

Re.FLECTIONS

RGA's Medical Underwriting Newsletter

LETTER FROM THE EDITOR



Welcome to the latest issue of *Re-flections*, RGA's medical underwriting newsletter. You'll notice that we've given *Re-flections* a fresh

new look that we think you will find pleasing and easy to read. The articles, of course, deliver the same expert and insightful commentary that you've come to expect from the Medical Directors of RGA.

This edition features an article from Dr. Richard Rougeau, who discusses his approach to evaluating insurance applicants with elevated liver function tests. In addition, Dr. Oscar Cartaya has written another article in his series examining the relationship between disability practice and life underwriting practice, using his extensive experience in the disability field to evaluate mortality risk in pulmonary disease cases.

I hope that you enjoy reading both of these articles.

J. Carl Holowaty, M.D.
cholowaty@rgare.com

PULMONARY DISABILITY AND LIFE UNDERWRITING

by Oscar Cartaya, M.D.

This is the third in a series of articles by Dr. Cartaya that examines the relationship between disability practice and life underwriting practice. This article focuses on the respiratory system.

The respiratory system, contrary to other systems, presents conceptual challenges to the underwriter, as there are a number of important disability issues that are not required in life insurance underwriting evaluations. I feel that in life underwriting some systems are dealt with in a rigorous, scientific fashion while others are not. I would argue that the respiratory system falls into the latter.

Most underwriters seem to take a rather mechanical approach to underwriting respiratory system disorders. For example, when it is necessary to separate asthma from Chronic Obstructive Pulmonary Disease (COPD), the knowledge base required of underwriters for accurate interpretation of Pulmonary Function Tests (PFTs) is often inadequate. In disability practice, PFTs are required together with Arterial Blood Gasses (ABGs) in order to reach a true understanding of the functional capacity of the individual being evaluated. In life underwriting, by contrast, PFTs and ABGs are generally used when available, but are seldom required. Therefore it is easy to see that disability evalua-

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tions are more accurate than life insurance evaluations as far as the respiratory system is concerned. This discrepancy raises several issues.

In order to address this discrepancy without stating what is already widely known, I will start by discussing some of the medical issues that may cause difficulty in the future—specifically, remodeling of lung tissue as a response to COPD, and the differences between permanent obstruction and spasm-related obstruction of the airways.

The lung parenchyma is an extremely sheer and insubstantial tissue, largely formed of capillaries and epithelial cells in a somewhat uniform pattern throughout the lungs. Parenchymal tissue is rather lacking in structure or strength, so the bronchial tree provides whatever structure there is within the lungs. Considering the lack of substance and strengthening elements of the lung parenchyma, one can see how the alveoli can literally pop when the air pressure inside them increases beyond a certain level. In COPD, this is the basic mechanism that causes the typical blebs associated with emphysema.

The bronchial tree is substantial in structure with a fixed shape, cartilage reinforcements (to a certain level), and features such as muscle and gland tissue within its walls. When irritated, the bronchial tree reacts with secretions and becomes inflamed. The muscle tissue within the walls reacts to the inflammation by contracting; this causes bronchospasm and reversible obstruction (reversible with bronchodilators). Infection is common in these cases and eventually permanent strictures are formed which are unresponsive to bronchodilators. The process is chronic in adults and results in lung remodeling. That is, the parenchymal tissue is altered by the creation of blebs and the loss of surface area suitable for gas exchange—an irreversible change.

Therefore it should be evident that pure asthma or pure bronchospasm is not a condition common in adults as it is in children. Adults generally have mixed degrees of permanent and reversible obstruction in their bronchial trees. An adult with “asthma” has bronchospastic obstruction that is generally superimposed upon a background of permanent obstruction in the bronchial trees.

All of these factors can be evaluated satisfactorily with PFTs. Forced Expiratory Volume measurements (FEV) will document the degree of obstruction to air-flow through the bronchial tree, and FEV measurements before and after the inhalation of bronchodilators will document what portion, if any, of the obstruction is reversible (or due to bronchospasm), and what portion is permanent. As the process of lung remodeling progresses and blebs are formed, the lung loses surface area available for gas exchange and the volume of air that becomes trapped inside the lung increases. The increased amount of trapped air decreases the Forced Ventilatory Capacity (FVC). PFTs are generally the most valuable test of lung function evaluation.

