OBSTRUCTIVE JAUNDICE: UNDERSTANDING THE PATHOPHYSIOLOGY

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ABSTRACT
Jaundice is one of the most prevalent symptom in hepatobiliary disorders. The nature of jaundice may vary from hepatocellular to obstructive pattern. In a few cases, it may be haemolytic in nature. Identifying and ascertaining the type is pivotal for further investigation. A combination of haematological and radiological investigations will not only provide information on the severity and the impact of obstructive jaundice on various organ systems of the body but also help in determining the prognosis. Endoscopy can also provide diagnostic as well as a therapeutic benefit in obstructive jaundice. The pathophysiology, clinical evaluation and investigations in a case of obstructive jaundice is discussed in this paper.

KEYWORDS
Jaundice, obstructive, causes, complications, investigations

Introduction
Obstructive jaundice is one of the most challenging types of jaundice. It can be treated successfully once the cause is ascertained. Understanding the basic physiology of bilirubin metabolism and the structure of the extrahepatic biliary passages is essential for the adequate diagnostic evaluation of a patient presenting with obstructive jaundice. [1]

Surgical anatomy of the extrahepatic biliary passages
The intrahepatic ducts converge to form the right and left hepatic ducts which exit from the liver and join to form the common hepatic duct. The cystic duct emerges from the gall bladder and joins the common hepatic duct which then descends as the common bile duct. The common bile duct has four parts, supraduodenal, retroduodenal, intrapancreatic and intraduodenal. The common bile duct is joined by the main pancreatic duct to open into the ampulla of Vater situated in the second part of the duodenum. The diameter of the normal CBD is less than 8mm, and the diameter of the main pancreatic duct is less than 4 mm. The ducts

of Luschka are small biliary ducts that lie in the gall bladder fossa and connect the liver and gall bladder directly. The normal thickness of the gall bladder wall is less than 4 mm. Therefore obstruction can occur at any level. It may be intraluminal or due to extrinsic compression. Backpressure leads to dilatation of the passages. Identifying the level and cause for obstruction is, therefore, the main aim of clinical evaluation and imaging.

Physiology of bilirubin metabolism
Bilirubin is of two types, direct which is water soluble and indirect, which is water insoluble. Identifying the rise of each type is essential in the evaluation of the type of jaundice. Hence it is essential to review the normal process of bilirubin formation and clearance from the gastrointestinal tract. Fragile and senescent RBC’s are broken down in the spleen. When the RBC membrane ruptures, haemoglobin is released. The macrophages of the reticuloendothelial system phagocytose this. Haemoglobin is further broken down into heme and globin. The heme component is then further broken into free iron which combines with ferritin and the straight remnant chain of four pyrrole nuclei that serves as a substrate for the formation of bile pigments.

Biliverdin is formed which then gets converted into bilirubin. Bilirubin is released into the plasma. In the plasma, it is bound to albumin and transported to the liver. There it gets absorbed across the hepatic cell membrane. During this process, it is released from the albumin but remains attached to two proteins Y and Z proteins inside the hepatocytes. Soon the bilirubin is detached from these proteins and is conjugated. The end
products are bilirubin glucuronide (80%), bilirubin sulphate (10%), and other substances (10%). An active transport process then excretes bilirubin glucuronide into the bile canalliculi.

A small quantity of conjugated bilirubin enters the plasma. Through the extrahepatic biliary passages, it inter to the intestine. Conjugated bilirubin is acted upon by the bacteria converting it into urobilinogen. Urobilinogen undergoes oxidation to stercobilinogen which is excreted into the stools as stercobilin. Stercobilin imparts the yellowish colour to normal stools. A part of urobilinogen is absorbed and passes to the kidneys from where it is excreted into the urine as urobin which imparts a yellowish colour to normal urine.

