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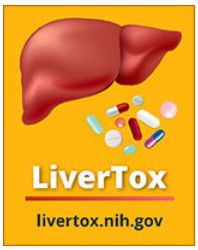

Vanishing Bile Duct Syndrome

Updated: December 11, 2019.

Description. Vanishing bile duct syndrome (VBDS) is a rare but serious outcome and complication of drug induced liver injury marked clinically by chronic cholestasis and histologically by loss of intrahepatic bile ducts. VBDS typically occurs after a bout of severe cholestatic hepatitis, often with immunoallergic features.

Latency to Onset. VBDS is a complication of acute drug induced liver injury, generally becoming manifest 1 to 6 months after the onset of injury.

Symptoms. Typical symptoms of VBDS are persistent pruritus, fatigue and jaundice, sometimes with severe dyslipidemia, hypercholesterolemia and skin xanthomata that can be painful and interfere with everyday activities, particularly when present on palms and soles.

Serum Enzyme Elevations. VBDS typically arises in the setting of severe acute cholestatic hepatitis in which there is an inadequate recovery as shown by persistent elevations in alkaline phosphatase levels and bilirubin, which often occur despite a decrease in serum aminotransferase levels into the normal or near-normal range. Serum cholesterol levels are also raised as are serum bile acid levels.

Drugs. Drugs that have been implicated in causing VBDS include amoxicillin/clavulanate, other penicillins, macrolide antibiotics, fluoroquinolones, sulfonamides, antifungal agents, nonsteroidal antiinflammatory agents, phenothiazines, tricyclic antidepressants and aromatic anticonvulsants. However, any cause of severe acute cholestatic or mixed hepatitis may lead to VBDS. A list of medications linked to at least one case of VBDS in the literature is given below.

Differential Diagnosis. Other conditions that can mimic or cause vanishing bile duct syndrome include graft-vs-host disease, Hodgkin's disease, sclerosing cholangitis and primary biliary cholangitis. These conditions are readily excluded based upon clinical setting, medical history and serological testing.

Criteria for Definition. VBDS is a pathological diagnosis although certainly the condition can be diagnosed clinically without liver histology. Furthermore, there are great variations in severity and outcome of VBDS. Most cases of VBDS arise within a few months of onset of severe cholestatic hepatitis, often with immunoallergic features such as rash, fever, facial edema, lymphadenopathy and eosinophilia; and in more dramatic cases with Stevens Johnson syndrome or toxic epidermal necrolysis. VBDS can be relentless and progressive, with almost complete loss of bile ducts accompanied by severe cholestasis and hepatic failure leading to death or need for liver transplantation within 1 to 3 years of onset. In other situations, the bile duct loss is partial and early but not progressive and ultimately reverses, at least partially. In many instances, clinical recovery occurs but there is evidence of residual chronic liver injury, with mild pruritus and abnormal serum enzymes and liver biopsy showing hepatic fibrosis and a relative decrease in hepatic ducts (ductopenia). In the mildest forms, patients may recover clinically and no longer have symptoms or jaundice, but exhibit persistent alkaline phosphatase and GGT elevations and have a relative paucity of bile ducts if a liver biopsy is performed. The diagnosis of VBDS,

and particularly its milder forms, requires expertise in hepatic pathology and a liver biopsy with adequate numbers of portal areas to fully assess bile duct loss. Elements in the diagnosis of VBDS are:

1. Persistent elevations in serum alkaline phosphatase and bilirubin for more than 6 months after onset of drug induced liver disease
2. Absence of clinical or serologic evidence of primary biliary cholangitis, sclerosing cholangitis and graft-vs-host disease
3. Liver biopsy findings of paucity of intralobular bile ducts (<50% of portal areas with bile duct in a biopsy with at least 10 portal areas) in a sample taken at least 1 month after onset of injury.

The diagnosis can also be considered if there are persistent elevations in serum alkaline phosphatase and/or GGT for more than 12 months after onset of drug induced liver injury, particularly if a liver biopsy demonstrates a decrease in intralobular bile ducts (as shown by <50% of portal areas with an intralobular bile duct in a biopsy with at least 10 portal areas). Mild, partial or "incomplete" forms of vanishing bile duct syndrome may be accompanied by lesser decrease in bile ducts, with 50-75% of portal areas having an identifiable intralobular bile duct.

Management. VBDS may be accompanied by troublesome symptoms including pruritus, fatigue and hypercholesterolemia with xanthomata. Mild pruritus can be managed with antihistamines such as diphenhydramine and hydroxyzine. The sedative effects of these antihistamines may be beneficial as pruritus can be worse at night and disturb sleep. With more difficult pruritus, bile acid resins such as cholestyramine and colistipol may be helpful as they can bind and trap pruritogenics in the intestine. These agents, however, are not always well tolerated and must be taken before meals and in adequate doses. Other less well established treatments for pruritus include rifampin and naltrexone which have been reported to be beneficial in small case series. Hyperlipidemia may require therapy as well and it responds minimally to HMG Coenzyme A inhibitors (statins) which are best avoided. Severe hyperlipidemia with painful xanthomata may plasma exchange for management. Indeed, severe intractable pruritus can be an indication for liver transplantation. Corticosteroids are often used in treatment of severe cholestasis and VBDS, but there is no evidence that they are beneficial and they can worsen the secondary metabolic effects of end stage liver disease and cholestasis. Ursodiol is almost universally used in the treatment of VBDS, and while prospective controlled trials have not been conducted to demonstrate their benefit, anecdotal reports have suggested that they are beneficial in ameliorating the injury. Importantly, VBDS can slowly resolve on its own and a major focus of management should be avoidance of further injury. Careful attention to nutrition and vitamin and mineral replacement (vitamin D, E, K and calcium) are important in managing patients with this rare but challenging condition. Experimental approaches to treating VBDS include immunosuppression with calcineurin inhibitors or monoclonal antibodies. Despite all interventions, however, a proportion of patients with VBDS due to medications eventually develop cirrhosis and end stage liver disease requiring liver transplantation.

Drugs Associated with Vanishing Bile Duct Syndrome

Drug Class	Specific Agents
Antibiotics	
Penicillins	**Amoxicillin**, Amoxicillin/**Clavulanic Acid**, Flucloxacillin
Cephalosporins	Cefdinir, Cefazolin, Cephalexin
Fluoroquinolones	**Ciprofloxacin, Levofloxacin, Moxifloxacin**
Sulfonamides	**(Trimethoprim)-Sulfamethoxazole**
Macrolides	**Azithromycin**, Erythromycin
Lincomycins	Clindamycin

Table continued from previous page.

