

Cholestasis, Itching, Xanthomas and Diversion

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Complications of Alagille Syndrome

- Related to cholestasis (failure to secrete bile)
 - Nutritional
 - Growth Failure
 - Vitamin Deficiencies
 - Pancreatic insufficiency
 - Bone disease
 - Pruritus
 - Hypercholesterolemia
 - Xanthomata

Pruritus (Itching)

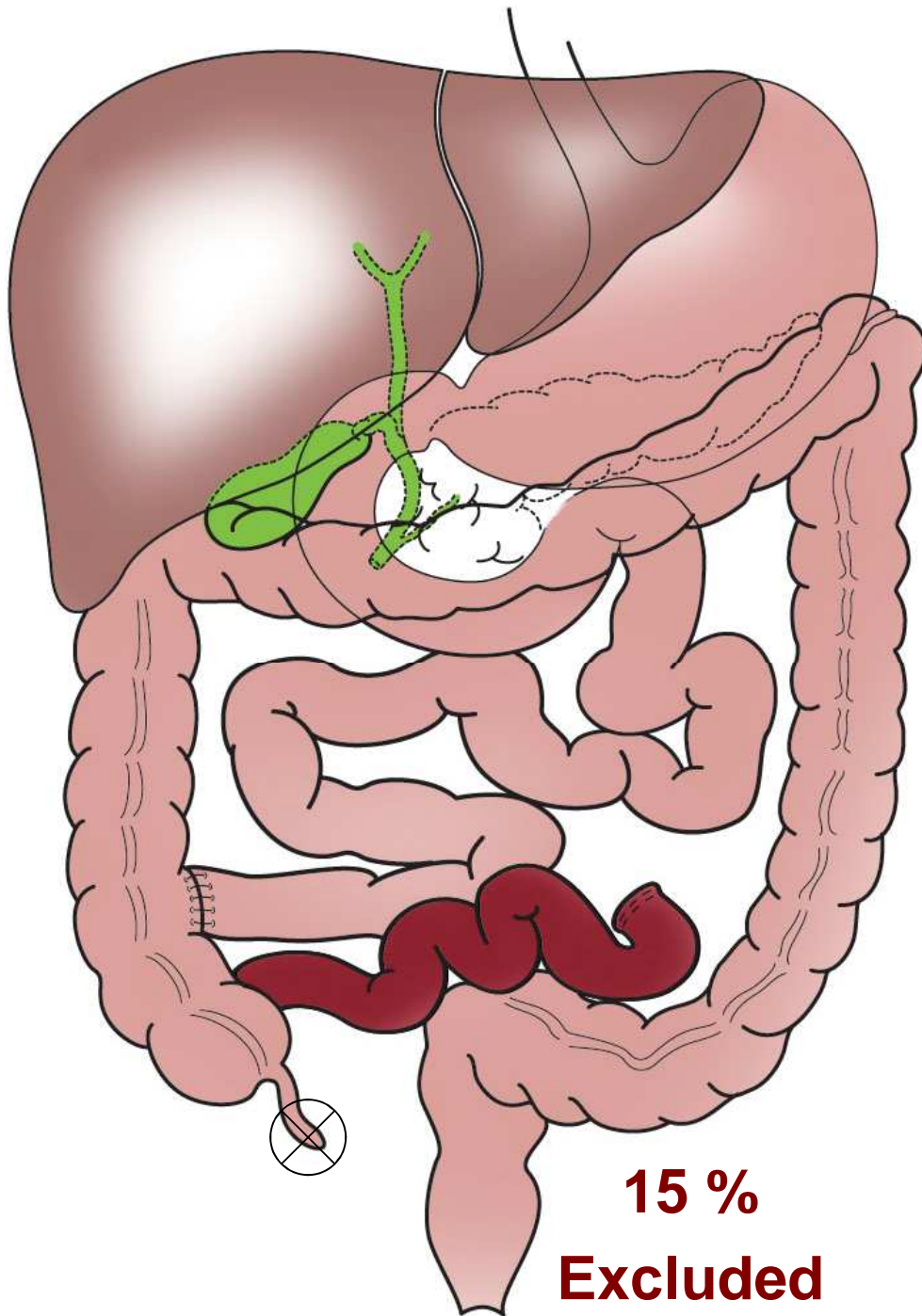
- Roughly correlates with cholestasis and serum bile acid concentrations
- Potential causes
 - Bile acids
 - Endogenous opiates

