# *Biliary Atresia Guideline*

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# Biliary Atresia Guideline

## Definition

Biliary atresia is an occlusive inflammatory cholangiopathy that affects intra- and extrahepatic bile ducts. This disease strictly affects neonates. There is no known analogous pathology that exists in older children or adults. Outcomes are much better with early diagnosis and treatment, which includes Kasai portoenterostomy and liver transplantation. Biliary atresia is subcategorized according to the presence or absence of other anomalies and malformations.

**Biliary atresia without any other anomalies or malformations** (Perinatal BA) – This pattern occurs in 70 to 85 percent of infants with BA. It is usual for children to be born without jaundice, but within the first two months of life, jaundice develops and stools become progressively acholic.[26]

**Biliary atresia in association with laterality malformations** – (Biliary atresia splenic malformation (BASM) or "embryonal" biliary atresia). This pattern occurs in 10 to 15 percent of infants with BA. The laterality malformations include situs inversus, asplenia or polysplenia, malrotation, interrupted inferior vena cava, and cardiac anomalies.[26]

**Biliary atresia in association with other congenital malformations** – This occurs in the remaining 5 to 10 percent of BA cases; associated congenital malformations include intestinal atresia, imperforate anus, kidney anomalies, and/or heart malformations.[26]

## Incidence

The incidence of biliary atresia in the US was 4.47 per 100 000 and was higher in females (risk ratio[RR], 1.43; 95% CI, 1.27-1.62), Asian/Pacific Islanders (RR, 1.89; 95% CI, 1.44-2.47), and blacks (RR, 1.30; 95% CI, 1.06-1.58) compared with whites. The incidence of biliary atresia increased by an average of 7.9% per year from 1997 to 2012.[28] In the United States, approximately 300 new cases are diagnosed each year. Biliary atresia accounts for about 75% of liver transplantations in those younger than 2 years. About one in ten babies with biliary atresia have other congenital conditions.

## Etiology

Biliary Atresia

Biliary Atresia is a rare disease of uncertain etiology.[26,34] Viral infections, toxic exposures, genetic mutations and other causes have all been implicated. Likely biliary atresia is the end result of several separate problems depending on what form a patient has as noted above.

**Guideline Inclusion Criteria**

Patients positively identified, or suspected of having, biliary atresia.

**Guideline Exclusion Criteria**

Patients diagnosed with disease other than biliary atresia.

**Differential Diagnosis of Neonatal Cholestasis**

Obstructive

- Biliary atresia
- Choledochal cyst
- Bile duct paucity
- Neonatal sclerosing cholangitis
- Inspissated bile syndrome
- Gallstones/biliary sludge
- Cystic fibrosis
- Caroli disease

Intrahepatic

- Viral infection: HSV, CMV, HIV, Parvovirus B19, other
- Bacterial infection: sepsis, UTI, syphilis
- Genetic/metabolic disorders: alpha-1 antitrypsin deficiency, tyrosinemia, galactosemia, progressive familial intrahepatic cholestasis, Alagille syndrome, disorders of bile salt meta, other
- Endocrine disorders: hypothyroidism, hypopituitarism
- Toxic: drugs, parenteral nutrition
- Systemic: shock, heart failure, neonatal lupus

Frequency of diagnoses in patients with Neonatal cholestasis
Biliary atresia 25% (range 2-55%)
Idiopathic neonatal hepatitis 25% (range 4 to 45%)
Infectious hepatitis (typically CMV) 11% (range 3 to 38%)
TPN associated 6% (range 7 to 30%)
Metabolic disease (galactosemia) 4%
Alpha-1 antitrypsin deficiency 4%
Alagille syndrome 1%
Progressive familial intrahepatic cholestasis (PFIC 1, 2, 3) 1%
Disorders of bile salt metabolism
Congenital disorders of glycosylation
Gestational alloimmune liver disease GALD
Overwhelming hemolysis such as Rh incompatibility
Cystic fibrosis (inspissated bile plug syndrome)

Idiopathic gallstones or sludge with obstruction
Various tumors
Neonatal sclerosing cholangitis (generally associated with histiocytosis x, diabetes insipidus, and rash)
Spontaneous perforation of the bile duct

The National Pediatric Gastroenterology Clinical Network has agreed that ALL infants with conjugated hyperbilirubinemia should be referred to a Pediatric Gastroenterologist or Hepatologist for initial investigation and subsequent management.