Drug Class	Specific Agents
Tetracyclines	Troleandomycin
Carbapenems	Meropenem
Antiviral Agents	**Nevirapine**
Antifungal Agents	Itraconazole, Terbinafine
Anthelmintic Agents	Thiabendazole
Antimalarial Agents	Atovaquone-Proguanil
Anticonvulsants	**Carbamazepine**, Oxcarbazepine, Phenytoin, Valproate, Phenobarbital, **Lamotrigine**, Zonisamide
Antidepressants	Amitriptyline, Imipramine, Sertraline
Antipsychotic Agents	Olanzapine, Haloperidol, **Phenothiazines**
Lipid lowering Agents	Atorvastatin, Fenofibrate
Rheumatologic Agents	**Allopurinol**, Azathioprine, Infliximab, Gold
Antineoplastic Agents	**Temozolomide**, Thalidomide, Lenalidomide
Hormones	Anabolic Steroids, Estrogens
NSAIDs	**Ibuprofen**, Acetaminophen, Celecoxib, Phenylbutazone
Antidiabetic Agents	Glibenclamide, Tolbutamide
Herbal Agents	Glycyrrhizin, Artemisinin, Tibolone
Gastrointestinal Agents	Cimetidine, Metoclopramide, Lansoprazole, Omeprazole
Respiratory Agents	Cromolyn, Montelukast
Cardiovascular Agents	Hydrochlorothiazide, Enalapril

Agents in **bold** font are the most frequently reported causes of VBDS. Agents in some general classes such as the macrolide and fluoroquinolone antibiotics may all be capable of causing this complication of acute cholestatic hepatitis.

CASE REPORTS

Case 1. Prolonged cholestatic liver injury and vanishing bile duct syndrome due to prochlorperazine.(1)

A 68 year old man was treated with trimethoprim/sulfamethoxazole (800/400 mg three times daily) for one week and prochlorperazine (10 mg daily) for 4 weeks for suspected otitis media. A few weeks after stopping prochlorperazine he developed jaundice and pruritus. When first seen one month after stopping medications, serum bilirubin was 18.4 mg/dL, alkaline phosphatase was 1.5 times normal and ALT was minimally elevated (Table). Tests for viral hepatitis and abdominal ultrasound were normal. After persistence of jaundice for 3 months, a liver biopsy was done which showed centrilobular cholestasis with minimal hepatocyte necrosis or portal inflammation. The intralobular bile ducts were normal. He continued to have jaundice and severe pruritus and developed skin hyperpigmentation. Tests for hepatitis B and mitochondrial antibody were negative. Endoscopic retrograde cholangiopancreatography was normal. Serum bilirubin levels peaked 4 months after presentation and then began to decline, not becoming normal until one year later. Pruritus and hyperpigmentation also resolved, but serum alkaline phosphatase and GGT levels remained elevated. A repeat liver biopsy, done two years after onset and 9 months after resolution of jaundice and symptoms, showed minimal cholestasis but bridging hepatic fibrosis and paucity of intralobular bile ducts. Two and a half years after onset, serum alkaline phosphatase levels were still abnormal but he had no symptoms.

Key Points

Medication:	Prochlorperazine (10 mg daily for 4 weeks)
Pattern:	Cholestatic
Severity:	4+ (prolonged jaundice and hepatic fibrosis)
Latency:	4 weeks
Recovery:	Incomplete after 2 years
Other medications:	Trimethoprim/sulfamethoxazole

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
		Prochlorperazine (10 mg daily)			
1 month	0	49	116	18.4	
	3 months	80	210	26.2	Biopsy #1
	4 months	88	219	19.3	ERCP normal
	6 months	85	365	11.2	
	10 months	65	430	2.6	
1 year	12 months	60	410	1.5	
2 years	22 months	85	445	1.0	Biopsy #2
Normal Values		**<42**	**<90**	**<1.2**	

* Some values estimated from Figure 1 and bilirubin converted from μmol/L to mg/dL.

Comment

An example of the evolution of an acute cholestatic hepatitis to prolonged cholestasis and VBDS. The patient eventually improved and was asymptomatic, but alkaline phosphatase levels were persistently elevated and liver biopsy showed paucity of intralobular bile ducts and bridging hepatic fibrosis 2 years after initial onset. Not all cases of VBDS progress to hepatic failure and eventual clinical improvement is common and may be accompanied by reappearance of bile ducts. Long term follow up on such cases usually demonstrates well compensated and nonprogressive liver disease with fibrosis and persistence of mild elevations in serum alkaline phosphatase.

Case 2. Acute cholestatic hepatitis due to chlorpromazine evolving into chronic cholestatic syndrome with vanishing bile duct syndrome.(2)

A 34 year old pregnant woman was treated with chlorpromazine (25 mg twice daily) for hyperemesis gravidarum and developed fatigue and dark urine 2 weeks later followed by pruritus and jaundice. Chlorpromazine was stopped. Blood testing showed marked increases in serum bilirubin, ALT and alkaline phosphatase (Table). Tests for acute hepatitis A, B and C were negative as were autoantibodies including antinuclear, smooth muscle and mitochondrial antibodies. She had no previous history of liver disease, risk factors for viral hepatitis or alcohol abuse. She was approximately 2 months pregnant. She remained jaundiced throughout pregnancy that was terminated by Caesarian section at week 28. A concurrent liver biopsy showed severe intrahepatic cholestasis, portal inflammation and bile duct injury. After delivery of twin girls she remained jaundiced and had persistent and unrelenting pruritus. Various therapies including antihistamines, phenobarbital, cholestyramine, S-adenosylmethionine, prednisone, phototherapy and plasmapheresis were of

minimal benefit. A repeat liver biopsy at 8 months after onset showed increased cholestasis and reduction in number of bile ducts and a third liver biopsy after 14 months showed bridging fibrosis and paucity of bile ducts (detectable in only 3 of 16 portal tracts). She had enlargement of the liver and spleen, marked weight loss, steatorrhea, and symptoms of severe pruritus and fatigue. She was started on ursodiol (900 mg daily) and simultaneously began to improve clinically. Jaundice resolved 20 months after initial onset after which serum alkaline phosphatase and ALT levels fell into the range of 1.5 to 3 fold elevated. Serum albumin and prothrombin time remained normal throughout the course. Ultrasound of the abdomen showed changes suggestive of cirrhosis and a fourth liver biopsy, 46 months after initial onset, showed biliary cirrhosis with minimal inflammation and focal areas of cholestasis and bile duct paucity (ducts detected in 5 of 12 portal tracts).