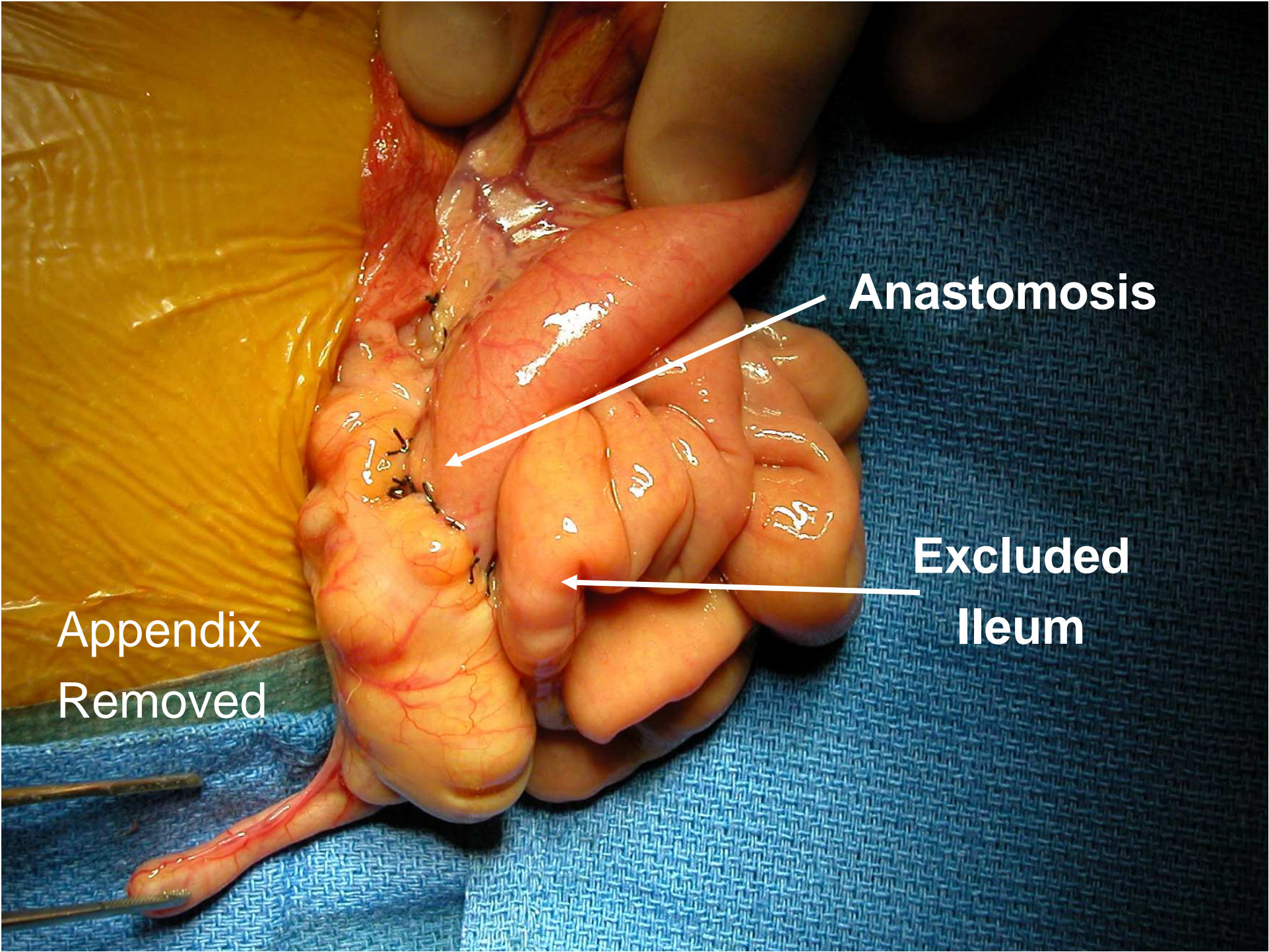
Treatment of Pruritus

- Local
 - Avoid dry skin (use emollients)
- Drug Therapy
 - Ursodeoxycholic acid (URSO, Actigall)
 - Antihistamines
 - Rifampin
 - Anionic resin binders (cholestyramine, colestipol, colesevelam)
 - Opiate antagonists (naloxone, naltrexone)
 - Other drugs (sertraline, ondansetron, phenobarbital)
- Surgical
 - Partial external diversion
 - Ileal exclusion

