



Atypical causes of cholestasis

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Abstract

Cholestatic liver disease consists of a variety of disorders. Primary sclerosing cholangitis and primary biliary cirrhosis are the most commonly recognized cholestatic liver disease in the adult population, while biliary atresia and Alagille syndrome are commonly recognized in the pediatric population. In infants, the causes are usually congenital or inherited. Even though jaundice is a hallmark of cholestasis, it is not always seen in adult patients with chronic liver disease. Patients can have "silent" progressive cholestatic liver disease for years prior to development of symptoms such as jaundice and pruritus. In this review, we will discuss some of the atypical causes of cholestatic liver disease such as benign recurrent intrahepatic cholestasis, progressive familial intrahepatic cholestasis, Alagille Syndrome, biliary atresia, total parenteral nutrition induced cholestasis and cholestasis secondary to drug induced liver injury.

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Key words: Cholestasis; Benign recurrent intrahepatic cholestasis; Progressive familial intrahepatic cholestasis; Alagille syndrome; Biliary atresia; Total parenteral

nutrition; Drug induced liver injury

Core tip: The approach and management of cholestasis remain an important aspect of the clinical practice. Different causes of cholestasis have been identified. We will review in this paper some atypical causes of cholestasis that clinicians should be aware off and consider in their approach to management of patients with cholestasis.

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INTRODUCTION

Cholestasis is the impairment of bile flow due to biliary tract obstruction or impairment of bile acid uptake, conjugation, or excretion^[1]. It is classified as intrahepatic or extrahepatic. Intrahepatic cholestasis primarily involves the bile canaliculi and the intrahepatic bile ducts. Extrahepatic cholestasis involves the extrahepatic ducts, the common hepatic duct or the common bile duct.

The diagnosis of intrahepatic cholestasis is made once extrahepatic biliary obstruction is ruled out by various imaging modalities, and depending on the clinical situation, may be confirmed by liver biopsy. Among the most common causes of cholestatic liver disease are primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). As those diseases are discussed thoroughly in guidelines from the American Association for Study of Liver Disease and the European Association for Study of Liver Disease, the primary focus of this review is discussion of atypical causes of cholestasis.

BENIGN RECURRENT INTRAHEPATIC CHOLESTASIS

Originally described by Summerskill and Walshe, benign

recurrent intrahepatic cholestasis (BRIC) is a rare genetic disorder characterized by repeated episodes of severe pruritus and jaundice lasting from weeks to months^[2]. The pathophysiology of BRIC is not well understood. It is an autosomal-recessive disease with incomplete penetrance secondary to a mutation in the *ATP8B1* gene located on chromosome 18. It encodes for the FIC1 protein, an aminophospholipid flippase^[3-6].

Pruritus is commonly the prodromal symptom of each attack, followed by jaundice several weeks later. Patients may also present with malaise, anorexia, nausea, vomiting, steatorrhea, malabsorption, and weight loss. Laboratory studies show a rise in the serum alkaline phosphatase (ALP) level following the onset of pruritus. It is subsequently followed by a rise in serum conjugated bilirubin level, while serum gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase, and alanine aminotransferase (ALT) levels remain normal or only mildly elevated.

No specific treatment is available for preventing or reducing the duration of attacks. Treatment is primarily focused on symptomatic relief until spontaneous resolution of each episode. Prognosis remains good without progression toward cirrhosis^[7]. With resolution of an attack, pruritus will rapidly and completely resolve along with gradual improvement to jaundice and liver enzyme abnormalities. Patients generally remain asymptomatic between attacks with asymptomatic periods lasting from months to years^[7].