Key Points

Medication:	Chlorpromazine (50 mg daily for 20 days)
Pattern:	Cholestatic (R=~0.1 at peak)
Severity:	4+ (prolonged jaundice, cirrhosis)
Latency:	2 weeks
Recovery:	Incomplete after 4 years
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
Pre	Chlorpromazine (50 mg daily for 20 days) given for nausea				
3 weeks	0	60	100	7.0	2 months pregnant
5 months	4 months	60	510	35.0	Delivery: liver biopsy #1
	6 months	120	400	22.0	
	8 months	184	4128	32.7	Liver biopsy #2
	10 months	140	1800	19.0	
	12 months	150	2100	22.9	
	14 months	110	550	20.5	Liver biopsy #3
	4 years	100	280	1.5	Liver biopsy #4
Normal Values		**<42**	**<90**	**<1.2**	

* Some values estimated from Figure 4 and bilirubin converted from μmol/L to mg/dL.

Comment

A typical cholestatic hepatitis from chlorpromazine was followed by persistent cholestasis with jaundice and pruritus. Her pregnancy was terminated early because of the jaundice, with a Caesarian section during which a liver biopsy was done which showed severe cholestatic hepatitis with bile duct injury. Follow up liver biopsies at 8, 12 and 46 months after onset showed loss of bile ducts but, eventually, a gradual improvement in cholestasis. Nevertheless, the patient developed cirrhosis and the long term prognosis remains uncertain. This is a dramatic and well documented example of VBDS developing after an acute cholestatic hepatitis due to chlorpromazine. Ursodiol therapy appeared to improve both symptoms and laboratory test results, but some degree of clinical improvement had started before therapy was initiated. Many instances of vanishing bile duct syndrome due to chlorpromazine have been published. Ursodiol is often used, but its efficacy in ameliorating or shortening the course of illness is not clear. It is appropriate to use particularly if there is symptomatic improvement.

Case 3. Vanishing bile duct syndrome after acute cholestatic injury attributed to ibuprofen.(3)

A 29 year old man with history of multiple allergies developed jaundice and abdominal pain 3 weeks after starting low doses of ibuprofen (600 mg/day) for nonspecific body aches. He was admitted with the suspected diagnosis of cholangitis, and ibuprofen was stopped. Serum bilirubin was 6.5 mg/dL and both ALT and alkaline phosphatase were moderately elevated (Table). He had no risk factors for viral hepatitis and denied alcohol abuse. Serologic tests for hepatitis A, B and C were negative as were autoantibodies including ANA and AMA. Ultrasound of the abdomen showed no evidence of gallstones or biliary obstruction. He was treated with antibiotics, but jaundice worsened and he developed pruritus. A liver biopsy showed intrahepatic cholestasis, marked portal inflammatory infiltrates with damage to and reduced numbers of bile ducts in portal areas. An endoscopic retrograde cholangiopancreatography (ERCP) was normal. A course of corticosteroids had no apparent effect, and serum bilirubin levels continued to rise. A second liver biopsy 6 weeks after onset showed less portal inflammation, but worsening cholestasis and further decrease in numbers of small bile ducts. Therapy for pruritus included antihistamines, ursodiol and cholestyramine with only modest effects. A third biopsy at 6 months showed markedly reduced bile ducts ("ductopenia"). At 12 months, he continued to be deeply jaundiced and was symptomatic with marked pruritus and xanthomata. He was referred for liver transplantation.

Key Points

Medication:	Ibuprofen (600 mg daily)
Pattern:	Initially mixed (R=4.5), later cholestatic (R=<1.0)
Severity:	4+ (jaundice, hospitalization, progressive hepatic failure)
Latency:	3 weeks
Recovery:	No; jaundice and vanishing bile duct syndrome one year later
Other medications:	Allergy injections for six weeks before onset

Laboratory Values

Time After Starting	Time After Stopping	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0		Ibuprofen started			
3 weeks	0	488	309	6.5	Hospitalized, Ibuprofen stopped
5 weeks	2 weeks	400	2151	11.9	First liver biopsy, ERCP normal
7 weeks	4 weeks	150	750	24.0	
4 months	3 months	300	1000	21.0	Second liver biopsy
6 months	5 months	180	850	16.5	
8 months	7 months	140	4000	19.0	Third liver biopsy
10 months	9 months	200	900	8.0	
1 year	11 months	300	3000	13.0	Referred for liver transplant
Normal Values		**<41**	**<115**		

Comment

Clinically apparent, acute liver injury from ibuprofen is very rare. This case was associated with a latency of 3 weeks and presentation with an acute cholestatic hepatitis that evolved into chronic cholestasis and the VBDS. On the first determination, the serum enzyme pattern was "mixed," but it rapidly became distinctly cholestatic,

matching the symptoms of deep jaundice and pruritus as well as the liver biopsy showing marked cholestasis with scant hepatocellular injury. The rapid onset followed by prolonged course of cholestasis combined with a history of allergies point towards an immunoallergic mechanism for this reaction. The patient had a decreased number of bile ducts on initial liver biopsy, which became progressively fewer on follow up biopsies, thus demonstrating the progressive nature of vanishing bile duct syndrome. This poor outcome occurred despite prompt discontinuation of the medication. The course of vanishing bile duct syndrome is variable, some patients eventually recover, but it can be unremitting, severe, leading as in this case to need for liver transplantation or death.

Case 4. Fatal case of vanishing bile duct syndrome after amoxicillin/clavulanate therapy.(4)

A 78 year old woman received a one week course of amoxicillin/clavulanate with tenoxicam for cervical pain and fever. At the end of antibiotic therapy, she was diagnosed as having cluster headaches and prednisolone was started. At that point, all liver tests were normal. Her headaches improved, but 6 weeks later she developed jaundice, pruritus and abdominal pain. On admission, she was jaundiced but was without fever, rash or stigmata of chronic liver disease. Serum bilirubin was 6.3 mg/dL, ALT 775 U/L, and alkaline phosphatase 245 U/L. Tests for viral hepatitis and autoantibodies were negative and imaging tests showed no evidence of biliary obstruction. Prednisolone was continued, but her jaundice worsened and serum alkaline phosphatase levels continued to rise (Table). Liver biopsy showed marked centrilobular cholestasis, minimal hepatocyte necrosis and mild portal inflammation. Importantly, interlobular bile ducts were absent in 6 of 12 portal tracts, and the ducts that were present had dystrophic changes. In the course of the following months, her condition worsened with progressive weakness, poor appetite, weight loss, intractable pruritus and appearance of keratoconjunctivitis sicca. Ursodiol was given without improvement. Death from hepatic failure occurred 4 months after initial presentation.

Key Points

Medication:	Amoxicillin/clavulanic acid (500/125 mg three times daily for 10 days)
Pattern:	Initially hepatocellular (R=10.2) and later cholestatic (R=0.3)
Severity:	5+ (fatal)
Latency:	8 weeks (6 weeks after stopping drug)
Recovery:	No
Other medications:	Tenoxicam, prednisone

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
0	Pre	Amoxicillin/clavulanate given for 10 days			
2 weeks	4 days	20	60	1.0	Shortly after stopping antibiotic
8 weeks	6 weeks	775	245	6.3	Hospitalization
9 weeks	7 weeks	480	585	23.4	Liver biopsy: bile duct paucity
11 weeks	9 weeks	160	650	12.9	
12 week	10 weeks	232	884	21.9	
14 weeks	12 weeks	116	793	21.3	Ursodiol started
17 weeks	15 weeks	88	780	13.2	
19 weeks	17 weeks	40	858	11.1	

Table continued from previous page.