Pathophysiology of Jaundice

Jaundice is best described as yellowish discolouration of the sclera. Obstructive jaundice results from obstruction to the free flow of bile from the liver to the gall bladder and then to the small intestine. Jaundice or raised total bilirubin may be due to an increase in either conjugated or unconjugated component. This depends upon the level at which the normal bilirubin metabolism is altered. This can happen at three levels Pre hepatic wherein there is increased production of bilirubin which exceeds the capability of the liver to conjugate the bilirubin and excrete it into the gut. There is a predominant increase in the unconjugated bilirubin. The most frequent prehepatic cause is haemolytic anaemia, where there is an excessive breakdown of heme. [2]

Intrahepatic cause for hyperbilirubinaemia is usually due to parenchymal liver disease, thereby causing an inability to either conjugate or excrete bilirubin. This may initially cause a transient increase in the conjugated component, followed by the indirect component. This is seen in viral hepatitis, drug-induced and primary biliary cirrhosis. [3]

Post hepatic causes lead to an impediment to the flow of bile, which may be either due to partial or complete obstruction of the extrahepatic biliary passages between the liver and duodenum. There is predominantly conjugated hyperbilirubinaemia. This is a characteristic feature of obstructive jaundice. [3]

Aetiology of biliary obstruction

Biliary obstruction may either be intrahepatic or extrahepatic in origin. [4] Intrahepatic cholestasis could be at the level of the hepatocyte or the canalicular bile membrane. The causes include hepatitis (hepatitis A, B & C) leading to inflammation of the liver with necrosis, cirrhosis (primary biliary cirrhosis) leading to nodular regeneration and scarring, drug-induced (anabolic steroids, chlorpromazine) and space-occupying lesions of the liver such as cysts, abscesses and tumours. [5]

Extrahepatic causes can further be classified as intraductal, which include choledocholithiasis, neoplasms (cholangiocarcinomas), biliary strictures and parasitic infestations (ascariasis, liver flukes). [6] For better understanding extrahepatic causes of obstructive jaundice can be classified into four types (Table 1).

Extra ductal causes include neoplasms, pancreatitis, pseudocysts of pancreas and portal hilar lymphadenopathy. Tumours causing extra ductal compression deserve special mention. These include pancreatic head tumours, cholangiocarcinoma, ampullary carcinomas, gall bladder carcinomas extending up to the CBD and metastatic lymphadenopathy. [7] Choledocholithiasis, biliary strictures and malignant tumours are the most important and common causes of obstructive jaundice. Uncommon postoperative causes need to be considered as well.

This includes sump syndrome seen in a side to side choledochojunostomy in which food, stones or debris accumulate in the CBD and obstruct the normal biliary outflow. The other such cause is seen in Roux-en Y limb wherein stasis may cause biliary obstruction after biliary enteric anastomosis. [8]

Effects of biliary obstruction:

Complications of cholestasis are proportional to the duration and intensity of jaundice. Jaundice has a negative impact on various organ systems of the body.

Intestines:

Bile and bile acids have essential functions in maintaining the normal integrity and function of the intestines. Bile and bile acids contribute significantly to the normal gut barrier function. It has positive effects on the intestinal immune function. In experimental studies, it affects homing and distribution of T lymphocytes in the gut-associated lymphatic tissue. Absence of bile acids in the gut causes a fall in the CD4+ and CD8+ lymphocytes. It exerts a trophic effect on the intestinal mucosa by increasing the villous density and inducing hypertrophy of various components of the intestinal wall. Bile acids inhibit the growth of certain bacteria such as Bacteroides, clostridia, lactobacillus and streptococci. [9]

Absence of bile in the intestine has a series of deleterious effects leading to septicemia. Absence of bile salts leads to disturbance of intestinal bacterial balance with overgrowth of gram-negative bacteria. There is an alteration of intestinal tight junction expression and increased intestinal apoptosis, causing significant alterations in the intestinal oxidative state, thereby exacerbating the gut injury. There is increased intestinal permeability causing bacterial and endotoxin translocation leading to septic and renal complications. Absence of bile causes suppression of clearing capacity of Kupffer cells, the main hepatic macrophage population due to accumulation of bile acids in the liver thereby permitting spillover of endotoxins from the portal circulation into the systemic circulation with the release of pro-inflammatory cytokines. These lead to the development of “gut-derived sepsis”. [10, 11, 12]

Coagulation system:

The liver has a significant synthetic role to play in the coagulation system. It synthesizes fibrinogen, prothrombin, factors II, VII, IX and X. The production of these factors is dependent on vitamin K, which is a fat-soluble vitamin requiring bile in the intestine for absorption. Due to the absence of bile in the intestine, this vitamin cannot be absorbed, leading to deficiency. Hence glycosylation of lysyl residues cannot take place in the liver, thereby leading to deficiency of factors II, VII, IX and X. This causes disturbances in the extrinsic pathway of coagulation. The liver also manufactures natural anticoagulants such as antithrombin III, protein C, protein S and heparin cofactor II. With respect to the fibrinolytic system, it produces plasminogen and alpha two anti-plasmin. Therefore alteration in liver function can lead to serious coagulation defects. If septic and pancreatic complications develop then a prothrombotic state may develop initially. Mucinous adenocarcinomas of the pancreas and hepatocellular carcinomas can induce activation of the haemostatic system. Thromboembolic events usually follow. Unresolved cholestasis leads to a generalized alteration in the haemostatic system. The effects are thrombocytopenia, decreased synthesis...
**Table 1** Classification of obstructive jaundice (Benjamin).