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Progressive familial intrahepatic cholestasis (PFIC) is a rare heterogeneous group of autosomal-recessive disorders resulting in intra-hepatic cholestasis during childhood. PFIC usually presents during the neonatal period or within the first year of life. Unlike BRIC, it will eventually progress to cirrhosis and death. The exact incidence of PFIC is unknown but it has been estimated to occur in 1/50000 to 1/100000 births^[8]. Three types of PFIC have recently been identified based on genetic testing. They are the results of mutations in three different genes: *ATP8B1* gene encoding for the FIC1 protein in PFIC1 (similar to BRIC), *ABCB11* gene encoding for the bile salt export pump protein in PFIC2, and *ABCB4* gene encoding for the multidrug resistance-associated protein 3 (MRP3) in PFIC3^[9-11]. FIC1 functions as an aminophospholipid flippase. It is also expressed in many extrahepatic tissues. A disturbed function of FIC1 results in loss of lipid asymmetry in the canalicular membrane of the hepatocytes. This disturbance leads to impaired biliary bile acid secretion by altering the bile salt export pump (BSEP) in the liver^[9]. MRP3 is a phospholipid translocator involved in the biliary phosphatidylcholine excretion. It is predominantly expressed in the canalicular membrane of the hepatocytes. In PFIC3, cholestasis is mainly the result of the absence of the biliary phospho-

lipids in the setting of the hydrophobic bile salt exposure. There is evidence that the loss of the FIC1 flippase increases the susceptibility of the canalicular membrane to damage from the hydrophobic bile salts^[12].

The onset and severity of jaundice and cholestasis differ with each type of PFIC. PFIC1 generally presents within the first month of life with recurrent episodes of jaundice and eventually progresses to permanent jaundice. PFIC2 is more severe compared to PFIC1, usually resulting in permanent jaundice at time of presentation within the first month of life and liver failure within the first year of life. PFIC2 may be complicated by hepatocellular carcinoma and cholangiocarcinoma. Patients with PFIC1 may have extrahepatic features not seen in PFIC2, such as watery diarrhea, short stature, sensorineural deafness, pancreatitis and liver steatosis. PFIC3 generally occurs later in life with majority of patients presenting either in late infancy, childhood, or even early adulthood^[11]. Serum GGT level is normal in PFIC1 and PFIC2 but is elevated in PFIC3. The types of PFIC can be distinguished using these clinical and laboratory features along with immunostaining of liver biopsy tissue, biliary lipid analysis, and DNA/RNA sequencing. Ursodiol should be considered in all types of PFIC but appears to be most beneficial in those with less severe disease^[11]. Liver transplantation is currently the only definitely treatment available for PFIC.

ALAGILLE SYNDROME

Alagille syndrome (ALGS), also known as Alagille-Watson syndrome or arteriohepatic dysplasia, is an autosomal-dominant disorder with variable penetrance. ALGS may involve five body areas (liver, heart, skeleton, face, and eye). The involvement of these areas is the basis for the "Classic Criteria" described by Alagille to establish the diagnosis^[13] (Table 1). Other findings include vascular malformations, vascular accidents, and renal structural problems. The severity of the disease is determined primarily by the degree of the liver and cardiac involvement.

The etiology in approximately 97% of cases is due to mutations in the *JAG1* gene^[14,15] while the remainder is due to mutations in the *NOTCH2* gene^[16]. Both genes are involved in the highly conserved Notch signaling pathway. A diagnosis is made if the Classic Criteria is met (bile duct paucity with at least three of five clinical features) or by genetic testing of *JAG1* and *NOTCH2* if only some features of ALGS are present^[17]. Accurate diagnosis continues to be challenging because some clinical features are not specific to ALGS and overlap with other genetic disorders and syndromes.

Patients usually present at birth or within the first three months of life with jaundice, alkaline phosphatase elevation, and conjugated hyperbilirubinemia, due to bile duct paucity as seen on liver biopsy. Bile duct obliteration is progressive and increases with age. It eventually results in cirrhosis and liver failure. The most common congenital heart disease seen in ALGS is peripheral pulmonary stenosis^[18,19]. Other abnormalities include atrial septal

Table 1 The “Classic criteria” for diagnosis of Alagille Syndrome

Organ system	Disorder	Description
Liver	Cholestasis	Chronic cholestasis due to bile duct paucity
Heart	Congenital heart disease	Peripheral pulmonary artery hypoplasia or stenosis
Musculoskeletal	Vertebral abnormalities	“Butterfly” vertebral arch defects
Face	Dysmorphic facies	“Triangle face” with broad forehead, deep-set eyes, upslanting palpebral fissures, prominent ears, straight nose with bulbous tip, and pointed chin
Eye	Anterior chamber defects	Posterior embryotoxon (prominent Schwalbe's line)

defect, ventricular septal defect, and Tetralogy of Fallot^[18,19].