Pediatric Gastroenterology should consult surgery and interventional radiology immediately upon identifying a patient who might have biliary atresia. It is understood that time is of an essence. Any child reasonably considered to have biliary atresia will undergo rapid IR and then surgical evaluation. Early notification is intended to allow for anticipatory scheduling to prevent delays in surgical care.

**Diagnostic Evaluation**

Rapid evaluation of neonatal cholestasis with an emphasis on the early diagnosis of biliary atresia is essential to allow for early surgical palliation. Optimal outcomes may be achieved when the portoenterostomy is performed prior to 4 weeks of life. Evaluation of the bile ducts should be done via percutaneous or operative cholangiogram if another diagnosis is not apparent and biliary atresia is reasonably suspected. This evaluation requires clinical decision making by the pediatric gastroenterologist and pediatric surgeon. A combination of clinical, laboratory and radiological studies are used to diagnose BA.

In many cases, the concomitant work up of cholestasis will be occurring.

**Evaluation of Neonatal Cholestasis - Early identification and surgical treatment of biliary atresia**

*These evaluations are done concomitantly. Depending upon the age and presentation, many results will still be pending prior to the performance of a cholangiogram. The following are guidelines; not intended to be immutable or exhaustive.*

| | |
|---|---|
| **General** | • Matrix metalloproteinase-7 (MMP-7) may be useful for screening for EHBA. Turn around time less than 5 days. Positive and negative predictive values above 90 percent. (Offered by U of Cincinnati.) |
| **ID** | • Review maternal serologies<br>• Assess all infants for CMV (culture, PCR and/or serology IgG and IgM)<br>• Consider other infections, as appropriate (toxoplasmosis, UTIs, HSV, Rubella, echovirus, hepatitis A, B, C, Parvovirus etc.). Consider ophthalmology exam |

| | |
|---|---|
| **Anatomic** | • Complete abdominal ultrasound with doppler (choledochal cyst, presence of gallbladder, tumor, bile duct dilatation, gallbladder stones/sludge), associated spleen or renal anomalies<br>• CXR for heart size, vertebral anomalies<br>• Consider Ophthalmology exam for posterior embryotoxon (Alagilles)<br>• Echocardiogram (low threshold to obtain)<br>• Careful consideration for Alagille's syndrome including facies (cholangiograms may be misleading and misinterpreted when ducts are hypoplastic yet patent). |
| **Genetic metabolic** | • Review state screens<br>• CF additional genetic testing if indeterminate<br>• Obtain urine for reducing substances (if on breast milk or lactose containing formula)<br>• alpha 1 antitrypsin phenotype and level (one order for phenotype includes both)<br>• Emory genetic cholestasis panel (PFIC 1,2,3, Jag1, disorders of bile salt metabolism)<br>• Urine for abnormal bile acids to Cincinnati to evaluate for disorders of bile salt metabolism (some are treatable)<br>• Urine for organic acids looking mainly for tyrosinemia (presence of succinylacetone) which is treatable, and disorders of fatty acid oxidation (MCAD). Also obtain carnitine and acylcarnitine profile. (amino acids are rarely helpful)<br>• Consider disorders of lipid metabolism (Wolman, Niemann-Pick and Gaucher disease) which may present as neonatal cholestasis.<br>• Consider mitochondrial disorders may present with abnormal LFTs, hypoglycemia, coagulopathy and lactic acidosis. Neurological dysfunction is common.<br>• Consider disorders of glycosylation, multiorgan dysfunction is common. |
| **Endocrine** | • FT, TSH. Do not depend on State Screens.<br>• Preprandial glucoses as screen for panhypopituitarism, examine for high palate, wandering nystagmus, consider brain imaging for pituitary anatomy. |
| **Immune** | • Consider GALD if early liver failure.<br>• Consider HLH |