<table>
<thead>
<tr>
<th>Type I: Complete obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumours of the head of pancreas</td>
</tr>
<tr>
<td>Ligation of the CBD</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Parenchymal liver disease</td>
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<tr>
<th>Type II: Intermittent obstruction</th>
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<tbody>
<tr>
<td>Choledocholithiasis</td>
</tr>
<tr>
<td>Choleodochal cyst</td>
</tr>
<tr>
<td>Duodenal diverticulum</td>
</tr>
<tr>
<td>Intrapancreatic parasites</td>
</tr>
<tr>
<td>Haemobilia</td>
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<tr>
<th>Type III: Chronic incomplete obstruction</th>
</tr>
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<tbody>
<tr>
<td>Strictures of the CBD</td>
</tr>
<tr>
<td>Stenosed biliary enteric anastomosis</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Stenosis of the sphincter of Oddi</td>
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<th>Type IV: Segmental obstruction</th>
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<tbody>
<tr>
<td>Traumatic</td>
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<tr>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>Intrahepatic stones</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
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</tbody>
</table>

**Table 2** Types of jaundice.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-heaptic</th>
<th>Hepatocellular (hepatic)</th>
<th>Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of raised bilirubin</td>
<td>Haemolysis leading to excess production</td>
<td>Deficient uptake, conjugation or excretion by hepatocytes</td>
<td>Deficient excretion due to obstruction in the biliary tract</td>
</tr>
<tr>
<td>Type of serum bilirubin affected</td>
<td>Mainly unconjugated</td>
<td>Unconjugated+ conjugated</td>
<td>Predominantly conjugated (&gt;50%)</td>
</tr>
<tr>
<td>Urine bilirubin</td>
<td>absent</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>Urine urobilinogen</td>
<td>increased</td>
<td>variable</td>
<td>absent</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>normal</td>
<td>Abnormal that is not correctable by vitamin K</td>
<td>Abnormal that is corrected with vitamin K</td>
</tr>
<tr>
<td>Additional features</td>
<td>Features of haemolysis on blood smear (reticulocytosis, low haptoglobin, low Hb)</td>
<td>Marked increase in ALT and AST</td>
<td>Marked increase in ALP &gt; 3 times the normal upper limit</td>
</tr>
<tr>
<td>Prototypes</td>
<td>Haemolytic anaemia</td>
<td>Viral hepatitis</td>
<td>Common bile duct stones</td>
</tr>
</tbody>
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**Table 3** Prognostic factors (Pitt’s score)

<table>
<thead>
<tr>
<th>Parameters (one point per factor)</th>
</tr>
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<tbody>
<tr>
<td>Type of obstruction (benign or malignant)</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
</tr>
<tr>
<td>Serum albumin &lt; 3gml/dl</td>
</tr>
<tr>
<td>Serum bilirubin &gt; 10 mg%</td>
</tr>
<tr>
<td>Serum Alkaline phosphatase &gt; 100 IU</td>
</tr>
<tr>
<td>Serum creatinine &gt; 1.3 mg%</td>
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<tr>
<td>TLC &gt; 10000/mm³</td>
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<tr>
<td>Haematocrit &lt; 30%</td>
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Interpretation of scores

<table>
<thead>
<tr>
<th>Factors</th>
<th>Mortality</th>
</tr>
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<tbody>
<tr>
<td>Up to 2</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>7%</td>
</tr>
<tr>
<td>5</td>
<td>44%</td>
</tr>
<tr>
<td>6</td>
<td>67%</td>
</tr>
<tr>
<td>8</td>
<td>100%</td>
</tr>
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and clearance of coagulation factors and inhibitors, dysfibrinogenemia, hyperfibrinolysis, over DIC, portal vein stasis and thrombosis. [13, 14]

Renal system
Jaundice alone independent of the parenchymal liver disease affects the integrity of the cardiovascular system. [15] The effects are

1. Reduction in peripheral vascular resistance resulting in systemic hypotension.
2. Depression of myocardial function.
3. Profound natriuresis and diuresis, leading to volume depletion.