Pruritus may be very severe and difficult to treat in ALGS. Special attention is paid to nutrition as growth retardation is seen in a significant portion of patients. Liver transplantation appears quite successful with a 5-year survival rate of 80% but is linked to the degree of cardiac and renal dysfunction^[20,21].

BILIARY ATRESIA

Biliary atresia (BA) is a rare disorder of neonates with multiple etiologies resulting in obliteration of the biliary tree. BA is classified into three types based on the most proximal level of biliary obstruction. BA type 1 has patency to the common bile duct. BA type 2 has patency to the common hepatic duct. BA type 3, the most common type occurring in greater than 90% of cases, results in complete occlusion of extrahepatic bile ducts up to the level of the porta hepatis. In the majority of cases, BA is an isolated finding not associated with any other congenital abnormalities. Less common clinical variants associated with congenital abnormalities include cystic biliary atresia (BAS) which is associated with cystic changes within the obliterated biliary tree^[22] and biliary atresia splenic malformation syndrome which is associated with asplenia or polysplenia, situs inversus, absence or obliteration of the inferior vena cava, and cardiac abnormalities^[23].

The incidence of BA is estimated to be from 1/14000 to 1/20000 live births in European countries^[24,25], and 1/15000 live births in the United States^[26]. It is most common in East Asian countries with up to 1/2700 live births in Taiwan^[27,28]. The pathogenesis is poorly understood but probably multifactorial. Current hypotheses include perinatal viral infections, inflammatory and immune dysregulation, genetic predisposition, abnormality in embryogenesis, and toxic insult^[29].

Liver biopsy is generally performed in all suspected cases of BA and is also used to rule-out other causes of neonatal cholestasis. Early diagnosis is essential and should be followed promptly by the Kasai procedure. The Kasai procedure involves complete resection of the gallbladder and extrahepatic biliary tree at the porta hepatis to expose any remaining patent ductules. The porta hepatis is then anastomosed to a jejunal Roux-en-Y limb, allowing for drainage of bile into the intestinal tract. Complete resolution of jaundice with restoration

of liver function can be achieved. However, the majority of patients will eventually require liver transplantation, since only 23%-25% of patients can survive without liver transplantation until the age of 20^[30,31].

Nevertheless, prognosis remains good with an overall survival rate with or without liver transplantation of upwards of 89% at 10 years in the United Kingdom^[32] and up to 90% at 20 years in Switzerland^[33].

SEPSIS

Cholestasis is commonly seen in the setting of sepsis due to multiple mechanisms. Generally, a conjugated hyperbilirubinemia is seen in the ranges of 2-10 mg/dL. It is associated with an elevation in the serum ALP typically no greater than 2-3 times the upper limit of normal and often seen without significant elevation in serum transaminases^[34].

The principal mechanism of cholestasis during sepsis is from disruption of bile flow. Bile salts are normally synthesized in hepatocytes or reabsorbed in the intestine and imported into the hepatocytes using the sodium-dependent transporter taurocholate cotransporter and organic anion transport proteins (OATPs). Bile salts are then excreted into canaliculi by the BSEP and MRP proteins. Similar to its effect on bilirubin metabolism, lipopolysaccharide (LPS) has also been shown to impede bile acid transport in animal models through both inhibition of transporter activities as well as down-regulation of gene expressions^[35-37]. This ultimately leads to decreased bile flow, cholestasis, and jaundice without biliary obstruction.

Cholestasis associated with sepsis is also attributable to impairment in bilirubin metabolism. Bilirubin is normally transported into hepatocytes by OATPs, conjugated by the uridine diphosphate-glucuronosyltransferase enzyme, and excreted into bile by the canalicular multispecific organic anion transporter 1 (cMOAT) or commonly known as the multidrug resistance-associated protein 2 (MRP2). Endotoxin, specifically LPS, has been shown in a rat model of sepsis to inhibit bilirubin uptake and excretion without significant effect on conjugation^[38]. The mechanism is probably due to dysfunction of OATPs and MRP2 by endotoxemia^[35].