Diffusion capacity of the lungs is measured by the Diffusion Lung Carbon Monoxide (DLCO) test. This test directly measures the gas exchange capacity of the lungs, but results are not easy to interpret because they are based upon many variables. A loss of surface area (as with bleb formation in emphysema), or a thickening of the alveolar walls (as with interstitial fibrosis), decreases the DLCO. However, the DLCO will also be decreased by the surgical removal of a lung (or a portion of) and by severe anemia. Polycythemia will have the reverse effect. The DLCO test is important because it provides a direct overall measurement of the gas exchange capacity of the respiratory system. Whatever the cause, a severe decrease of the DLCO value will always cause a significant degree of functional limitation due to insufficient gas exchange capacity.

Adult asthma is a problem when combined with significant underlying permanent obstruction. A person with COPD who also has frequent attacks of “asthma”, or who is under treatment with multiple bronchodilators, needs a careful evaluation that includes PFTs whenever possible. It is important to properly interpret PFTs and to understand when the results are valid or when they are likely to be due to poor effort. However, this topic is beyond the scope of this article.

The common thread shared by disability practice and life underwriting practice is pulmonary function. Severe impairment of respiratory gas exchange and alterations of the blood gases can result in many physiological problems including: arrhythmias, neurological deficits (both transient and permanent), and ischemia of various organs (depending on the adequacy of the organ’s blood supply and the level of arteriosclerosis present). Pulmonary disease with low oxygen levels is a major contributor to myocardial, cerebral and gut infarctions. Shortness of breath is the primary manifestation of serious respiratory disorder, and although limiting in itself, is also an important indicator of underlying gas exchange problems.

Pulmonary disability can be defined as the level of respiratory impairment that prevents gainful work. Symptomatically, the level of exertion required to produce severe shortness of breath is an important factor in determining pulmonary disability. However, in order to standardize the process, the U.S. Social Security Administration (SSA) has published guidelines relating levels of pulmonary impairment as determined by standard PFTs to inability to work gainfully. These are summarized in Tables 1 and 2.

Table 1 shows disability-causing levels of pulmonary disease as determined by PFT values. Please note that disability levels occur when the value is equal to or lower to the value in the table. For example, a person 65 inches tall is considered disabled if the FEV1.0

is equal to or below 1.25 liters and the FVC is below 1.45 liters. Table 2 relates abnormalities in ABG determinations to disability. Disability can also be determined by gas exchange capacity measured as a DLCO. SSA rules dictate that a DLCO value equal to or below 40 percent of predicted values completely disables an individual from gainful work.

TABLE 1

Height (inches)	FEV 1.0 (liters)	FVC (liters)
<60	1.05	1.25
61-63	1.15	1.35
64-65	1.25	1.45
66-67	1.35	1.55
68-69	1.45	1.65
70-71	1.55	1.75
>72	1.65	1.85

TABLE 2

Arterial pCO2	Arterial pO2
<31	<65
31	<64
32	<63
33	<62
34	<61
35	<60
36	<59
37	<58
38	<57
39	<56
40 or above	<55

There are a few issues regarding the use of these tables. The underwriter must first consider the nature of the basic underlying disorder before any decision is made in a case. Not all test values will be abnormal in every case. For example, cases of severe pulmonary fibrosis with very low DLCOs (and probably low ABGs as well) may present little evidence of obstruction as measured by the FEV1.0. In a case of chronic sarcoidosis with advanced lung fibrosis, PFTs alone will not provide an underwriter with adequate information to make an underwriting decision. A DLCO is also needed.

PFT reports should be obtained whenever an applicant's physician has already performed the test. However, it may not be wise for an underwriter to order the test, as there may be a significant difference in the level of cooperation and effort put forth by a patient when a PFT is ordered by the physician for diagnostic purposes, and when it is ordered by the insurance company for underwriting purposes. Therefore, ordered tests may not provide very reliable information, and they are also expensive to obtain.

Finally, it is important to realize that levels of pulmonary and respiratory function limitation required to qualify for disability payments are not the same as the levels used in standard life insurance underwriting practice. In effect, underwriting practice is much more liberal in evaluating pulmonary disorders. This discrepancy should be taken as indicative of a need for caution in underwriting respiratory impairments. It is questionable whether insurers want to issue policies at relatively low mortality rates to applicants who qualify for disability due to limited pulmonary function status. This is particularly true in cases with documented Coronary Artery Disease, a prior history of Transient Ischemic Attacks, or generalized arteriosclerosis and Peripheral Vascular Disease. ■

PRAGMATIC UNDERWRITING APPROACH TO LIVER FUNCTION TEST ELEVATIONS

by Richard Rougeau, M.D.

Underwriters are frequently challenged when one or more abnormal serum enzyme elevations are found upon routine lab testing. Most are various asymptomatic combinations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and gamma-glutamyltransferase (GGT). Although these enzymes are present in tissues throughout the body, they are most often elevated in patients with liver disease and may reflect liver injury.