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
5 months	20 weeks	88	936	12.9	
6 months		129	1040	12.6	Death
Normal Values		**<40**	**<130**	**<1.2**	

* Estimated from figure 1.

Comment

This case is an example of a relentless and rapidly fatal course of VBDS with persistence of deep jaundice and pruritus. Interestingly, the pattern of serum enzyme elevations was initially hepatocellular (R=10.2), but the pattern soon changed to a cholestatic index (R=0.3). The appearance of keratoconjunctivitis sicca suggests that the epithelial cell injury was widespread, also affecting the small ducts of the salivary and lacrimal glands (a pattern that occurs with other causes of VBDS). Tenoxicam (a nonsteroidal antiinflammatory agent [NSAID]) was started and stopped at the same time as the antibiotic, and might also have contributed (several NSAIDs have been linked to VBDS), but the timing of onset of cholestatic hepatitis is also typical for amoxicillin/clavulanate hepatotoxicity. The patient received prednisolone for the whole course of illness and ursodiol was added during the cholestatic phase without obvious evidence for benefit of either.

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1. Lok AS, Ng IO. Prochlorperazine-induced chronic cholestasis. J Hepatol 1988; 6: 369-73. PubMed PMID: 3392386.
2. Moradpour D, Altorfer J, Flury R, Greminger P, Meyenberger C, Jost R, Schmid M. Chlorpromazine-induced vanishing bile duct syndrome leading to biliary cirrhosis. Hepatology 1994; 20: 1437-41. PubMed PMID: 7982642.
3. Alam I, Ferrell LD, Bass NM. Vanishing bile duct syndrome temporally associated with ibuprofen use. Am J Gastroenterol 1996; 91: 1626-30. PubMed PMID: 8759674.
4. Richardet JP, Mallat A, Zafrani ES, Blazquez M, Bognel JC, Campillo B. Prolonged cholestasis with ductopenia after administration of amoxicillin/clavulanic acid. Dig Dis Sci 1999; 44: 1997-2000. PubMed PMID: 10548348.

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Zimmerman HJ. Cholestatic injury. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999. p. 434-7.

(Expert review of hepatotoxicity published in 1999; discusses chronic cholestatic injury that can resemble primary biliary cirrhosis and result in loss of bile ducts; more than 3 dozen agents have been associated with VBDS including amitriptyline, amoxicillin-clavulanate, azathioprine, carbamazepine, clindamycin, erythromycin, fluoroquinolones, imipramine, phenytoin, phenothiazines, SMZ-TMP, tetracycline, terbinafine, and thiabendazole).

Read AE, Harrison CV, Sherlock S. Chronic chlorpromazine jaundice: with particular reference to its relationship to primary biliary cirrhosis. Am J Med 1961; 31: 249-58. PubMed PMID: 13740051.

(4 women developed prolonged jaundice due to chlorpromazine, ages 28 to 57 years, onset in 2-4 weeks, jaundice lasting for 7-36 months, peak bilirubin 15-21.6 mg/dL, Alk P 5-20 times ULN, high cholesterol, xanthomas and weight loss in 3, itching in all; all women, 2 pregnant; ultimately slow recovery but residual biochemical and histologic abnormalities and fibrosis frequent; probable vanishing bile duct syndrome).

Horst DA, Grace ND, LeCompte PM. Prolonged cholestasis and progressive hepatic fibrosis following imipramine therapy. Gastroenterology 1980; 79: 550-4. PubMed PMID: 7429116.

(53 year old woman developed rash and fever 7 days after starting imipramine followed by jaundice with eosinophilia [bilirubin 10 mg/dL, AST 115 U/L, Alk P ~4 times ULN] with persistent jaundice and severe pruritus for 1 year, followed by gradual improvement; but 12 year follow up showed minor alkaline phosphatase and AST elevations with normal bilirubin; liver biopsies showed duct absence initially, but returning in follow up, although fibrosis was present).

Turner IB, Eckstein RP, Riley JW, Lunzer MR. Prolonged hepatic cholestasis after flucloxacillin therapy. Med J Aust 1989; 151: 701-5. PubMed PMID: 2593915.

(5 cases of cholestatic hepatitis arising after stopping flucloxacillin with latency of 13-35 days [bilirubin 13.3-38.2 mg/dL, ALT 85-525 U/L, Alk P 263-1580 U/L], with prolonged jaundice and abnormal liver tests still present 4-9 months later suggestive of VBDS).

Lok AS, Ng IO. Prochlorperazine-induced chronic cholestasis. J Hepatol 1988; 6: 369-73. PubMed PMID: 3392386.

(68 year old man developed jaundice 4 weeks after starting prochlorperazine [peak bilirubin 26 mg/dL, ALT 50-90 U/L, Alk P 120-500 U/L], jaundice and pruritus persisting for more than a year, but then gradual clinical improvement but with persistent enzyme elevations, and biopsy 22 months after onset showed fibrosis and paucity of bile ducts: Case 1).

Bach N, Thung SN, Schaffner F, Tobias H. Exaggerated cholestasis and hepatic fibrosis following simultaneous administration of chlorpromazine and sodium valproate. Dig Dis Sci 1989; 34: 1303-7. PubMed PMID: 2502367.

(45 year old man developed fatigue and fever 12 days after starting chlorpromazine for intractable hiccups [bilirubin 21.5 mg/dL, ALT 1312 U/L, Alk P 617 U/L], with persistent jaundice and pruritus for several years and eventual presence of cirrhosis and varices; paucity of bile ducts on biopsy indicating VBDS).

Sherlock S. The syndrome of disappearing intrahepatic bile ducts. Lancet 1987; 2: 493-6. PubMed PMID: 2887786.

(Concise overview of the clinical and histological features, outcome and causes of VBDS: drug induced causes were not discussed).

Larrey D, Amouyal G, Danan G, Degott C, Pessayre D, Benhamou JP. Prolonged cholestasis after troleandomycin-induced acute hepatitis. J Hepatol 1987; 4: 327-9. PubMed PMID: 3496378.

(62 year old woman given multiple antibiotics including 6 days of troleandomycin when she developed jaundice and pruritus [bilirubin 3.0 rising to 9.8 mg/dL, ALT ~7 times ULN, Alk P 4.5 times ULN], biopsy after one month showing no loss of ducts, but jaundice was slow to clear [3 months] and pruritus lasted 1.5 years later).