**History and Physical Examination**

The physician will conduct a history and physical examination of the patient. Symptoms of biliary atresia may include:

- Jaundice
- Dark urine
- Pale stools (stool color is key to early detection)

- Swollen abdomen
- Large liver and spleen
- Poor weight gain/malnutrition

**Laboratory Tests**

Baseline labs include: CBC, BMP, PT, PTT, Hepatic Function tests (AST, ALT, GGT, total and direct bilirubin, albumin, total protein, globulin).
If there is sufficient time an MMP-7 will be obtained as it appears to be one of the most specific tests available for Biliary Atresia (33) but may take 5 days to return. An MMP-7 less than 83 is associated with a low probability of biliary atresia. 83-100 is considered borderline and anything greater than 100 is considered high likelihood for biliary atresia.
Additional laboratory testing will be guided by clinical features.

**Imaging**

All patients with suspected biliary atresia will undergo screening ultrasonography. Additional studies may include magnetic resonance cholangiography, percutaneous or intraoperative Cholangiogram, or HIDA scan.

- Cholangiogram is performed when biliary atresia is clinically suspected and another diagnosis is not forthcoming.
- Percutaneous transhepatic cholecysto-cholangiogram (via the gallbladder) vs operative cholangiogram. Timing is ideally early in the 4th week of life (21-25 days of life) or if the child is presenting later, then as soon as possible.
    - Note: there is concern that percutaneous cholangiogram could miss a "proximal atresia" since contrast may not reflux proximal into the hepatic ducts. The simultaneously obtained liver biopsy will help to identify these unusual cases.
- A percutaneous cholangiogram with liver biopsy is considered after consultation with IR who will assess the likelihood of a successful study based upon the ultrasound. If no target and a low likelihood of success then a percutaneous cholangiogram will not be attempted. If the percutaneous cholangiogram is not successful or deemed unlikely to be successful then pediatric surgery (biliary team) will perform operative cholangiogram and Kasai if necessary.

Noteworthy Features:

- The absence of direct/conjugated hyperbilirubinemia at birth likely excludes biliary atresia. The absence of direct hyperbilirubinemia at presentation for evaluation absolutely excludes biliary atresia.
- Acholic stools when present are highly suggestive of biliary atresia. However acholic stools are inconsistently present prior to 4 weeks of age and may be seen with other conditions.

- Laboratory including ALT, AST and GGT are inconsistently elevated in the first 4 weeks of life and cannot be depended upon to rule out biliary atresia.
- Hepatosplenomegaly on physical exam likewise is inconsistently present in the first 4 weeks of life and cannot be depended upon.
- Matrix metalloproteinase-7 (MMP-7) has positive and negative predictive values above 90 percent (33). Not standard of care as of yet.

**Initial Surgical Management**

The Kasai procedure is performed upon the diagnosis of biliary atresia. The only contraindications for a Kasai is a patient who presents so delayed that their liver disease is felt to be nonrecoverable and immediate liver transplant is needed.

The Kasai procedure is the first-line treatment of biliary atresia. It involves the removal of the gallbladder and damaged bile ducts that normally connect the liver to the intestine. A segment of the child's small intestine is then sewn to the liver to enable whatever bile the liver is making to flow into the intestine.

If not diagnosed and treated, complications of biliary atresia include:

- Progressive cirrhosis
- Ascites
- Enlargement of the spleen
- Portal hypertension
- Bleeding from varices
- Malnutrition from inability to absorb fat

**Surgical Technique - Kasai Hepatoportoenterostomy** [19-25]

Recommendations based on best practices as described in the literature. Goals of surgery are to establish biliary drainage, clear jaundice and avoid cholangitis.