In experimental models, renal complications are attributed to pre-renal factors. Various factors related to liver parenchymal damage associated with obstructive jaundice may have an independent contribution to the pathogenesis of arterial underfilling, which predisposes to pre-renal failure and acute tubular necrosis. Peripheral and renal haemodynamic effects of obstructive jaundice are more marked than medical jaundice. High level of bile acids in the circulation seen in obstructive jaundice has a direct cardio depressant and hypovolemic effect. In addition to the direct effects of bile acids on circulation, a higher concentration of circulating endotoxins has deleterious effects on both the peripheral and renal microcirculation.

Liver:
High-grade biliary obstruction leads to increased intraductal pressure. There is bacterial overgrowth leading to cholangitis which eventually culminates to septic shock. Severe functional derangements of the hepatic function lead to alteration of liver regeneration. High-grade obstructive jaundice causes cell damage. Bile acids cause liver cell apoptosis by directly activating death receptors inducing oxidative damage and mitochondrial dysfunction, which as a combination strongly sensitizes to apoptosis. The net result of gross hepatic dysfunction is endotoxaemia. Long-standing biliary obstruction leads to secondary biliary cirrhosis. [16]

CNS:
Long-standing jaundice leads to the formation of pseudo transmitters which predispose to precoma and finally into a hepatic coma.

Clinical evaluation:
Jaundice is the main presenting symptom. The main aims of clinical evaluation are:

1. Determining the obstructive nature of jaundice.
2. Identifying the cause for obstructive jaundice.
3. Whether the aetiology is benign or malignant in nature.
4. If malignant then whether the disease is metastatic in nature.
5. Impact of jaundice on other organ systems.
6. The need for multiorgan system support.
7. Postulate an investigation algorithm based on the clinical findings.

Jaundice can be haemolytic, hepatocellular or obstructive in nature. (Table 2) The onset duration and progress of the jaundice is important. Rapidly developing jaundice associated with symptoms of pruritus, the passage of clay coloured stools and high coloured urine is seen in the obstructive pattern of jaundice. Significant nausea, vomiting and loose motions are suggestive of medical aetiology. History of alcoholism, intravenous drug abuse and multiple tattoos over the body go in favour of medical causes of jaundice. Persistent anaemia with mild abdominal symptoms is suggestive of the haemolytic pattern. History of drug ingestion followed by jaundice is seen in the hepatocellular type of jaundice. Multiple blood transfusions predispose hepatitis B and cirrhosis. [17]

Pain as an associated symptom is important in identifying the cause of obstructive jaundice. Jaundice associated with pain and fever suggestive of cholangitis is seen in bile duct stones. Jaundice typically shows waxing and waning. Intermittent attacks of right upper abdominal pain accompanied by vomiting is seen in cholecystitis. Severe pain and associated symptoms suggestive of pancreatitis can also cause transient obstructive jaundice. Painless progressive jaundice related to weight loss is highly suspicious of malignant aetiology. The previous history of biliary surgery presenting as jaundice is suggestive of a biliary stricture. History of inflammatory bowel disease presenting as jaundice is suggestive of primary sclerosing cholangitis. [18]

Weight loss, bone pains, and abdominal distension due to ascites are suggestive of malignant aetiology. History of abdominal masses is highly suggestive of malignancy.

Long-standing jaundice can affect other organ systems. Neurological symptoms are suggestive of impending coma. Renal

dysfunction is a common accompaniment in severe jaundice. Coagulopathies are seen in advanced stages. Generalized oedema due to hypoproteinaemia is a bad prognostic sign.

Physical examination reveals deepening of scleral icterus. Vital parameters may be altered if the patient presents late. Fever is an important feature. Pain, fever and jaundice is Charcot’s triad seen in cholangitis. In addition to these, if there is hypotension and mental obtundation, then that constitutes Reynold’s pentad. Reynold’s pentad is seen in suppurative cholangitis. Scratch marks of pruritus are commonly visible in obstructive jaundice. Signs of hepatocellular failure are seen in advanced cases. Flapping tremors and mental obtundation are red flags of poor prognosis. Fullness due to a mass in the left supraclavicular region is suggestive of an inoperable malignancy.