Cavanzo FJ, Garcia CF, Botero RC. Chronic cholestasis, paucity of bile ducts, red cell aplasia, and the Stevens-Johnson syndrome. An ampicillin-associated case. Gastroenterology 1990; 99: 854-6. PubMed PMID: 2116345.

(35 year old woman developed Stevens-Johnson syndrome with cholestatic hepatitis and red cell aplasia 4 days after starting oral ampicillin with subsequent prolonged cholestasis and VBDS but with gradual improvement after several years).

Degott C, Feldmann G, Larrey D, Durand-Schneider AM, Grange D, Machayekhi J-P, Moreau A, et al. Drug-induced prolonged cholestasis in adults: a histological semiquantitative study demonstrating progressive ductopenia. Hepatology 1992; 15: 244-51. PubMed PMID: 1735527.

(Clinical and histological description of drug induced prolonged cholestasis and ductopenia, the severe form of which can lead to VBDS, cirrhosis and hepatic failure: 8 cases with 3 due to ajmaline and one each to cyamemazine, troleandomycin, erythromycin, amitriptyline, and cyproheptadine).

Forbes GM, Jeffrey GP, Shilkin KB, Reed WD. Carbamazepine hepatotoxicity: another cause of the vanishing bile duct syndrome. Gastroenterology 1992; 102: 1385-8. PubMed PMID: 1551543.

(59 year old man developed fever, rash and jaundice 2 months after starting carbamazepine [bilirubin 12.4 mg/dL, AST 99 U/L, Alk P 1030 U/L], evolving into chronic cholestasis and VBDS, which ultimately improved clinically, but liver tests were still abnormal 1 year later).

Altraif I, Lilly L, Wanless IR, Heathcote J. Cholestatic liver disease with ductopenia (vanishing bile duct syndrome) after administration of clindamycin and trimethoprim-sulfamethoxazole. Am J Gastroenterol 1994; 89: 1230-4. PubMed PMID: 8053440.

(Two cases of VBDS: Case 1 was a 67 year old man with jaundice arising 1 week after completion of a 10 day course of clindamycin [bilirubin 14.6 mg/dL, ALT 315 U/L, Alk P 271 U/L, GGT 468 U/L], followed by prolonged jaundice for 2-4 years [bilirubin 4.2 mg/dL, Alk P 179 U/L, ALT 67 U/L], liver biopsies showing progressive loss of bile ducts; Case 2 was 30 year old man with TMP/SMZ induced allergic hepatitis with jaundice evolving into a prolonged cholestatic syndrome and ductopenia).

Moradpour D, Altorfer J, Flury R, Greminger P, Meyenberger C, Jost R, Schmid M. Chlorpromazine-induced vanishing bile duct syndrome leading to biliary cirrhosis. Hepatology 1994; 20: 1437-41. PubMed PMID: 7982642.

(33 year old pregnant woman had onset of jaundice 2 weeks after starting chlorpromazine, jaundice lasting 22 months with pruritus and high Alk P; ultimately resolving jaundice but with biliary cirrhosis and absence of bile ducts: Case 2).

Davies MH, Harrison RF, Elias E, Hübscher SG. Antibiotic-associated acute vanishing bile duct syndrome: a pattern associated with severe, prolonged, intrahepatic cholestasis. J Hepatol 1994; 20: 112-6. PubMed PMID: 8201211.

(Two cases of VBDS: 37 year old woman developed rash within one day of starting amoxicillin and jaundice one week later, liver biopsies showing paucity of bile ducts and cholestasis lasting 16 months; 42 year old woman developed jaundice 2 weeks after finishing a 14 day course of flucloxacillin, liver biopsy showing on bile ducts in portal areas [0%], but follow up biopsies demonstrating gradual increase to 50%).

Ryley NG, Fleming KA, Chapman RW. Focal destructive cholangiopathy associated with amoxicillin/clavulanic acid (Augmentin). J Hepatol 1995; 23: 278-82. PubMed PMID: 8550991.

(Five patients developed jaundice and cholestatic hepatitis after receiving amoxicillin/clavulanate, and all had destructive cholangitis on liver biopsy, but only one patient continued to have abnormal liver tests beyond six months).

O'Brien CB, Shields DS, Saul SH, Reddy KR. Drug-induced vanishing bile duct syndrome: response to ursodiol. Am J Gastroenterol 1996; 91: 1456-7. PubMed PMID: 8678017.

(58 year old woman developed jaundice 6 weeks after starting phenytoin and prochlorperazine [bilirubin 11.8 mg/dL, ALT 139 U/L, Alk P 1797 U/L], liver biopsy showing ductal paucity; subsequent persistent pruritus and Alk P elevations [800 U/L], improved with starting ursodiol therapy with ultimate resolution).

Alam I, Ferrell LD, Bass NM. Vanishing bile duct syndrome temporally associated with ibuprofen use. Am J Gastroenterol 1996; 91: 1626-30. PubMed PMID: 8759674.

(29 year old man developed acute cholestatic hepatitis followed by vanishing bile duct syndrome after a 3 week course of ibuprofen: Case 3).

Mallat A, Zafrani ES, Metreau JM, Dhumeaux D. Terbinafine-induced prolonged cholestasis with reduction of interlobular bile ducts. Dig Dis Sci 1997; 42: 1486-8. PubMed PMID: 9246051.

(75 year old woman developed weakness followed by jaundice and pruritus several days after completing a 3 week course of terbinafine [bilirubin 5.2 rising to 7.3 mg/dL, ALT 277 U/L, Alk P 375 U/L]; pruritus persisted and biopsy at 6 months showed decrease in bile ducts; symptoms resolved but GGT was still abnormal 17 months later).

Yao F, Behling CA, Saab S, Li S, Hart M, Lyche KD. Trimethoprim-sulfamethoxazole-induced vanishing bile duct syndrome. Am J Gastroenterol 1997; 92: 167-9. PubMed PMID: 8995964.

(57 year old man developed VBDS after acute hepatic injury [bilirubin 2.0 rising to 40.4 mg/dL, ALT 465 U/L, Alk P 295 U/L] arising within 1 week of starting TMP-SMZ; no allergic features; ultimately underwent liver transplantation).

Srivastava M, Perez-Atayde A, Jonas MM. Drug-associated acute-onset vanishing bile duct and Stevens-Johnson syndromes in a child. Gastroenterology 1998; 115: 743-6. PubMed PMID: 9721172.

(9 year old girl developed fever, rash and jaundice within 10 days of starting ibuprofen [bilirubin 3.3 rising to 15 mg/dL, ALT 649 U/L, Alk P 519 U/L] with Stevens Johnson syndrome and persistent jaundice, liver biopsies showing paucity of bile ducts and progression to cirrhosis within 6 months of onset, despite ursodiol, corticosteroid and tacrolimus therapy).

