infusion for the duration of the patient's life. The American Food and Drug Administration, Health Canada and regulatory authorities in several European nations have approved this drug.

Because emphysema secondary to alpha-1 antitrypsin deficiency is a relatively rare disease, long-term trials showing the effect of alpha-1 antitrypsin on lung function in large numbers of patients have not been possible. In North America, augmentation therapy has been licensed based on pharmacokinetic, safety and in vitro efficacy studies. Subsequent approval in Europe was also based on nonrandomized observational data gathered over the initial 25 years of use.

Intravenous augmentation therapy has been shown by 3 observational studies<sup>39–41</sup> to significantly slow the decline of FEV<sub>1</sub> in patients with baseline moderate-to-severe obstruction (variably defined). One of these studies also showed that those with mild baseline obstruction but with rapidly declining lung function may also derive benefit.<sup>41</sup> A mortality benefit was shown in 1 of these reports,<sup>40</sup> but not studied in the other 2.

Two high-quality randomized controlled trials have studied augmentation therapy in a pilot fashion in small numbers of people to assess feasible trial outcomes.<sup>42,43</sup> The first did not find a significant difference between augmentation therapy and placebo in terms of FEV<sub>1</sub> decline, but it suggested a trend toward preservation of lung density as measured by computed tomography densitometry.<sup>42</sup> The second study also used computed tomography densitometry as an outcome and found a similar trend toward preservation of lung tissue.<sup>43</sup> The pooled analysis of these 2 trials showed preservation of lung density with augmentation therapy compared with placebo, such that the loss of lung density was 71% greater per year in patients who received placebo compared with those who received augmentation

therapy (treatment difference 2.297 g/L, 95% confidence interval [CI] 0.669–3.926; *p* = 0.006).<sup>44</sup> However, exacerbations and quality of life were similar in the 2 groups.

This lack of measured difference in clinical outcomes reflects the rarity of the disorder and the necessarily small sample size of the randomized trials. Studies of tobacco-related COPD showing therapeutic effects on exacerbation and quality of life outcomes typically include several hundred patients, while the sample size of alpha-1 antitrypsin deficiency emphysema trials is typically less than 100 patients, a number insufficiently robust to assess such outcomes.

A meta-analysis, which included both observational and randomized trials, showed a significantly slower decline in FEV<sub>1</sub> with augmentation therapy.<sup>45</sup> This effect reflected predominantly the results in a subset of patients with a baseline FEV<sub>1</sub> that was 30%–65% of predicted. In this subset, augmentation was associated with a 26% reduction in the rate of FEV<sub>1</sub> decline (absolute difference 17.9 mL/yr, 95% CI 9.6–26.1). The American Thoracic Society recommends augmentation therapy for patients with severe alpha-1 antitrypsin deficiency and clinically important obstructive lung disease;<sup>46</sup> the Canadian Thoracic Society also endorses its use for patients with an FEV<sub>1</sub> of 25%–80% of predicted and who have received optimal medical therapy.<sup>10</sup>

Similar to other blood products for rare diseases, alpha-1 antitrypsin augmentation therapy is expensive, costing \$60 000–\$100 000 per year. In Canada, reimbursement is available from some private insurance plans and through the

### Box 4: Recommendations for the management of lung disease related to alpha-1 antitrypsin deficiency

- All patients should be counselled and receive assistance in smoking cessation.<sup>9</sup>
- Patients should be advised to avoid detrimental respiratory exposures, such as second-hand tobacco smoke and occupational inhalational exposures (e.g., dusts and fumes).<sup>9</sup>
- Patients should receive influenza vaccines and pneumococcal vaccines.<sup>9</sup>
- Patients should receive general medical therapy for COPD, including supplemental oxygen, as per local COPD guidelines.<sup>9</sup>
- Patients with major dyspnea and exercise limitation despite optimal medical therapy should be referred for pulmonary rehabilitation.<sup>9</sup>
- Surgery for lung volume reduction appears to be of less benefit in alpha-1 antitrypsin deficiency than in more typical tobacco-related COPD.<sup>9,35,36</sup>
- Lung transplantation should be considered for patients with very severe disease.<sup>9,34</sup>
- Augmentation therapy with intravenous alpha-1 antitrypsin should be considered for nonsmokers or those who have quit smoking and have an FEV<sub>1</sub> of 25%–80% of predicted.<sup>10</sup>

Note: COPD = chronic obstructive pulmonary disease, FEV<sub>1</sub> = forced expiratory volume in 1 second.

provincial formularies of British Columbia, Alberta, Manitoba and Quebec.

## Are there any treatment options for liver disease?

Augmentation therapy is not indicated to treat liver disease resulting from alpha-1 antitrypsin deficiency, and there is currently no other available therapy that targets the underlying defect in the liver. Management of liver disease related to alpha-1 antitrypsin deficiency begins with important preventive measures, including vaccination against hepatitis A and B and avoidance of alcohol and other hepatotoxic agents.<sup>9</sup>

Progression of liver disease to cirrhosis may be heralded by the development of splenomegaly, thrombocytopenia, changes to the liver that are visible by ultrasonography, or the development of the complications of portal hypertension, such as variceal hemorrhage, ascites or hepatic encephalopathy. Guidelines recommend that patients with cirrhosis be screened for hepatocellular carcinoma with abdominal ultrasounds every 6 months.<sup>47</sup> An initial endoscopy when cirrhosis is diagnosed can assess for the presence and appearance of esophageal varices. Relevant guidelines can help determine the timing of future screening endoscopies and the management of varices with nonselective  $\beta$ -blockers or endoscopic band ligation therapy.<sup>48</sup> Treatments for ascites include a low-salt diet, diuretics and paracentesis when necessary.<sup>49</sup> Patients with cirrhosis should receive nutritional advice and support as indicated to maintain an adequate nutritional status as long as possible in the face of advancing liver disease.

The indications for liver transplantation for alpha-1 antitrypsin deficiency do not differ from other chronic liver diseases. Transplant is curative of alpha-1 antitrypsin deficiency, although the patient will be required to remain on immunosuppressive medications and must live with the usual risks of transplantation, including biliary and vascular surgical complications, rejection, infection and cancer.

Appendix 1 (available at [www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.111749/-/DC1](http://www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.111749/-/DC1)) provides a fictional example of how to apply the results of this review in clinical practice.

## Gaps in knowledge

The efficacy of augmentation therapy in slowing the progression of emphysema in patients with COPD associated with alpha-1 antitrypsin deficiency has not been definitively established

through randomized controlled trials. Future research should also explore the optimal dose and scheduling of augmentation therapy, as well as the efficacy of alternative routes of delivery. Treatments for liver disease secondary to alpha-1 antitrypsin deficiency are urgently needed.

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