The abdominal examination needs to be done meticulously. Tenderness in the right hypochondrium suggests cholecystitis. A palpable gall bladder in a jaundiced patient is highly suggestive of malignant obstruction. (Courvoisier law) Hepatomegaly may be due to hepatitis or due to chronic cholestasis. Metastases in the liver can also cause hepatomegaly. A mass in continuity with the liver can be due to an advanced gall bladder tumour. Free fluid in the abdomen due to ascites is a sign of advanced malignant disease.

**Investigations:**

Investigations are aimed at

1. Determining the severity of illness
2. Urgency of intervention
3. Level of care required

Haematological investigations are very critical in the evaluation of obstructive jaundice. A complete blood count will reveal anaemia in malignant cases. Leucocytosis is seen in cholangitis. Total bilirubin will be raised. There will be a predominant increase in the direct reading component. Alkaline phosphatase is a membrane-bound enzyme located in the bile canalicular pole of the hepatocyte. A value of three times the upper limit of normal value is seen in the obstructive pattern of jaundice. It is elevated in almost all patients of biliary obstruction except for incomplete or intermittent obstruction. Gamma-glutamyl transpeptidase is raised in bile duct obstruction. Its level parallels the level of alkaline phosphatase in patients with cholestasis.

Serum transaminases (ALT, AST) are mildly elevated in cholestasis while markedly elevated in cholangitis. PT/INR is prolonged due to malabsorption of vitamin K. It is corrected by parenteral administration of vitamin K. If PT/INR improves with vitamin K injections, then it is more in favour of obstructive pattern while no improvement is seen in the liver parenchymal disease.

Renal function is best assessed and monitored by evaluation of serum creatinine, blood urea nitrogen and electrolytes. Viral markers for hepatitis B and C should be done in all cases of obstructive jaundice.

Ultrasound is a preliminary investigation. It enables documentation of the presence, extent and level of obstruction. [19]

It helps in

1. It is identifying the cause of obstruction.
2. Level of obstruction and degree of back pressure changes.
4. Splenic enlargement.
5. Ascites.

Endoscopic ultrasound further helps in the assessment of malignant obstruction. [20] Advantages are:

1. Helps in evaluating the distal CBD.
2. It is accurately diagnosing CBD calculi including small calculi in a nondilated system which are missed on routine ultrasonography.
3. Small resectable pancreatic masses can also be identified.

Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive investigation for evaluation of the biliary tract. It has a sensitivity of 95% and a specificity of 95% as well. It helps in diagnosing the cause and level of biliary obstruction.

Contrast-enhanced computed tomography (CECT) is the investigation of choice for staging the disease in cases of malignant obstruction. [21] CECT reveals the following:

1. Site of obstruction
2. Nature of obstruction, whether benign or malignant.
3. Extent or severity of backpressure changes
4. Echotexture of the liver.
5. Presence of metastases
6. Ascites.
7. Vascular encasement in cases of pancreatic head cancers.

Endoscopic retrograde cholangiopancreatography (ERCP) is the investigation of choice once a preliminary imaging assessment has been done. ERCP can be both diagnostic and therapeutic. The diagnostic role is to collect tissue for biopsy in periampullary growths or brush cytology samples. The exact level of the block and the severity of backpressure changes can also be ascertained. Therapeutic intervention is ideal for stones in the CBD, which saves unnecessary surgical exploration of the CBD. Preoperative stenting to relieve jaundice is of great help in preparing the patient for surgery. In inoperable cases, palliative stenting is useful to reduce the complications of jaundice. However, one needs to be careful of the complications of the procedure, which include pancreatitis, perforation, haemorrhage and sepsis by causing cholangitis. [22]

Percutaneous transhepatic cholangiography (PTC) is an alternative if ERCP fails as in hilar obstructions. It enables drainage of accumulated bile proximal to the obstruction. [23]

Prognosis in obstructive jaundice can be evaluated based on haematological and radiological findings. [24] Pitt’s score can be evaluated. Higher the score worst in the prognosis. (Table 3)
Conclusion
Understanding the pathophysiology of obstructive jaundice is essential for proper evaluation in order to prevent a delay in the diagnosis: a careful history and physical examination help in ascertaining the obstructive aetiology of jaundice. Various imaging modalities help in confirming the benign or malignant nature of the obstruction. ERCP has an added advantage of therapeutic intervention especially in choledocholithiasis. Once this road map is available the surgeon can formulate a surgical plan for the patient.

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References