Desmet VJ. Histopathology of chronic cholestasis and adult ductopenic syndrome. Clin Liver Dis 1998; 2: 249-64. PubMed PMID: 15560031.

(Expert review of the histological features and various causes of chronic VBDS).

Richardet JP, Mallat A, Zafrani ES, Blazquez M, Bognel JC, Campillo B. Prolonged cholestasis with ductopenia after administration of amoxicillin/clavulanic acid. Dig Dis Sci 1999; 44: 1997-2000. PubMed PMID: 10548348.

(78 year old woman developed jaundice 6 weeks after a 10 day course of amoxicillin/clavulanate [bilirubin 6.3 mg/dL, ALT 775 U/L, Alk P 245], with progressive cholestasis and bile duct paucity on liver biopsy, keratoconjunctivitis sicca and death within 6 months of onset: Case 4).

Anania FA, Rabin L. Terbinafine hepatotoxicity resulting in chronic biliary ductopenia and portal fibrosis. Am J Med 2002; 112: 741-2. PubMed PMID: 12079721.

(56 year old woman with jaundice after a short course of terbinafine who developed persistent pruritus and Alk P elevations [550 U/L], liver biopsy 20 months later showing paucity of bile ducts).

Schwarze C, Schmitz V, Fischer HP, Sauerbruch T, Spengler U. Vanishing bile duct syndrome associated with elevated pancreatic enzymes after short-term administration of amoxicillin. Eur J Gastroenterol Hepatol 2002; 14: 1275-7. PubMed PMID: 12439126.

(45 year old woman developed jaundice 8 weeks after a 7 day course of amoxicillin and subsequent persistence of cholestasis and pruritus [bilirubin 9.1 mg/dL, ALT 137 U/L, Alk P 949 U/L], a biopsy showed paucity of bile ducts and she died of hepatic failure one year later).

Basset C, Vadrot J, Denis J, Poupon J, Zafrani ES. Prolonged cholestasis and ductopenia following gold salt therapy. Liver Int 2003; 23: 89-93. PubMed PMID: 12654130.

(49 year old woman with suspected rheumatoid arthritis developed rash and jaundice one month after starting aurothiopropanol sulphonate injections [bilirubin 7 mg/dL, ALT 5 times, and Alk P 11 times ULN], biopsy showing bile duct injury, slow resolution, ductopenia in follow up liver biopsy).

Taghian M, Tran TA, Bresson-Hadni S, Menget A, Felix S, Jacquemin E. Acute vanishing bile duct syndrome after ibuprofen therapy in a child. J Pediatr 2004; 145: 273-6. PubMed PMID: 15289784.

(10 year old girl developed Stevens Johnson syndrome a few days after a second short course of ibuprofen for fever [bilirubin 5.4 mg/dL, ALT 639 U/L, Alk P 1697 U/L], with persistence of jaundice and pruritus and biopsy showing paucity of bile ducts [<50%], resolving slowly on ursodiol with liver test abnormalities lasting more than a year).

Smith LA, Ignacio JR, Winesett MP, Kaiser GC, Lacson AG, Gilbert-Barness E, González-Peralta RP, Wilsey MJ Jr. Vanishing bile duct syndrome: amoxicillin-clavulanic acid associated intra-hepatic cholestasis responsive to ursodeoxycholic acid. J Pediatr Gastroenterol Nutr 2005; 41: 469-73. PubMed PMID: 16205517.

(10 year old boy developed jaundice after receiving mebendazole, azithromycin and 5 days of amoxicillin/clavulanate [bilirubin 3.7 rising to 26.5 mg/dL, ALT 210 U/L, Alk P 424 U/L-normal], with biopsy after one month showing ductopenia and slow resolution, laboratory tests falling to normal 2 years later).

Capra F, Nicolini N, Morana G, Guglielmi A, Capelli P, Vantini I. Vanishing bile duct syndrome and inflammatory pseudotumor associated with a case of anabolic steroid abuse. Dig Dis Sci 2005; 50: 1535-7. PubMed PMID: 16110850.

(32 year old man developed jaundice 3 months after starting anabolic steroids for muscle building [bilirubin 37.4 mg/dL, ALT 182 U/L, Alk P 212 U/L], with liver biopsy showing paucity of bile ducts, resolving over next 4 months).

Choi SH, Yang SH, Song YB, Kim HJ, Seo YT, Choi DS, Moon KH, Byun JH, Yu ES. [A case of vanishing bile duct syndrome associated with hypersensitivity to allopurinol]. Korean J Hepatol 2005; 11: 80-5. PubMed PMID: 15788888.

Vuppalanchi R, Chalasani N, Saxena R. Restoration of bile ducts in drug-induced vanishing bile duct syndrome due to zonisamide. Am J Surg Pathol 2006; 30: 1619-23. PubMed PMID: 17122520.

(35 year old man developed jaundice 3 weeks after starting zonisamide for obesity [bilirubin 7.1 mg/dL, ALT 531 U/L, Alk P 578 U/L], with persistence of pruritus and serial biopsies showing return of bile ducts; initially no ducts found in 16 portal areas, at two years ducts present in 22 of 24 portal areas despite persistent Alk P elevations [~650 U/L]).

Jakab SS, West AB, Meighan DM, Brown RS Jr, Hale WB. Mycophenolate mofetil for drug-induced vanishing bile duct syndrome. World J Gastroenterol 2007; 13: 6087-9. PubMed PMID: 18023105.

(69 year old man developed rash 3 weeks after starting amoxicillin/clavulanate with subsequent jaundice [bilirubin 1.0 rising to 7.4 mg/dL, ALT 82 GGT 360 U/L], with prolonged jaundice and vanishing bile duct syndrome but subsequent resolution with mycophenolate mofetil therapy).

Ichikawa T, Sato H, Kaira K, Oh-I S, Kakizaki S, Sato K, Takagi H, Mori M. Prolonged intrahepatic cholestasis after exposure to loxoprofen. Clin Ther 2008; 30: 2402-6. PubMed PMID: 19167598.

(36 year old woman developed jaundice 5 days after starting loxoprofen [bilirubin 27.5 mg/dL, ALT 470 U/L, Alk P 1082 U/L], liver biopsy showing paucity of bile ducts, with protracted course and slow resolution 14 months after onset).

Okan G, Yaylaci S, Peker O, Kaymakoglu S, Saruc M. Vanishing bile duct and Stevens-Johnson syndrome associated with ciprofloxacin treated with tacrolimus. World J Gastroenterol 2008; 14: 4697-700. PubMed PMID: 18698687.

(26 year old woman developed fever and rash 2 weeks after starting ciprofloxacin [bilirubin 4.1 rising to ~32 mg/dL, ALT 326 U/L, Alk P 229 U/L], with persistence of jaundice despite ursodiol and corticosteroids and bile duct paucity on liver biopsy, eventually resolving during tacrolimus therapy).

