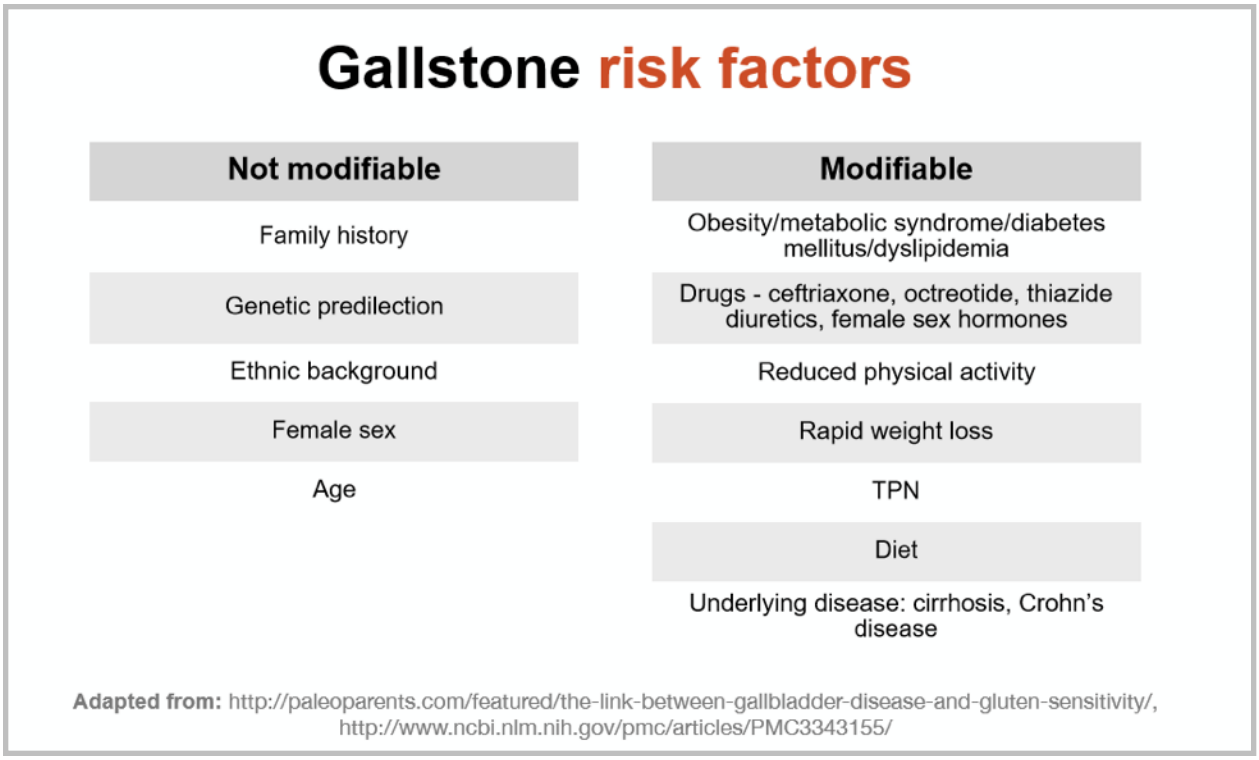
KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Impaired Gallbladder Function - Part One

Hey, everybody. In this presentation, we're going to discuss gallbladder dysfunction. There are several types of gallbladder disease, and these include gallstones; cholecystitis, which can be acute or chronic; Gilbert's disease; choledocholithiasis, which is a lodging of the gallstone in the neck or the duct of the gallbladder; biliary dyskinesia, which is gallbladder muscles or valves not working properly; sclerosing cholangitis, which is inflammation or scarring of the bile ducts; gallbladder cancer; gallbladder polyps; gangrene of the gallbladder; and abscess of the gallbladder.

As with liver dysfunction, we're not going to go into depth on any particular disease or problem here. The purpose is to teach you to identify gallbladder pathology, treat it when possible, and refer out when necessary. The most common gallbladder issues you will see are gallstones, cholecystitis, and Gilbert's disease, and we'll discuss these in a little more detail.