Though not a direct cause of cholestasis, hemolysis during sepsis may also lead to jaundice by releasing large quantities of bilirubin which overwhelms the liver's capacity to uptake and excrete bilirubin. This can occur through a

variety of mechanisms including toxin secretion, such as with *Clostridium perfringens* infection^[39,40], direct destruction of red blood cells, glucose-6-phosphate dehydrogenase deficiency, or immune-mediated hemolysis. An example of immune-mediated hemolysis is “cold agglutinin” association with *Mycoplasma pneumonia* and *Legionella* infections which causes intravascular hemolysis at low temperature^[41]. Drug-induced immune hemolytic anemia may also occur. It can be seen with antibiotics such as cefotetan, ceftriaxone, and piperacillin^[42].

Other causes of cholestasis to consider in the setting of sepsis are biliary obstruction, cholangitis, and ischemic liver injury due to septic shock.

TPN-INDUCED CHOLESTASIS

Total parenteral nutrition (TPN) is commonly administered in patients with intestinal failure, intolerance to enteral nutrition, or inadequate enteral intake. Mild elevation in liver transaminases and ALP commonly occurs after initiation of TPN, but is of little clinical consequence if it remains stable. TPN-induced cholestasis occurs when serum conjugated bilirubin rises to greater than 2 mg/dL. It may be associated with rises in serum ALP, GGT, and transaminases^[43]. If unrecognized and untreated, it can progress towards cirrhosis and liver failure. The pathophysiology of TPN-induced cholestasis is multifactorial and complex. It can be divided into three categories: (1) due to lack of enteral nutrition; (2) due to direct toxicity of TPN components and from overfeeding; and (3) due to the underlying disorders requiring the use of TPN^[43].

Lack of enteral nutrition contributes to cholestasis by multiple processes. There is a decrease of cholecystokinin release which slows gallbladder emptying and subsequently results in gallbladder stasis, sludging, stone formation, and promotes cholestasis. Lack of enteral nutrition also decreases gastrointestinal motility, dampens gut immunity, and increases intestinal permeability due to impaired mucosal healing. All of these changes contribute to bacterial overgrowth and translocation, resulting in increased endotoxin within the portal circulation. The increase in portal endotoxin eventually leads to a decrease in bile flow and cholestasis^[35,44].

The components of TPN itself, especially when given in excess, may cause cholestasis. Infusion of lipids at greater than 1 g/kg per day may exceed the liver's capacity to clear the lipid particles, resulting in steatosis and cholestasis^[45,46]. High rate of glucose infusion causes elevation in insulin level, which activates fatty acid synthesis and inhibits fatty acid breakdown. Once the liver's capacity to transport the fatty acids through lipoproteins production is overwhelmed, fatty acids will accumulate within the hepatocytes, resulting in steatosis and cholestasis^[47]. This is particularly true when TPN is administered continuously without periods of fasting and in states of insulin resistance. Trace elements such as copper and manganese have also been implicated in causing cholestasis^[48].

Additionally, the picture may be complicated by the fact that patients who require TPN have primary gastrointestinal disorders that can cause liver dysfunction and cholestasis. Short bowel syndrome is usually seen in patients who had extensive small bowel resection. It is also a common indication for TPN. It is associated with cholestasis due to bacterial overgrowth in the remnant bowel loop^[49,50]. Furthermore, these patients tend to be malnourished and have failure to thrive. They are also prone to recurrent infections and may be on multiple medications. All of these factors may contribute to cholestasis that is difficult to delineate from TPN-induced cholestasis.

TPN-induced cholestasis is managed initially by ruling out other causes of cholestasis. Afterwards, it can be managed by adjusting TPN formulations, initiating cyclical TPN, encouraging and maximizing oral nutrition. TPN-induced cholestasis usually resolves with discontinuation of TPN and resumption of full enteral nutrition. In the TPN dependent patient, metronidazole has been shown to prevent cholestasis by suppressing bacterial overgrowth^[51,52].

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy (ICP) is a reversible form of cholestasis, which occurs in the second or third trimester of pregnancy and is characterized by symptoms of pruritus, elevation in fasting serum bile acid levels, and spontaneous relief of signs and symptoms within 4-6 wk after delivery^[53,54]. The incidence of ICP ranges from 0.1% to 15.6%^[55]. Geographic variations in incidence rates have been noted, reflecting greater susceptibility in certain regions of the world such as Bolivia, Chile and the Scandinavian countries^[56,57].