Etogo-Asse F, Boemer F, Sempoux C, Geubel A. Acute hepatitis with prolonged cholestasis and disappearance of interlobular bile ducts following tibolone and Hypericum perforatum (St. John's wort). Case of drug interaction? Acta Gastroenterol Belg 2008; 71: 36-8. PubMed PMID: 18396749.

(57 year old woman developed jaundice two years after starting tibolone and 3 months after starting "infusions" of St. John's wort [bilirubin 6.3 mg/dL, ALT 424 U/L, Alk P 162 U/L], with persistent pruritus and jaundice and liver biopsy showing paucity of bile ducts, recovering over next year on ursodiol; St. John's wort may have altered metabolism of tibolone, a known hepatotoxin).

Reau NS, Jensen DM. Vanishing bile duct syndrome. Clin Liver Dis 2008; 12: 203-17. PubMed PMID: 18242505.

(Review of the histology and causes of VBDS, listing 42 agents reported to cause chronic cholestasis and ductopenia).

Schumaker AL, Okulicz JF. Meropenem-induced vanishing bile duct syndrome. Pharmacotherapy 2010; 30: 953. PubMed PMID: 20812433.

(60 year old woman developed jaundice and pruritus while on meropenem and 3 weeks after course of ceftriaxone, metronidazole and vancomycin [bilirubin 11.2 rising to 26 mg/dL, ALT 83 U/L, Alk P 1467 U/L], with persistent jaundice and liver biopsy showing absence of bile ducts, improving but not completely resolving over next 6 months on ursodiol).

Kochar R, Nevah MI, Lukens FJ, Fallon MB, Machicao VI. Vanishing bile duct syndrome in human immunodeficiency virus: nevirapine hepatotoxicity revisited. World J Gastroenterol 2010; 16: 3335-8. PubMed PMID: 20614492.

(28 year old pregnant woman with HIV infection developed jaundice 4 weeks after starting zidovudine, lamivudine and nevirapine to prevent perinatal transmission of HIV [bilirubin 10.5 mg/dL, ALT 179 U/L, Alk P 496 U/L], with persistent jaundice and liver biopsy showing ductopenia; follow up not provided).

Gökçe S, Durmaz O, Celtik C, Aydogan A, Güllüoglu M, Sökücü S. Valproic acid-associated vanishing bile duct syndrome. J Child Neurol 2010; 25: 909-11. PubMed PMID: 20388938.

(8 year old girl developed persistent jaundice and itching 2 months after starting valproic acid [bilirubin rising to 20.2 mg/dL, ALT 118 U/L, Alk P 2787 U/L, normal INR], liver biopsy showing severe bile duct loss, bilirubin falling to normal after 8 months on ursodiol therapy but with persistence of Alk P elevations).

Juricic D, Hrstic I, Radic D, Skegro M, Coric M, Vucelic B, Francetic I. Vanishing bile duct syndrome associated with azithromycin in a 62-year-old man. Basic Clin Pharmacol Toxicol 2010; 106: 62-5. PubMed PMID: 19906050.

(62 year old man developed Stevens Johnson syndrome 3 days after a 3 day course of azithromycin and became jaundiced during recovery [bilirubin 15.2 mg/dL, ALT 1545 U/L, Alk P 545 U/L], with persistent jaundice and pruritus and liver biopsy showing absence of interlobular bile ducts at time of transplantation 10 months later).

Robinson W, Habr F, Manlolo J, Bhattacharya B. Moxifloxacin associated vanishing bile duct syndrome. J Clin Gastroenterol 2010; 44: 72-3. PubMed PMID: 19581811.

(82 year old man received azithromycin, ceftriaxone and 7 days of moxifloxacin and developed jaundice [bilirubin 15.3 rising to 25.8 mg/dL, ALT 441 U/L, Alk P 821 U/L], with biopsy showing ductopenia with persistence of jaundice; outcome not provided).

Bhayana H, Appasani S, Thapa BR, Das A, Singh K. Lamotrigine-induced vanishing bile duct syndrome in a child. J Pediatr Gastroenterol Nutr 2012;55:e147-8. PubMed PMID: 22008955.

(12 year old boy developed rash 2 weeks after starting lamotrigine followed by jaundice [bilirubin 14.8 mg/dL, ALT 321 U/L, Alk P 123 U/L], liver biopsy showing ductal paucity with incomplete recovery on ursodiol and referral for transplantation 2 years later).

Orman ES, Conjeevaram HS, Vuppalanchi R, Freston JW, Rochon J, Kleiner DE, Hayashi PH; DILIN Research Group. Clinical and histopathologic features of fluoroquinolone-induced liver injury. Clin Gastroenterol Hepatol. 2011; 9: 517-523.e3. PubMed PMID: 21356330.

(12 cases of liver injury due to fluoroquinolones including one due to moxifloxacin that resulted in VBDS and liver transplantation 16 months after onset of acute cholestatic hepatitis).

Cho HJ, Jwa HJ, Kim KS, Gang DY, Kim JY. Ursodeoxycholic acid therapy in a child with trimethoprim-sulfamethoxazole-induced vanishing bile duct syndrome. Pediatr Gastroenterol Hepatol Nutr 2013; 16: 273-8. PubMed PMID: 24511525.

(7 year old boy developed pruritus and jaundice 2 weeks after starting a 4 day course of trimethoprim-sulfamethoxazole for diarrhea [bilirubin 8.4 mg/dL, ALT 220 U/L, Alk P 1028 U/L, GGT 708 U/L], liver biopsy showing paucity of bile ducts and cholestasis, subsequently improving on ursodiol therapy with resolution of jaundice and all liver tests with 4 months of onset).

Nader K, Mok S, Kalra A, Harb A, Schwarting R, Ferber A. Vanishing bile duct syndrome as a manifestation of Hodgkin's lymphoma: a case report and review of the literature. Tumori 2013; 99: e164-8. PubMed PMID: 24326854.

(64 year old woman developed jaundice within a few days of starting trimethoprim-sulfamethoxazole for urinary tract infection [bilirubin 15.1 rising to 45 mg/dL, ALT 56 U/L, Alk P 1114 rising to 3412 U/L, INR 1.9], liver biopsy showing paucity of bile ducts and severe cholestasis, a lymph node biopsy showing Hodgkin's disease, but not responding to chemotherapy and dying of multiorgan failure 1 month after presentation).

Kawasaki Y, Matsubara K, Hashimoto K, Tanigawa K, Kage M, Iwata A, Nigami H, et al. Nonsteroidal anti-inflammatory drug-induced vanishing bile duct syndrome treated with plasmapheresis. J Pediatr Gastroenterol Nutr 2013; 57: e30-1.