Gallstones affect 10 to 15 percent of the adult population, which is 20 to 25 million Americans. Gallstone disease is the leading cause for hospital admissions related to gastrointestinal problems. Although the mortality rate for gallstones is relatively low at 0.6 percent, because they are so common, there are over 1,000 deaths per year caused by gallstones. The majority of people with gallstones won't develop symptoms. Up to 80 percent never experience biliary pain or complications such as acute cholecystitis, cholangitis, or pancreatitis. When symptoms do present, they can be either episodic or steady, and the pain is located in the upper abdomen. It can be severe and last for more than 30 minutes, and then there can be some accompanying features such as nocturnal onset, nausea, vomiting, and radiation through to the back.



The risk factors for gallstones are both non-modifiable and modifiable. The non-modifiable factors include ethnicity. North American Indians and aboriginal South Americans have the highest incidence. Whites and Mexicans have an intermediate incidence, and sub-Saharan Africans have the lowest incidence. Genetics and family history play a role. There is a fivefold higher risk in relatives of gallstone patients. Age also plays a role. Risk increases with age and escalates quickly after age 40. People who are over 40 years of age have four- to tenfold higher risk of gallstones than people under 40. Sex also plays a role. Females are twice as likely to develop gallstones. In school you probably learned the not-so-nice mnemonic fat, female, and 40 for gallstones because of the increased risk of people who are overweight, female, and over the age of 40.

Now, modifiable risk factors, obesity is one of the primary ones; 25 percent of those who are morbidly obese have gallstones. People with metabolic syndrome, low HDL, and high triglycerides have a higher risk. On the other hand, 30 to 71 percent of individuals who experience rapid weight loss from bariatric surgery or low-calorie diets get gallstones. Several dietary characteristics have been associated with gallstones. Mostly they fall under the Western industrialized diet. Some research has specifically linked gluten intolerance and celiac to increased prevalence of gallstones. If a patient has gallbladder issues, and they are still eating gluten, it's absolutely crucial to screen them for nonceliac gluten sensitivity or celiac disease, and I've definitely saved some gallbladders from being removed this way.

Underlying diseases such as IBD, liver disease, and cystic fibrosis can contribute to gallstones, and some drugs, which are listed on the slide, such as ceftriaxone, octreotide, thiazide, diuretics, and female sex hormones can contribute to gallstones.

Cholecystitis usually occurs as a complication of gallstone disease. About 6 to 11 percent of patients with gallstones will develop it, which means approximately 1 percent of Americans have cholecystitis. Cholecystitis without gallstones is called acalculous cholecystitis or biliary dyskinesia. Chronic cholecystitis is the term used to describe chronic inflammatory cell infiltration of the gallbladder seen on histopathology. It is almost always associated with gallstones and thought to be the result of recurring, acute cholecystitis attacks, which then leads to fibrosis and thickening of the gallbladder.

Risk factors for acute acalculous cholecystitis

Acute myelogenous leukemia	End-stage renal disease
Acquired immune deficiency syndrome	Heart failure
Ampullary stenosis	Hemobilia
Bone marrow transplantation	Immunosuppression
Burns	Infections
Cardiopulmonary resuscitation	Major trauma
Childbirth	Mechanical ventilation
Choledochal cyst	Medications (e.g., opiates, sunitinib)
Cholesterol emboli	Metastases to porta hepatis
Coronary heart disease	Multiple transfusions
Cystic duct obstruction by a percutaneous transhepatic catheter in the bile duct	Nobiliary surgery
Diabetes mellitus	Sepsis/hypotension
	Total parenteral nutrition
	Vasculitis

Adapted from: https://www.uptodate.com/contents/acalculous-cholecystitis

Acalculous cholecystitis accounts for approximately 10 percent of all cases of acute cholecystitis and is associated with high morbidity and mortality rates. Acalculous cholecystitis has numerous risk factors, which are beyond the scope of this presentation, but the mechanism primarily involves gallbladder stasis and ischemia, resulting in local inflammatory responses in the gallbladder wall. I've listed some of the risk factors for acute acalculous cholecystitis on the table on this slide.

Gilbert's syndrome is a benign condition sometimes referred to as familial nonhemolytic jaundice. It involves an overproduction of unconjugated or indirect bilirubin, which leads to recurrent episodes of mild jaundice, but other than this, most patients with Gilbert's typically are asymptomatic, and no treatment is necessary. Gilbert's has a genetic and familial association. It can be triggered by dehydration, fasting, concurrent disease, menstruation, and overexertion. The prevalence of Gilbert's syndrome is between 4 and 16 percent depending on the population. Patients typically present during adolescence when alterations in sex steroid concentrations affect bilirubin metabolism, and it is sometimes identified in routine blood work, including bilirubin. We'll talk about how to diagnosis Gilbert's when we discuss bilirubin workup algorithm.