The pathogenesis of ICP is multifactorial and includes genetic, hormonal and environmental factors. Studies have demonstrated mutations in the ABCB4 gene leading to abnormalities in the MDR3 protein in approximately 16% of patients with ICP^[58-62]. Such mutations lead to dysfunction of bile transport across the canaliculus. Hormonal factors also play a role. There is a greater incidence of ICP in twin pregnancies where peak estrogen levels are higher than in singleton pregnancies. ICP also occurs most commonly in the third trimester when serum concentrations of estrogen are highest. In addition, high-dose of oral contraceptives and progesterone can trigger ICP^[53]. We recommend that progesterone treatment be avoided in pregnant women with a prior history of ICP and discontinued in patients with cholestasis occurring during pregnancy. For reasons that are unclear, ICP occurs more commonly in the colder months in Chile and Scandinavia, indicating that undefined environmental factors may also contribute to the occurrence of ICP^[57].

The primary presenting symptom of ICP is intense

Table 2 Common causes of drug-induced liver injury in the United States

Types of drugs	Specific drugs (number of cases)	
Analgesics/NSAIDs	Acetaminophen (124)	
	Drugs in combination with APAP (3)	
Antimicrobials	Diclofenac (4)	
	Celecoxib (2)	
	Isoniazid (37)	
	Amoxicillin/clavulanate (24)	
	Nitrofurantoin (13)	
	Trimethoprim/sulfamethoxazole (9)	
	Ciprofloxacin (5)	
	Levofloxacin (4)	
	Terbinafine (4)	
	Telithromycin (5)	
	Fialuridine (3) ¹	
	Azithromycin (3)	
	Oxacillin (3)	
	Minocycline (3)	
	Amoxicillin (2)	
Doxycycline (2)		
CNS Agents	Fluconazole (2)	
	Nevirapine (2)	
	Valproate (16)	
	Phenytoin (15)	
	Methyldopa (8)	
	Lamotrigine (5)	
	Duloxetine (6)	
	Atomoxetine (3)	
	Fluoxetine (2)	
	Nefazodone (2)	
	Bupropion (2)	
	Anti-inflammatory/ Immunologics	Interferon beta (6)
		Sulfasalazine (3)
Etanercept (3)		
Mercaptopurine (3)		
Antithymocyte globulin (2)		
Endocrine	Propylthiouracil (13)	
	Troglitazone (4) ¹	
Statins	Atorvastatin (3)	
	Cerivastatin (2) ¹	
Anesthetics	Halothane (3)	
	Desflurane (2)	
Cardiovascular	Labetolol (2)	
	Amiodarone (2)	
Others	Disulfiram (6)	
	Allopurinol (2)	
	Ranitidine (2)	

¹Discontinued or non-FDA approved drugs. APAP: Acetaminophen; NSAIDs: Non-steroidal anti-inflammatory drugs; CNS: Central nervous system; FDA: Food and drug administration. Adapted From: Russo *et al*^[90] and Chalasani *et al*^[80].

pruritus, which can occur throughout the body and is usually worst at night. Occurrence of such symptoms during pregnancy should prompt evaluation for liver function test abnormalities and fasting serum bile acid levels. A diagnosis is made if fasting serum bile acid levels are greater than 10 μmol/L^[63]. However, symptoms may precede laboratory abnormalities in liver transaminases or serum bile acid levels. Furthermore, liver function tests and bile acid levels should be repeated if pruritus is persistent. Even though isolated elevation of bile acids may occur, elevation of serum transaminases as high as 1000 units/L is often seen. A liver biopsy is generally not

needed for diagnosis.

The clinical importance of ICP lies primarily in the potential fetal risks, including prematurity, asphyxiation during delivery, or intrauterine death. Bile acid levels > 40 μmol/L any time during pregnancy might be associated with greater risk of fetal complication rates^[64-67]. A large cohort study demonstrated women with severe ICP and a singleton pregnancy had increased risks of preterm delivery, neonatal unit admission and stillbirth compared to controls. Furthermore, risks of preterm delivery, meconium-stained amniotic fluid and stillbirth rose with increasing maternal serum bile acid concentrations^[68]. Therefore, delivery at 36-38 wk of gestation is an important strategy to preventing stillbirth or other fetal complications^[57].