In clinical practice it is customary to repeat significant abnormal test results. This is usually done when underwriting a case where the amount of insurance applied for is above a certain threshold. It is therefore incumbent upon every underwriter to have a basic understanding of the most common causes of abnormal elevations and the more or less routine clinical investigations involved in further elucidating the specific etiology, to the extent that such an investigation has been undertaken.

The first consideration involves assessing the magnitude of any increase(s). You may recall that reference ranges for 'normal' lab values are usually the mean value +/- 2 standard deviations. Given that the reference population is by definition healthy, then approximately 5.0 percent of healthy subjects will have lab values that fall outside of the upper/lower limits for the range and do not signify abnormality. The greater the deviance, however, the less likely it is that a particular subject is free of any abnormality.

Secondly, considerations involved in evaluating the significance of hepatocellular enzyme elevations (AST/ALT) differ from those in evaluating (AP/ GGT) elevations. Both enzymes are normally present at low levels in serum although normal lab ranges may vary considerably. Serum ALT is predominantly from liver origin and hence reasonably specific. AST however can arise from many tissues

including liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes and erythrocytes. Liver cell necrosis is not required for AST/ALT elevation to occur. These enzymes are increasingly released to serum in response to damage to the liver cell membrane. In fact, correlation between the magnitude of the elevated hepatocellular enzyme levels and degree of liver cell damage is often lacking.

Accurately assessing the most likely cause of any significant elevation in AST/ALT begins with a thorough history. The differential diagnosis includes those conditions listed in Table 1. The specific cause of AST/ALT elevations can usually be inferred by assessing the pattern of results obtained by subsequent additional testing (see Table 2 on page 8).

TABLE 1. CAUSES OF CHRONICALLY ELEVATED AMINOTRANSFERASE LEVELS¹

HEPATIC CAUSES

- Alcohol abuse
- Medication
- Chronic hepatitis B and C
- Steatosis and nonalcoholic steatohepatitis
- Autoimmune hepatitis
- Hemochromatosis
- Wilson's Disease (in patients < 40 years old)
- Alpha 1-antitrypsin deficiency

NONHEPATIC CAUSES

- Celiac sprue
- Inherited disorders of muscle metabolism
- Acquired muscle diseases
- Strenuous exercise

¹Pratt, Daniel S. M.D., and Marshall M. Kaplan M.D., "Evaluation of Abnormal Liver-Enzyme Results in Asymptomatic Patients", *The New England Journal of Medicine*, April 27, 2000, p. 1267.

The following section highlights salient features of these various clinical conditions in an effort to assist underwriters in differentiating the specific cause(s).

Alcohol

A concealed chronic abusive drinking pattern remains the Achilles heel of underwriting elevated liver function tests. Helpful aids include finding an AST/ALT ratio of $\geq 2:1$, especially in association with an elevated GGT \geq twice normal. A study looking into this relationship found that 90 percent of those individuals with an AST/ALT ratio ≥ 2.0 had alcoholic liver disease. Very rarely will alcohol abuse raise the serum AST level $\geq 8x$ normal or the ALT level $\geq 5x$ normal. More often, the ALT level will be near normal even in individuals who severely abuse alcohol.

Medications

Almost any medication can cause an elevation in hepatocellular enzyme levels in a susceptible individual, so a high index of suspicion is necessary when reviewing medication histories. Common classes of medications responsible for such elevations include nonsteroidal anti-inflammatories (NSAIDs), antibiotics, anticonvulsants, statins, herbal preparations and many illicit drugs. Clinically, physicians will often discontinue a suspected medication in an attempt to prove the elevated enzymes are resulting from its use. This should be considered a valid explanation in such cases where the serum enzyme levels subsequently normalize (see Table 3).

Viral Hepatitis

The majority of viral hepatitis in North America is caused by hepatitis B and hepatitis C. Approximately 4 million Americans are estimated to be antibody-positive for hepatitis C which translates into 3.4 million individuals actively infected. This assumes that 85 percent of those acutely infected have become chronically infected. The risk is highest in those whose risk factors include a history of parenteral exposure to the virus (blood transfusions, IV drug use, needle-stick injuries, cocaine use, tattoos, body piercing and high-risk sexual behavior). A positive antibody test in an individual with any of the aforementioned risk factors is likely sufficient to justify a rating; however, the diagnosis is often confirmed with a qualitative polymerase chain reaction (PCR) test for hepatitis C viral RNA. A positive qualitative PCR will often warrant a biopsy that can be more accurately assessed based on the degree of inflammation and fibrosis involved.