Markers of impaired gallbladder function

Marker	Value
ALT	High
AST	High
Bilirubin	High
Alkaline phosphatase	High
5'-Nucleotidase	High
LDH	High
GGT	High

Here are the markers of impaired gallbladder function on the case review blood panel, with the exception of 5′-nucleotidase, which is not included on the case review blood panel. As you can see, it is the same as the liver workup with two additions. Bilirubin is added, and then 5′-nucleotidase is added.

We already talked about the workup and differential diagnosis for aminotransferases in the liver presentation, so refer to that for details. Here, we're going to focus on the markers that are more specific to gallbladder dysfunction, as well as how to interpret the other markers in the context of gallbladder dysfunction.

Let's start with bilirubin. The metabolism of bilirubin comprises four distinct stages: uptake from circulation, intracellular storage, conjugation with glucuronic acid, and biliary excretion. Normally, about 96 percent of bilirubin is unconjugated. Abnormalities of any of the four stages result in hyperbilirubinemia, with either high unconjugated bilirubin or both high unconjugated and conjugated bilirubin. When you see bilirubin is high, you need to do a follow-up test to see how much of that elevated bilirubin is conjugated and how much is unconjugated. The terms direct and indirect are also often used here, so the name of the test with LabCorp is total and direct bilirubin. This will give you a value for total and direct or conjugated bilirubin, and then you could subtract the direct bilirubin to get indirect or unconjugated.