Ileal Exclusion

- 15 % excluded ileum
- Appendectomy
- Intussusception prevention seems necessary



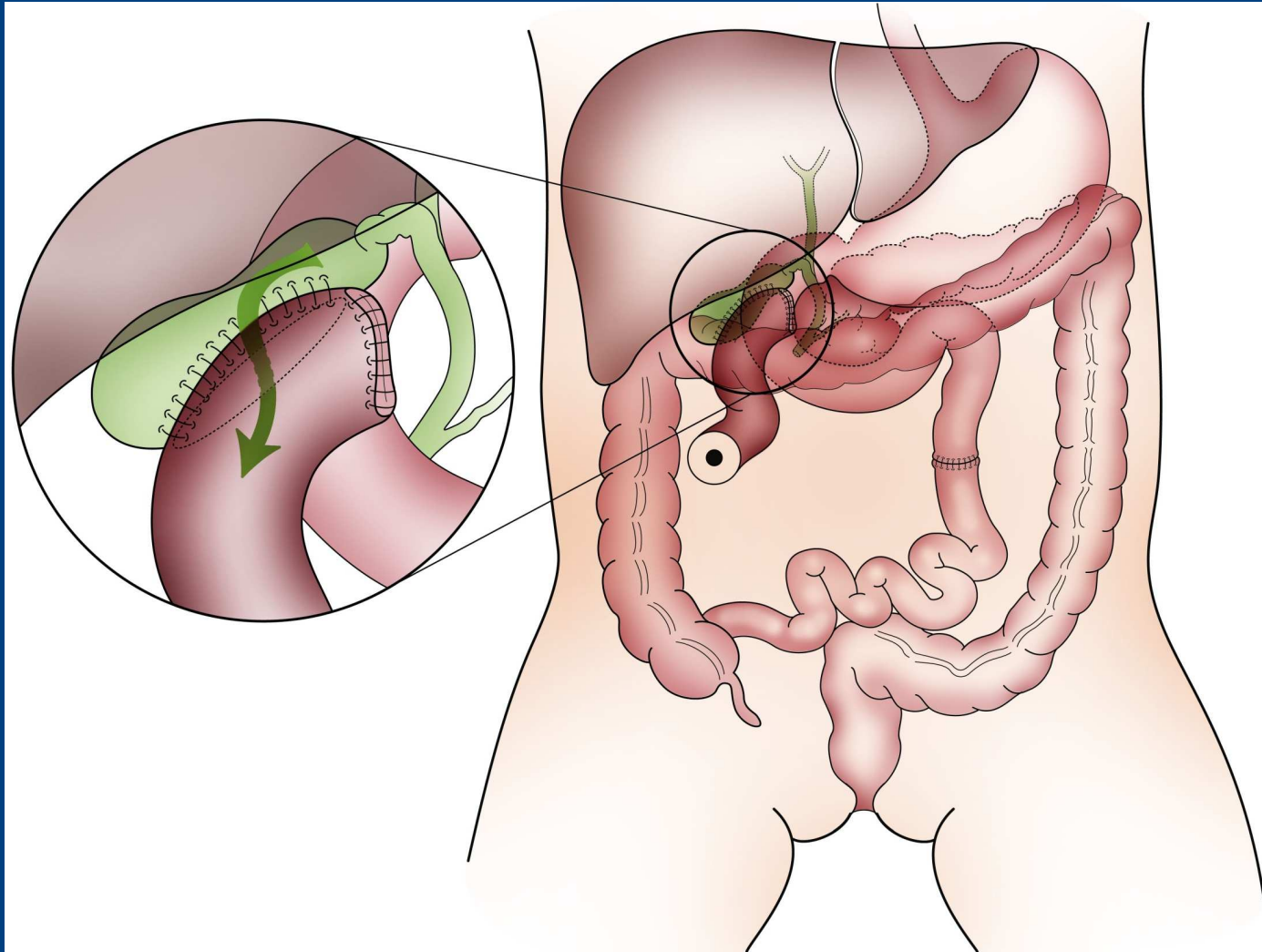