Hepatitis B testing will usually involve hepatitis B surface antigen (HbSAg) and some combination of surface antibody (HbSAb), core antibody (HbCAb) and E antigen (HbEAg). Various hepatitis panel permutations are possible, but in essence, a positive test for HbSAg indicates infection. Further, HbSAg and HbEAg together indicates active viral replication. In such patients, liver biopsy and treatment should be considered, and the patient deemed higher-risk.

Of note, in the specific situation where HbSAg is negative, HbCAb is positive and HbSAb is negative, four explanations are possible. (1) The individual may be recovering from acute hepatitis B infection but the HbSAb has not yet appeared. This is referred to as a window period. (2) It may signal distant past infection with the HbSAb below the limit of lab detection. (3) It may represent chronic hepatitis B infection with HbSAg below the limit of lab detection. (4) It may simply represent a false positive HbCAb and the individual is susceptible to hepatitis B infection, having never been previously exposed.

Autoimmune Hepatitis

This disease is most commonly found in young-to-middle-aged females with a 4:1 female-to-male incidence. The most helpful test in differentiating this entity is serum protein electrophoresis (SEP). Approximately 80 percent of those affected have hypergammaglobulinemia. Polyclonal immunoglobulins exceeding twice the upper limit of normal suggest this diagnosis. Additional testing for antinuclear antibodies, anti-smooth muscle antibodies and anti-mitochondrial antibodies is largely unhelpful due to low sensitivity. In the absence of other causes to explain the elevated hepatocellular enzymes (but given a suggestive SEP), a biopsy should be undertaken to confirm the diagnosis pathologically.

Non-Alcoholic Fatty Liver Disease

This entity includes both simple hepatic steatosis and non-alcoholic steatohepatitis (NASH). Usual findings include a mild elevation in both AST and ALT levels with an AST/ALT ratio less than 1, in contrast with that found in alcoholic hepatitis. Fatty infiltration of the liver can be identified by both ultrasound or computed tomography (CT). The diagnosis of NASH (combination of steatosis, mononuclear +/- polymorphonuclear infiltration of hepatic lobules, liver cell ballooning and spotty necrosis) requires a confirming biopsy. It should also be noted that pathologic findings in NASH and alcoholic hepatitis with fibrosis are indistinguishable.

In terms of natural history, hepatic steatosis usually follows a reasonably benign course, while NASH can proceed to more advanced fibrosis and eventual cirrhosis. The specific mechanism whereby a relative minority of individuals progress through the various stages remains to be elucidated.

Hemochromatosis

Hemochromatosis is a relatively common autosomal recessive genetic disorder whereby dietary iron is absorbed in excess and deposited in various tissue sites including liver cells. Screening consists of measuring serum iron and total iron binding capacity (TIBC). The ratio of serum iron over TIBC represents transferrin saturation and is considered suggestive when it rises beyond 45 percent. Measuring serum ferritin is much less helpful, as it tends to rise in a variety of inflammatory and infectious stressful conditions, lowering its specificity.

If the screening test is suggestive, a liver biopsy should be undertaken to assess liver iron levels and any liver damage. A hepatic iron index (hepatic iron level in micromoles per gram of dry weight divided by the patient's age) greater than 1.9 is consistent with this diagnosis.

Wilson's Disease

Wilson's Disease is a rare autosomal recessive disorder of copper metabolism whereby dietary copper is absorbed in excess and accumulates within liver cells, analogous to the situation in hemochromatosis. The onset of clinical signs and symptoms normally occurs between ages 5-25, however the diagnosis should be considered in individuals up to the age of 40. The screening test consists of measuring serum ceruloplasmin, a transport protein, which will be reduced in approximately 85 percent of affected individuals. The diagnosis is usually confirmed by liver biopsy to assess liver copper levels. Liver copper levels in excess of 250 micrograms per gram of liver, dry weight, are most suggestive.

Alpha 1 – Antitrypsin Deficiency

This is a rare cause of chronic liver disease. Serum levels of this inhibitory enzyme are usually detected by direct measurement. Low levels of enzyme activity result in excess proteolytic enzymes and inflammation that may eventually lead to cirrhosis.

Further to a hepatocellular or aminotransferase discussion, a brief review of alkaline phosphatase (AP) and gamma-glutamyltransferase (GGT) levels is in order.

Serum levels of AP arise largely from either liver or bone. Levels vary by age and by gender, with peaks noted in rapidly growing adolescents and adults between ages 40-65, particularly in females. Levels in these individuals may approach twice the upper limit of normal. For example, the normal AP level in a healthy 65 year-old female is 50 percent higher than the level in a healthy 30 year-old female.