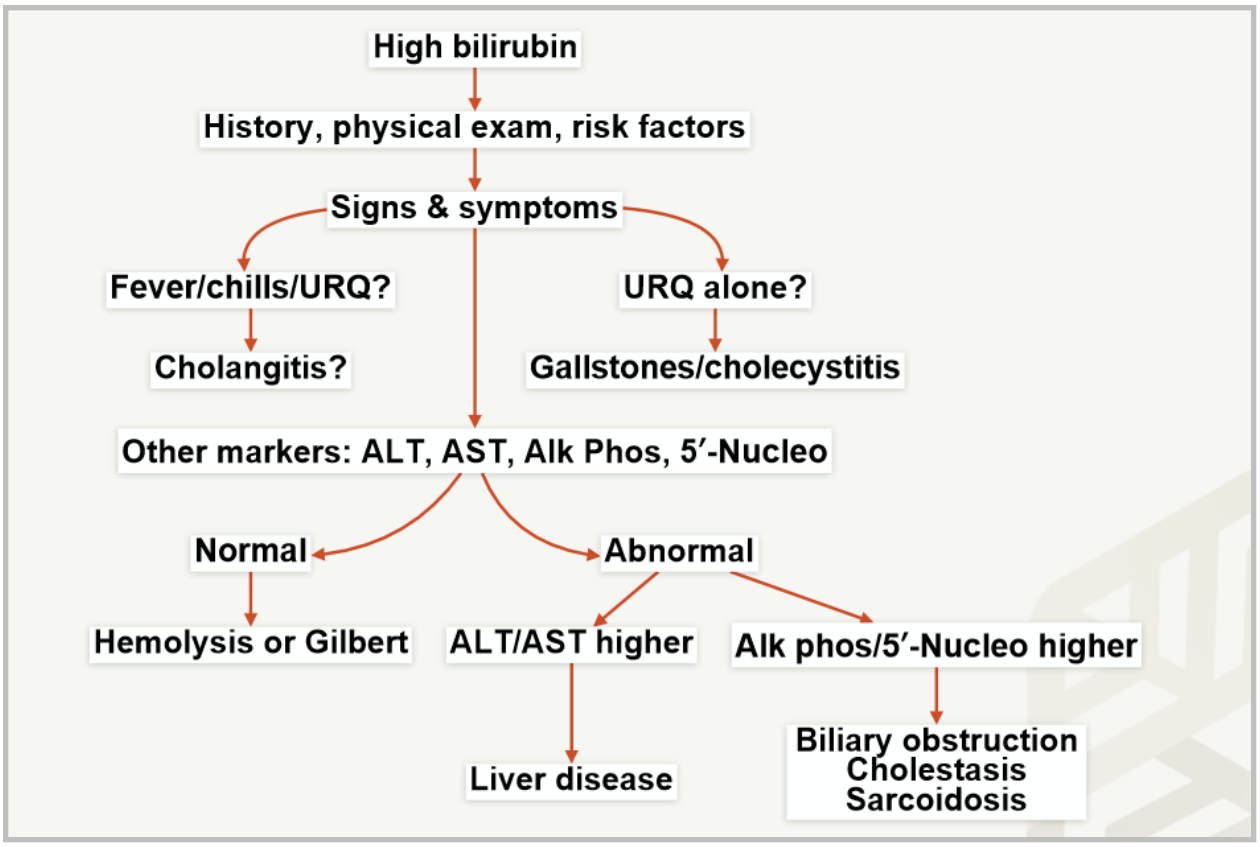
Bilirubin

Marker	Lab range	Functional range
Total	0–1.2 mg/dL	N/A
Direct	0–0.4 mg/dL	N/A

I've put the lab range for total and direct bilirubin on this slide. There is no functional range for these markers.

If bilirubin is high, pay attention to the patient's history and physical exam. Consider risk factors such as medications that harm the liver, which we talked about in the last presentation: alcohol, foreign travel, intravenous drug use, HIV status, and exposure to toxins. Also look at the skin to determine if jaundice is present.

Next, look at signs and symptoms. Does the patient have fever, chills, and upper right quadrant pain? If so, it could be cholangitis. Do they have anorexia, malaise, myalgias? You would consider hepatitis. If they have upper right quadrant pain alone, you might consider gallstones or cholecystitis. Next, look at other markers of liver and gallbladder function. If aminotransferases and alkaline phosphatase are normal, high bilirubin is unlikely to be caused by liver or gallbladder disease. It could be hemolysis or inherited disorders such as Gilbert's instead. If alkaline phosphatase and/or 5′-nucleotidase are elevated proportionally more than ALT or AST, that suggests biliary obstruction such as gallstone, intrahepatic cholestasis, or sarcoidosis. If ALT or AST are proportionally higher than alkaline phosphatase or 5′-nucleotidase, you would suspect liver disease and then refer to the liver presentation for details.



I've put this algorithm here on this slide in a diagram that you can refer to as a reference.

Causes of bilirubin elevation

Marker	Causes
High indirect/ unconjugated bilirubin	Hemolysis
	Extravasation of blood into tissue
	Dyserythropoiesis
	Stress situations (e.g., sepsis) leading to increased production of bilirubin
	Impaired hepatic bilirubin uptake
	Impaired bilirubin conjugation
High direct/ conjugated bilirubin	Biliary obstruction (e.g., gallstones, pancreatic or biliary malignancy, AIDS cholangiopathy, parasites)
	Viral hepatitis
	Alcoholic hepatitis
	Nonalcoholic steatohepatitis
	Primary biliary cholangitis
	Drugs and toxins
	Ischemic hepatopathy
	Liver infiltration
	Gilbert's syndrome
	Total parenteral nutrition
	Postoperative jaundice
	Intrahepatic cholestasis of pregnancy
	End-stage liver disease
	Organ transplantation (e.g., bone marrow, liver)

Follow-up testing for indirect unconjugated bilirubin and direct conjugated bilirubin can provide more information, and I've put the indications for each in the table on the slide.

The frequency with which different causes occur depends heavily on the population that's studied. For example, one study of Dutch adults, found that gallbladder cancer accounted for 20 percent of cases of bilirubin elevation, gallstones for 13 percent, and alcoholic cirrhosis for 10 percent. High levels of direct or conjugated bilirubin typically involve evaluation for hemolytic anemia, drugs that impair hepatic uptake of bilirubin, and Gilbert's syndrome. In my practice, and in a functional medicine setting, Gilbert's syndrome will be the most common cause.

High indirect or unconjugated bilirubin evaluation is based on whether the abnormalities are due to biliary obstruction, intrahepatic cholestasis, hepatocellular injury, or an inherited condition. If there is evidence of biliary obstruction such as high unconjugated bilirubin and high alkaline phosphatase and/or 5′-nucleotidase, then you can refer out for hepatic imaging such as ultrasound or MRI. If there is evidence of liver disease, like higher AST and ALT than alkaline phosphatase or 5′-nucleotidase, do further testing for causes of liver issues, like Wilson disease, hemochromatosis, hepatitis, etc. So refer to the Impaired Liver presentation for more detail there.