1. Chevron incision
2. Inspect liver and biliary tree, and confirm the diagnosis with a cholangiogram
3. Favorable results have been obtained with smaller incisions and minimal mobilization of the liver, resulting in:
    i. Decreased mortality
    ii. Decreased scarring
    iii. Decreased bleeding
    iv. Technically simpler subsequent liver transplantation
4. Divide distal fibrotic common bile duct, dissect proximally to the portal plate
5. Transect fibrous remnant posterior to the portal vein, avoid cautery or sutures
    a. IR-fluorescence with indocyanine green has not yet shown to aid in excision of the remnant

   b. Perform a frozen section of the portal plate to ensure patent bile ductules
6. Prepare the Roux-en-Y anastomosis by first dividing the small bowel at a location that provides for enough length and tension-free passage to the hilar plate
   a. The Roux limb should be at least 40-45 cm long
   b. The Roux limb should pass behind the transverse colon (retrocolic)
7. The enteroenterostomy should be performed per routine, data does not support creation of an anti-reflux valve
8. Perform a wedge and core needle biopsy of the liver
9. A closed suction drain is placed adjacent to the hepaticoenterostomy
10. Epidural catheter placement has been shown in retrospective studies to decrease time to extubation, improve pain control, and perhaps decrease ICU and hospital stay and should be encouraged
11. Laparoscopic and robotic-assisted Kasai has been shown to result in increased early complications and decreased native liver survival
12. Most components of diagnosis and treatment of biliary atresia have not been submitted to rigorous randomized controlled trials

**Clinical Care - In-Hospital Management after Kasai**

Patients who have just undergone a Kasai Portoenterostomy for biliary atresia (BA) should be managed on the Pediatric Surgery service with consultation from the Pediatric Gastroenterology service. These patients may be managed on the regular inpatient floor or in an intermediate or intensive care unit setting if necessary. Routine post operative care should include administration of intravenous fluids, monitoring of urine output, assessment of bowel function, administration of perioperative antibiotics and observation for signs of operative complications such as bleeding, bowel injury, obstruction, or anastomotic leak.

In addition, infants recovering from a Kasai may benefit by further medical treatment although there is not clear consensus or extensive controlled data on what this regimen should be [5]. Centers vary widely in post operative care for these patients but adjuvant treatment that is standard includes choleretics, nutritional supplementation, fat soluble vitamin supplementation, and prolonged antibiotics for prevention of cholangitis [5,1]. Routine use of glucocorticoids has had conflicting evidence of efficacy as will be discussed below.

**Choleretics**

Choleretic agents such as Ursodeoxycholic acid (UDCA) are naturally occuring hydrophilic bile acids that increase the hepatic clearance of toxic endogenous bile acids and promote a cytoprotective effect on hepatocytes. Although good prospective randomized trials in Kasai patients are not available, It has been demonstrated in many adult studies [1] and some

pediatric studies [2,3,4] to be beneficial for hepatic function. The effect of UDCA in adult conditions such as primary biliary cholangitis has been dramatic in lowering liver enzyme levels and decreasing mortality and need for transplant. In one prospective study of children with successful Kasai's who had been on UDCA for greater than a year, cessation of UDCA caused elevation of liver enzymes (ALT, GGT, AST) in 13/16 children which was reversed with restarting of the agent [3].

> ***Recommendation****:* UDCA may aid in the clearance of hepatic toxin and benefit hepatic function. For this reason, administration of UDCA is standard treatment for biliary atresia patients and should be delivered at a dose of 15-30 mg/kg/day. If the bilirubin level is noted to be greater than 15 mg/dl, UDCA should be stopped to avoid toxicity [1].

**Nutritional supplementation**

Cholestasis with malabsorption and liver inflammation often results in slow weight gain in patients with biliary atresia before and after surgery. A proactive rather than reactive approach to nutritional supplementation is recommended.. Malnutrition and growth failure are indications for liver transplant but also increase the risk of complications of liver transplantation in BA patients. Estimated energy requirements for these patients may be 130-150% of healthy babies [1]. Early institution of nasogastric tube feedings is recommended for infants who are not gaining weight appropriately and who are unable to consume this increased amount orally. Feedings should be concentrated to 24 (sometimes 27 cal/ounce if necessary) to meet these increased metabolic needs. Expressed breast milk concentrated with formula is preferred. Protein needs of 3-4 g/kg/day should be met for these infants by augmented feedings in order to establish adequate growth and weight gain. Glucose polymers and Medium Chain Triglycerides supplements may also be useful for providing calories. The advantage of MCT supplements in that they are not dependent on bile acids for absorption and are calorically dense.