Ursodeoxycholic acid, dosed at 10-20 mg/kg daily, is the first-line treatment for ICP based on evidence obtained from randomized clinical trials and a recent meta-analysis, which demonstrate improvement in pruritus, liver function tests, and reduction in fetal complications^[63,66,69]. Dexamethasone administration can be considered to increase fetal lung maturity, but is ineffective in improving pruritus and ALT levels^[70]. S-Adenosyl-L-methionine is less effective than UDCA^[71] but can be used as an adjunctive therapy if pruritus or bile acid levels do not adequately respond to ursodeoxycholic acid alone^[72,73]. After delivery, transaminase and bile acid levels should normalize. Persistent elevation in ALT, AST or bile acids should prompt evaluation for other etiologies of liver disease, including PBC and PSC. Given findings from a large Swedish cohort study, evaluation for hepatitis C should also be considered due to a strong association between ICP and hepatitis C infection^[74].

DRUG INDUCED LIVER INJURY

Drug-induced liver injury (DILI) due to idiosyncratic drug reactions from drugs and herbal products is a rare but devastating phenomenon accounting for 13% of all cases of fulminant hepatic failure in the United States; this number rises to 52% if hepatotoxicity due to acetaminophen is also included^[75]. The types of liver injury can be categorized into hepatocellular, cholestatic, or mixed (cholestatic and hepatocellular) injury based on the pattern of liver enzyme abnormalities. Cholestatic and mixed types of liver injury make up approximately half of all cases of DILI^[76]. The medication class that is most commonly associated with DILI in the United States and Europe is anti-microbials^[77-81]. Amoxicillin-clavulanic is the most common individual inciting agent reported in various studies^[77,79,80]. In Korea, and likely in other Asian countries, herbal products more frequently cause DILI than medications^[82]. Among the intravenous medications, anti-microbials remain the most common class of medication to cause DILI followed by anti-neoplastic drugs based on a recent study from the United States^[83].

Drug-induced cholestasis produces a wide spectrum of pathology that can be classified as either acute or chronic^[84]. Acute processes include cholestasis without hepatitis (minimal or no parenchymal inflammation),

cholestasis with hepatitis (with parenchymal inflammation), and cholestasis with bile duct injury and inflammation. Chronic drug-induced cholestasis may vary from asymptomatic with mild ductopenia noted on liver biopsy to progressive inflammation, fibrosis, loss of interlobular bile ducts, and eventually permanent cholestasis, resulting in a disorder known as the “vanishing bile duct syndrome”. Cholestasis may also involve the large extrahepatic biliary tract producing a pattern similar to PSC in rare occasions.

The pathophysiology of DILI is poorly understood. Few medications, such as acetaminophen or valproic acid, produce hepatotoxicity through a predictable dose-dependent mechanism. The mechanism in the majority of cases is rather due to idiosyncratic drug reactions unrelated to the dose or the mechanism of action of the drug^[76]. In some cases there may be a component of immunologic drug reactions contributing to DILI as illustrated by the presence of fever, rash, and eosinophilia^[85]. There is evidence of genetic predisposition given that certain HLA haplotypes are more susceptible to DILI associated with flucloxacillin and amoxicillin-clavulanate^[86,87].

In the majority of cases of DILI, complete recovery should occur upon discontinuation of the suspected medication or herbal product. Jaundice is one of the strongest prognostic factors and is associated with a higher rate of mortality/liver transplantation, also known as Hy’s Law^[88]. The rate of mortality/liver transplantation is about 9%-12% based on three large series from the United States, Spain, and Sweden^[77,80,89]. Prognosis is better for cholestatic compared to hepatocellular DILI, based on the data from Spain and Sweden but the opposite was found in results from the United States.

A list of medications commonly associated with intrahepatic cholestasis is listed in Table 2. A searchable database of hepatotoxic drugs and herbal products is available online from the National Institute of Health: <http://www.livertox.nih.gov>.

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