(13 year old girl developed fever and received loxoprofen for one day and diclofenac for 2 then developed jaundice [bilirubin 9.8 mg/dL, ALT 478 U/L, Alk P not given], liver biopsy showing paucity of bile ducts, treatment with ursodiol and plasmapheresis with subsequent improvement and resolution liver test abnormalities by two months and follow up liver biopsy sowing "regenerated bile ducts in the portal areas").

Oppenheimer AP, Koh C, McLaughlin M, Williamson JC, Norton TD, Laudadio J, Heller T, Kleiner DE, High KP, Morse CG. Vanishing bile duct syndrome in human immunodeficiency virus infected adults: a report of two cases. World J Gastroenterol 2013; 19: 115-21. PubMed PMID: 23326172.

(Two cases; 41 and 39 year old men with HIV infection presented with severe cholestasis while on antiretroviral therapy [bilirubin 4.7 and 10 mg/dL], liver biopsies showing bile duct loss [90% and 100%] and cholestasis, both subsequently dying of multiorgan failure, the cause of the VBDS not being clear in either patient).

Mason M, Adeyi O, Fung S, Millar BA. Vanishing bile duct syndrome in the context of concurrent temozolomide for glioblastoma. BMJ Case Rep 2014; 2014: bcr2014208117.

(62 year old woman with glioblastoma multiforme developed pruritus followed by jaundice 15 days after starting temozolomide [bilirubin 16.9 mg/dL, ALT 747 U/L, Alk P 1402 U/L, INR 0.9], liver biopsy showing absence of bile ducts in 60% of portal areas, but jaundice resolved within 3 and liver test abnormalities within 4 months of stopping).

White JC, Appleman S. Infliximab/Plasmapheresis in vanishing bile duct syndrome secondary to toxic epidermal necrolysis. Pediatrics 2014; 134: e1194-8. PubMed PMID: 25246624.

(6 year old boy developed fever and cough treated with cefdinir and one week later had abnormal liver tests [bilirubin 2.7 rising to 24 mg/dL, ALT 127 U/L, Alk P 631 U/L, GGT 608 U/L] and toxic epidermal necrolysis with respiratory failure and worsening jaundice; liver biopsy showing absence of bile ducts, therapy with infliximab, corticosteroids and plasmapheresis had little effect and he died of multiorgan failure 50 days after presentation).

Tekin F, Celik F, Nart D, Akarca U. The first report of oxcarbazepine-induced vanishing bile duct syndrome. J Gastrointestin Liver Dis 2014; 23: 222-3. PubMed PMID: 24949618.

(55 year old woman with Sjogren syndrome developed jaundice and pruritus 4 weeks after starting oxycarbazepine for seizures [bilirubin 22.7 mg/dL, ALT 110 U/L, Alk P 480 U/L, GGT 1255 U/L], liver biopsy showing no bile ducts, and subsequent progressive course led to septic shock and death1 month after presentation).

Levine C, Trivedi A, Thung SN, Perumalswami PV. Severe ductopenia and cholestasis from levofloxacin drug-induced liver injury: a case report and review. Semin Liver Dis 2014; 34: 246-51. PubMed PMID: 24879988.

(67 year old woman developed jaundice 2 months after starting levofloxacin [bilirubin 16.3 mg/dL, ALT 614 U/L, Alk P 483 U/L], liver biopsy showing severe bile duct loss and cholestasis, with slow improvement but persistent jaundice [bilirubin 13.0 mg/dL] when last seen 18 months after onset).

Kim HY, Yang HK, Kim SH, Park JH. Ibuprofen associated acute vanishing bile duct syndrome and toxic epidermal necrolysis in an infant. Yonsei Med J 2014; 55: 834-7. PubMed PMID: 24719156.

(7 month old girl developed toxic epidermal necrolysis 2 days after starting ibuprofen for fever [initial bilirubin 0.5 rising to 9.5 mg/dL, ALT 523 U/L, Alk P 500 U/L], liver biopsy showing paucity of bile ducts and cholestasis, improving over the next 3 months: "the biochemical data had shown tendency for resolution").

Conrad MA, Cui J, Lin HC. Sertraline-associated cholestasis and ductopenia consistent with vanishing bile duct syndrome. J Pediatr 2016; 169: 313- 5.e1. PubMed PMID: 26597434.

(15 year old boy with depression developed jaundice 6 months after starting sertraline [bilirubin 8.0 rising to 29.2 mg/dL, ALT 238 U/L, GGT 36 U/L, INR 1.0], biopsy showing decrease in bile ducts and marked cholestasis, but abnormalities resolved within 4 months of stopping sertraline).

Bakhit M, McCarty TR, Park S, Njei B, Cho M, Karagozian R, Liapakis A. Vanishing bile duct syndrome in Hodgkin's lymphoma: A case report and literature review. World J Gastroenterol 2017; 23: 366-72. PubMed PMID: 28127210.

Bonkovsky HL, Kleiner DE, Gu J, Odin JA, Russo MW, Navarro VM, Fontana RJ, et al.; U.S. Drug Induced Liver Injury Network Investigators. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. Hepatology 2017; 65: 1267-77. PubMed PMID: 27981596.

Xie W, Wang Q, Gao Y, Pan CQ. Vanishing bile duct syndrome with hyperlipidemia after ibuprofen therapy in an adult patient: a case report. BMC Gastroenterol 2018; 18: 142. PubMed PMID: 30268094.

Visentin M, Lenggenhager D, Gai Z, Kullak-Ublick GA. Drug-induced bile duct injury. Biochim Biophys Acta Mol Basis Dis 2018; 1864(4 Pt B): 1498-506. PubMed PMID: 28882625.

Abugroun A, Colina Garcia I, Ahmed F, Potts S, Flicker M. The first report of atovaquone/proguanil-induced vanishing bile duct syndrome: Case report and mini-review. Travel Med Infect Dis 2019; 32: 101439. PubMed PMID: 31238106.

Shah P, Larson B, Wishingrad M, Nissen N, Björnsson E, Sundaram V. Now you see it, now you do not: a case of infliximab-Induced vanishing bile duct syndrome. ACG Case Rep J 2019; 6: e00134. PubMed PMID: 31620531.

Tejedor-Tejada J, García-Pajares F, Madrigal Rubiales B. Hepatobiliary and pancreatic: sertraline-induced vanishing bile duct syndrome treated with plasmapheresis. J Gastroenterol Hepatol 2019; 34: 488. PubMed PMID: 30536927.

Larrey E, Patouraux S, Spreux A, Canivet CM, Piche T, Tran A, Anty R. Fatal cholestatic hepatitis after a single dose of celecoxib. Clin Res Hepatol Gastroenterol 2019; 43: e82-e85. PubMed PMID: 30449626.