Because of the possibility of progressive portal hypertension and development of gastric varices, placement of a feeding gastrostomy is in general not recommended [1].

> ***Recommendation***: Patients with biliary atresia after Kasai are at risk for malnutrition and once bowel activity has been established should be advanced to full diet. If they are unable to take 130% of estimated needs and weight gain is inadequate, then there should be early initiation of more calorically dense formula If caloric intake and weight gain remain inadequate the nasogastric tube feedings should be commenced promptly.

**Fat-soluble vitamin supplementation**

Absorption of fat soluble vitamins (A, D, E, and K) in patients with biliary atresia is markedly impaired and specific supplementation is usually necessary until they have cleared their jaundice after a successful Kasai. If total bilirubin levels decrease below 2 mg/dl, then supplementation with standard multivitamins and less frequent vitamin levels are appropriate. Table 1 has a suggested monitoring regimen as well as repletion recommendations.

**TABLE 1. Fat-soluble vitamin deficiencies and supplementation for patients with biliary atresia and cholestasis**

# Table 1: Fat-soluble vitamin supplements for biliary atresia

**Fat-soluble vitamin deficiencies and supplementation for patients with biliary atresia and cholestasis**

| Fat-soluble vitamin | How to monitor | Standard oral treatment recommendation | Signs and symptoms of deficiency | Recommended supplementation in setting of deficiency |
|---|---|---|---|---|
| Vitamin A | Measure serum or plasma retinol and RBP<br>Interpretation:<br>▪ Normal range for retinol 19 to 77 mcg/dL<br>▪ Retinol – RBP <0.8 mol/mol defines deficiency when retinol <20 mcg/dL | Liquid vitamin A:<br>▪ <10 kg – 5000 IU/day*<br>▪ ≥10 kg – 10,000 IU/day | ▪ Keratinization of the skin and mucous membranes<br>▪ Ocular effects such as xerophthalmia, night blindness, xerosis, and bitot spots<br>▪ Retinol:RBP molar ratio <0.8 and serum retinol <20 cgg/dL | Liquid vitamin A 5000 IU/day by mouth; recheck levels in 1 month<br>**OR**<br>25,000 to 50,000 IU/day by mouth for 1 to 4 weeks; recheck levels weekly<br>**OR**<br>50,000 IU intramuscularly once/month up to 2 months; recheck levels monthly |
| Vitamin D | Measure serum 25-OH vitamin D<br>Interpretation:<br>▪ Optimal levels >30 ng/mL | Cholecalciferol or ergocalciferol – 2000 to 5000 IU/day (50 to 125 mcg/day) | ▪ Rickets, fractures, osteomalacia<br>▪ 25-OH vitamin D <15 ng/mL | Cholecalciferol or ergocalciferol 1200 to 4000 IU/day by mouth; recheck levels in 1 month<br>If child remains deficient, give 4000 to 8000 IU/day; recheck levels in 1 month<br>**OR**<br>Give 1,25-$OH_2$ vitamin D 0.05 to 0.2 mcg/kg/day; recheck serum 1,25-$OH_2$ vitamin D levels in 1 month |
| Vitamin E | Measure serum vitamin E and total lipids<br>Interpretation:<br>▪ Normal vitamin E:total lipid ratio >0.6 mg/g (age <1 year) or >0.8 mg/g (age >1 year) | TPGS – 15 to 25 IU/kg/day (10 to 17 mg/kg/day) | ▪ Peripheral neuropathy, ataxia, ophthalmoplegia<br>▪ Vitamin E:total lipid ratio <0.6 mg/g (age <1 year) or <0.8 mg/g (age >1 year) is deficient | If deficient, 50 IU/kg/day of TPGS; recheck levels in 1 month |
| Vitamin K | Measure PT, INR, and PIVKA-II | Vitamin K1 2 to 5 mg daily | ▪ Prolonged PT, increased INR (INR >1.2), elevated PIVKA-II<br>▪ Coagulopathy, bruising, bleeding | If INR >1.5 and ≤1.8, give 5 mg vitamin K1 daily by mouth and/or 2 to 5 mg vitamin K intramuscularly 1 time; recheck PT/INR in 1 to 2 days |