When evaluating an elevated AP level it is best to simultaneously take note of the GGT level. When both enzymes are elevated in parallel this usually indicates a liver source. Conversely, when the AP is elevated in isolation this usually indicates a bone disorder.

If the AP elevation is likely of liver origin and is persistent, the individual may be manifesting either cholestatic (suppression of bile flow) or infiltrative liver disease. Cholestatic diseases include obstruction of bile ducts, primary biliary cirrhosis, primary sclerosing cholangitis or drug-induced cholestasis from medications such as anabolic steroids. Infiltrative diseases include sarcoidosis, other granulomatous diseases and occasionally liver metastases.

Appropriate initial investigation includes liver ultrasound to assess the liver and its bile ducts as well as serologic testing for antimitochondrial antibodies. When present, the antibodies strongly suggest primary biliary cirrhosis and are usually considered an indication for biopsy.

GGT is found in liver cells and biliary epithelial cells. GGT serum levels provide a very sensitive but equally non-specific indicator of possible hepatobiliary disease. Elevated GGT levels have been identified in a wide variety of clinical conditions including alcoholism, diabetes mellitus, chronic obstructive pulmonary disease, renal disease, myocardial infarction and pancreatic disease. Since the GGT enzyme

is an inducible enzyme, elevated levels are also often seen in individuals who take medication(s) for many chronic medical conditions.

Given this lack of specificity, an isolated GGT elevation is unlikely to prove helpful in discerning either the presence of a significant illness or its specific cause. It would seem the underwriting value of GGT lies then in evaluating the significance of other serum enzyme elevations. As mentioned, GGT can be used to confirm the hepatic origin of a parallel elevation in AP or to support a presumed diagnosis of alcohol abuse in an individual with other clinical and laboratory stigmata.

Unfortunately, however, it often leaves an underwriter with more questions than it does answers. ■

INFORMATION

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TABLE 2. LABORATORY TESTS THAT MAY IDENTIFY THE CAUSE OF ELEVATED AMINOTRANSFERASE LEVELS IN A PATIENT WITH NO SYMPTOMS

INITIAL TEST	DIAGNOSIS
Test for hepatitis C antibody in serum	Presence of hepatitis C antibody suggests chronic hepatitis C
Test for hepatitis B surface antigen, surface antibody, and core antibody in serum	Presence of hepatitis B surface antigen and core antibody indicates chronic hepatitis B
Measurement of serum iron and total iron-binding capacity	Iron overload suggests Hemochromatosis
Measurement of serum ceruloplasmin	Decreased ceruloplasmin level suggest Wilson's Disease (if patient is < 40 years old)
Serum protein electrophoresis	Increase in polyclonal immunoglobulins suggests autoimmune hepatitis
ADDITIONAL TESTS If the results of the initial set of tests are normal, these additional tests may pinpoint the specific cause of elevated aminotransferase levels.	DIAGNOSIS
Reverse-transcriptase polymerase chain reaction for hepatitis C virus RNA	Presence of viral RNA indicates chronic hepatitis C
Alpha 1-antitrypsin	Presence of the ZZ genotype indicates alpha 1-antitrypsin deficiency

TABLE 3. MEDICATIONS, HERBS, AND DRUGS OR SUBSTANCES OF ABUSE REPORTED TO CAUSE ELEVATIONS IN LIVER-ENZYME LEVELS

Medications

Antibiotics

- Synthetic penicillins
- Ciprofloxacin
- Nitrofurantoin
- Ketoconazole and fluconazole
- Isoniazid

Antiepileptic drugs

- Phenytoin
- Carbamazepine

Inhibitors of hydroxymethylglutaryl-coenzyme A reductase

- Simvastatin
- Pravastatin
- Lovastatin
- Atorvastatin

Nonsteroidal anti-inflammatory drugs

Sulfonylureas for Hyperglycemia

- Glipizide

Herbs and homeopathic treatments

- Chaparral
- Chinese herbs
 - Ji bu huan
 - Ephedra (Ma Huang)
- Gentian
- Germander
- Alchemilla (lady's mantle)
- Senna
- Shark cartilage
- Scutellaria (skullcap)

Drugs and substances of abuse

- Anabolic steroids
- Cocaine
- 5-Methoxy-3, 4-methylenedioxymethamphetamine (MDMA, "ecstasy")
- Phencyclidine ("angel dust", PCP)
- Glues and solvents
 - Glues containing toluene
 - Trichloroethylene, chloroform