The doses in this table are designed for **cholestatic**/jaundiced infants and children with biliary atresia. If the cholestasis resolves after Kasai portoenterostomy and vitamins are replete, children can be transitioned to standard doses of multivitamins, with routine monitoring of fat-soluble vitamins as outlined above. These doses are consistent with society guidelines[1].

RBP: retinol-binding protein; IU: international units; 25-OH vitamin D: 25-hydroxyvitamin D; 1,25-$OH_2$ vitamin D: 1,25-dihydroxyvitamin D; TPGS: tocopherol polyethylene glycol 1000 succinate (water-miscible form of vitamin E); PT: prothrombin time; INR: international normalized ratio; PIVKA-II: protein induced by vitamin K absence II; vitamin K1: phytonadione.
* For vitamin A, 1 IU = 0.3 micrograms retinol or 0.6 micrograms beta-carotene.

*Reference:*

https://www.uptodate.com/contents/image/print?imageKey=PEDS%2F51569&topicKey=PEDS%2F14369&search=biliary atresia&rank=1~60&source=see_link&sp=0 10/28/2020

***Recommendation**:* Jaundiced infants after Kasai are particularly susceptible to vitamin deficiencies and should be monitored and supplemented as needed. This supplementation may take place in the hospital as well as outpatient.

**Prevention of Cholangitis**

There are many factors felt to be playing a role in the high (40-90%)[1] rate of cholangitis noted in patients after a Kasai Portoenterostomy. Bile stasis in the Roux limb, exposure of the remnant biliary system to intestinal bacteria secondary to absence of the sphincter of Oddi, translocation of bacteria, or even hematogenous spread from the portal vein are all felt to play a role [10]. It should be suspected in any post-Kasai patients with fever, fussiness, elevated bilirubin or transaminases, or decreased coloration of stool. Blood cultures may be positive but frequently treatment is empiric based on these sometimes subtle findings.

Repeated episodes of cholangitis have been found to be associated with decreased hepatic function over time and need for liver transplant [7, 9] prompting the promotion of prophylactic antibiotics for post Kasai patients. In a small (n=37) prospective study by Bu et al, treatment with a regimen of either Tmp/Smz or Neomycin led to approximately half the recurrence of cholangitis and better survival as compared to a historical control group that did not receive prophylaxis [8]. Only 3 other good quality controlled studies have looked at this question and they were all retrospective cohort studies [10]. The smallest of these studies (n=41) demonstrated a decreased rate of cholangitis with prophylactic use of TMP/SMZ [11], but the remaining larger studies showed no improvement in the rate of cholangitis with antibiotic treatment [12,13]. Interestingly, in the larger of these 2 studies (n=204), although antibiotic use was not associated with decreased rates of cholangitis, it was associated with increased 4 year transplant-free survival rate (54% vs 34%) [13].

**Recommendation**: Although evidence for prophylactic antibiotic administration is of low quality, the downside to their administration is small and three of four controlled studies do demonstrate some benefit. Patients post Kasai portoenterostomy should be treated with either TMP/SMZ (4mg/kg/d TMP and 20mg/kg/d SMZ) or Neomycin(25mg/kg/d ) for potential prophylaxis of cholangitis.

**Glucocorticoids**

Because of the inflammatory hepatic changes noted in patients with biliary atresia and those post Kasai, as well as the choleretic effect of glucocorticoids, steroids have been used at many centers for years. The documented cytopathology of this disease includes increased vascular adhesion molecules, abnormal expression of HLA II, mononuclear cell infiltrate, and a surge of cytokines, among other changes [14]. The first prospective randomized controlled trial to look at

the potential benefit of steroids was by Davenport in 2007 [15] and demonstrated with low dose (2mg/kgd of methylprednisolone) that while early bilirubin clearance may be improved, no longer term (>6months) benefit was noted in terms of persistently low bilirubin, survival, or need for liver transplant. This group did a follow up study comparing higher dose (5mg/kg/d) steroids with their previous and ongoing placebo controlled patients and found improved bilirubin clearance and other biochemistries at one month but no change in 4 year survival or transplant rate. The START trial in 2014 [16] was a larger (n=140) prospective randomized controlled trial of 4mg/kg/d of steroids versus placebo. This study similarly did not demonstrate any improvement in survival or transplant rate and also didn't find significant resolution of hyperbilirubinemia. The authors of the START trial noted similar high rates of complications in the steroid and placebo group but noted that these complications were occurring earlier in the patients given steroids. This group noted in a later study [17] that patients treated with steroids had at least temporary a decrease in velocity of head circumference and linear growth. A meta-analysis from 2017 of cohort and controlled trials found a similar result in that while early (1 yr) clearance of bilirubin may be improved with steroid administration, there was no long term effects at 2 years on the rate of bilirubin clearance, liver transplant rate, or survival [18].

> ***Recommendation:*** Routine use of steroids for post-Kasai patients may result in temporary clearance of jaundice but evidence is lacking for benefit long term on native liver survival. There is some evidence that patients treated with steroids may have earlier complications including at least temporary growth inhibition. While there may be selected cases where steroids may be of benefit, routine use should not be employed.

**Clinical Outcome**

Biliary atresia, when untreated, is fatal within 2 years, with a median survival of 8 months. The natural history of biliary atresia has been favorably altered by the Kasai portoenterostomy. Approximately 25 to 35% of patients who undergo a Kasai portoenterostomy will survive more than 10 years without liver transplantation. Another one third of the patients with a good surgical outcome (resolution of jaundice) go on to develop and require liver transplantation before age 10. For the remaining one third of patients, the surgical outcome is poor with persistent jaundice and early progression to end-stage liver disease and the need for liver tranplantation in the first 2 years of life. . The portoenterostomy should be done before there is irreversible sclerosis of the intrahepatic bile ducts. Consequently, a prompt evaluation is indicated for any infant older than 14 days with jaundice to determine if conjugated hyperbilirubinemia is present. While considering other etiologies (infectious, metabolic and endocrine disorders) and when biliary atresia is reasonably suspected, then cholangiogram

(percutaneous vs open) should be done expeditiously. This should be followed by Kasai portoenterostomy when appropriate.[30]

- The short-term benefits for patients undergoing Kasai portoenterostomy are well-documented; however, 80–90% of these infants will eventually require liver transplantation.
- Predictors of a worse outcome after portoenterostomy include operative age greater than 2 months. The literature supports a benefit of diagnosis and surgical treatment prior to 1 months of age.
- Presence of cirrhosis at initial biopsy, absence of bile ducts at transected liver hilum and subsequent development of varices or ascites are predictors of a poor outcome.
- The long-term outcome of liver transplantation for children with biliary atresia has been excellent.
- Data suggest that children with BASM have poorer outcomes compared with those with BA without malformations or anomalies, possibly due to the associated cardiac abnormalities.

**Critical Points of Evidence**

***Evidence Supports***

*General*

- Surgical treatment with hepatoportoenterostomy (Kasai procedure) is the gold standard. *(Strong recommendation, High Quality Evidence)*
- Open Kasai portoenterostomy (as opposed to laparoscopic kasai) may be associated with superior early clearance of jaundice rate and 2-year native liver survival rate. *(Moderate recommendation, Moderate Quality Evidence)*
- Early diagnosis is critical for a successful Kasai procedure. *(Strong recommendation, High Quality Evidence)*

*Ultrasound*

- The triangular cord sign and gallbladder abnormalities are the two most accurate and widely accepted ultrasound characteristics associated with biliary atresia. Other ultrasound characteristics are less valuable for diagnosis or exclusion of biliary atresia.[27] *(Strong recommendation, High Quality Evidence)*

*Choleretics*

- Ursodeoxycholic Acid (UDCA) has been shown to benefit hepatic function and administration of UDCA is standard treatment for biliary atresia patients. Appropriate dosing is 15-30 mg/kg/day. If the bilirubin level is noted to be greater than 15 mg/dl, UDCA should be stopped to avoid toxicity[1]. (See Choleretics for additional information)

*Cholangitis*

- Although evidence for prophylactic antibiotic administration is of low quality, the downside to their administration is small and three of four controlled studies do demonstrate some benefit. Patients post Kasai portoenterostomy should be treated with either TMP/SMZ (4mg/kg/d TMP and 20mg/kg/d SMZ) or Neomycin(25mg/kg/d ) for potential prophylaxis of cholangitis. *(Moderate recommendation, Low Quality Evidence)* (See Prevention of Cholangitis for additional information)
- Cholangitis is one of the most important determinants of long-term survival after the Kasai procedure.

*Nutritional Supplementation*

- Patients with biliary atresia after Kasai are at risk for malnutrition and once bowel activity has been established should be advanced to full diet. If they are unable to take 130% of estimated needs, then supplementation with calorically more dense formula or MCT oil should be initiated and nasogastric feedings should be commenced if oral intake is inadequate. TPN may be indicated in patients for supplementation in patients with a failed Kasai and while awaiting transplant. *(Strong recommendation, High Quality Evidence)* (See Nutritional Supplementation for additional information)

*Vitamin Supplementation*

- Jaundiced infants after Kasai are particularly susceptible to vitamin deficiencies and should be monitored and supplemented as needed. This supplementation may take place in the hospital as well as outpatient. *(Strong recommendation, High Quality Evidence)* (See Fat Soluble Vitamin Supplementation for additional information)

*Perioperative Management Considerations*

- TPN- Routine use of TPN has not been demonstrated in literature to be advantageous however, in patients with failed Kasai, nutritional supplementation with TPN has been felt to be advantageous for weight gain and pre-transplant preparation. *(Strong recommendation, High Quality Evidence)*
- A central line should not be routinely placed, only used for malnourished patients or those with poor venous access. *(Moderate recommendation, Moderate Quality Evidence)*
- Total and direct bilirubin in early follow-up after HPE was highly predictive of outcome. Efforts to improve bile flow after HPE may lead to improved outcome in children with biliary atresia.[29]

Screening

- There are data that patients with Biliary Atresia have elevated normal direct/conjugated bilirubin (DB/CB) levels at birth. To detect affected infants earlier and improve outcomes, one could (1) screen all newborns for elevated DB/CB levels, rather than just those who appear jaundiced; and then (2) follow all newborns with elevated DB/CB levels, rather than just those with DB:TB ratios>0.2.[31] *(Strong recommendation, High Quality Evidence)*

***Evidence Lacking/Inconclusive***

- Bowel Prep - There is no convincing evidence that bowel prep improves outcomes or infection rates prior to Kasai and cannot be routinely advised. *(Moderate recommendation, Moderate Quality Evidence)*
- Adjuvant therapy using high-dose steroids may accelerate the clearance of jaundice but studies have not been convincing that they improve native liver survival.[32]
- Recent reports vary whether laparoscopic Kasai is inferior or equal to an open procedure. There is no clear evidence that it is superior and further study is needed. (34,35) *(Moderate recommendation, Moderate Quality Evidence)*

*Glucocorticoids*

- Routine use of steroids for post Kasai patients may result in temporary clearance of jaundice but evidence is lacking for its benefit long term on native liver survival. There is some evidence that patients treated with steroids may have earlier complications including at least temporary growth inhibition. While there may be selected cases where steroids may be of benefit, routine use should not be employed. *(Moderate recommendation, Moderate Quality Evidence)* (See Glucocorticoid for additional information)

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