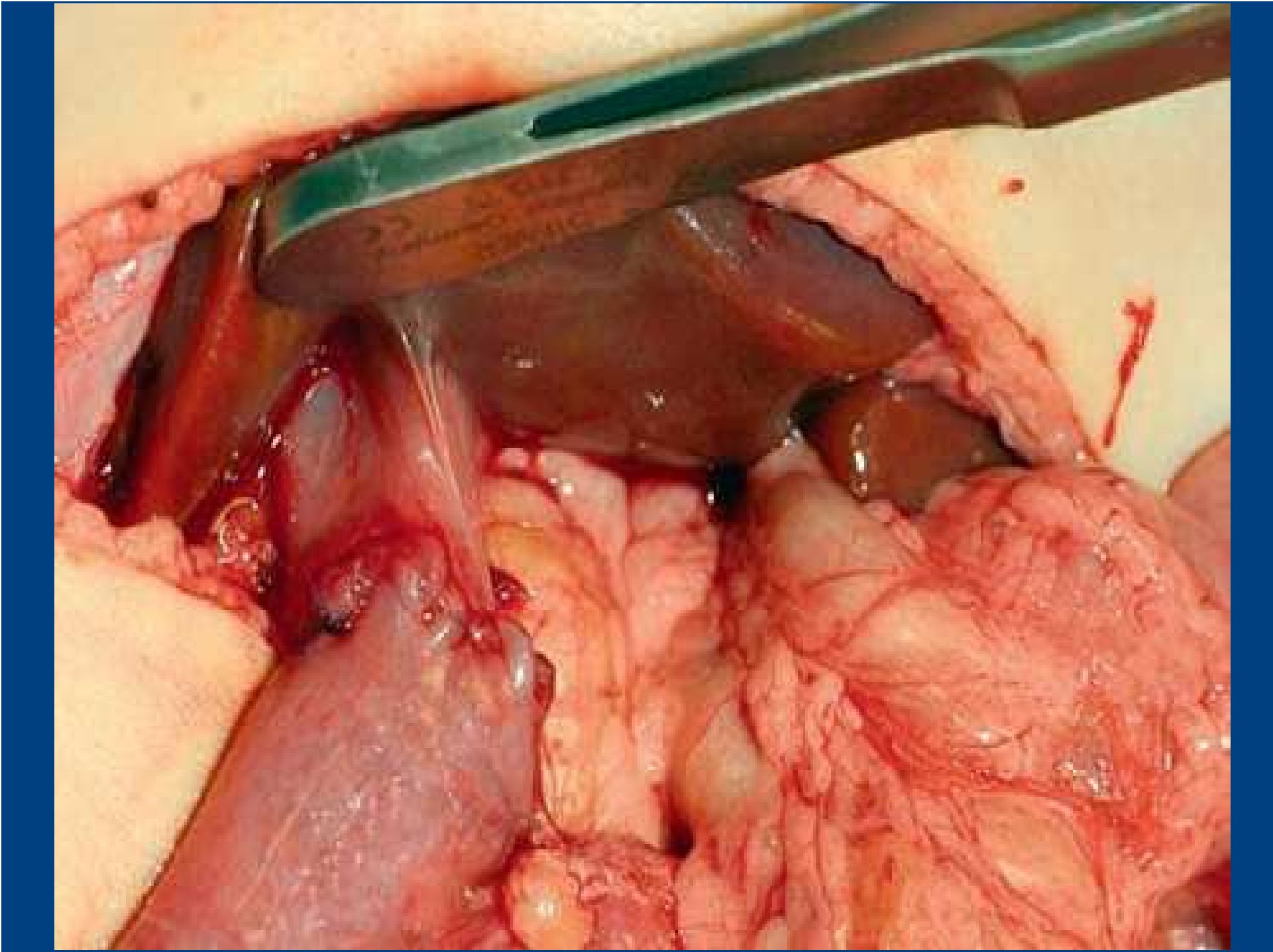
Anastomosis

**Excluded
Ileum**

**Appendix
Removed**

Partial External Biliary Diversion





Preop



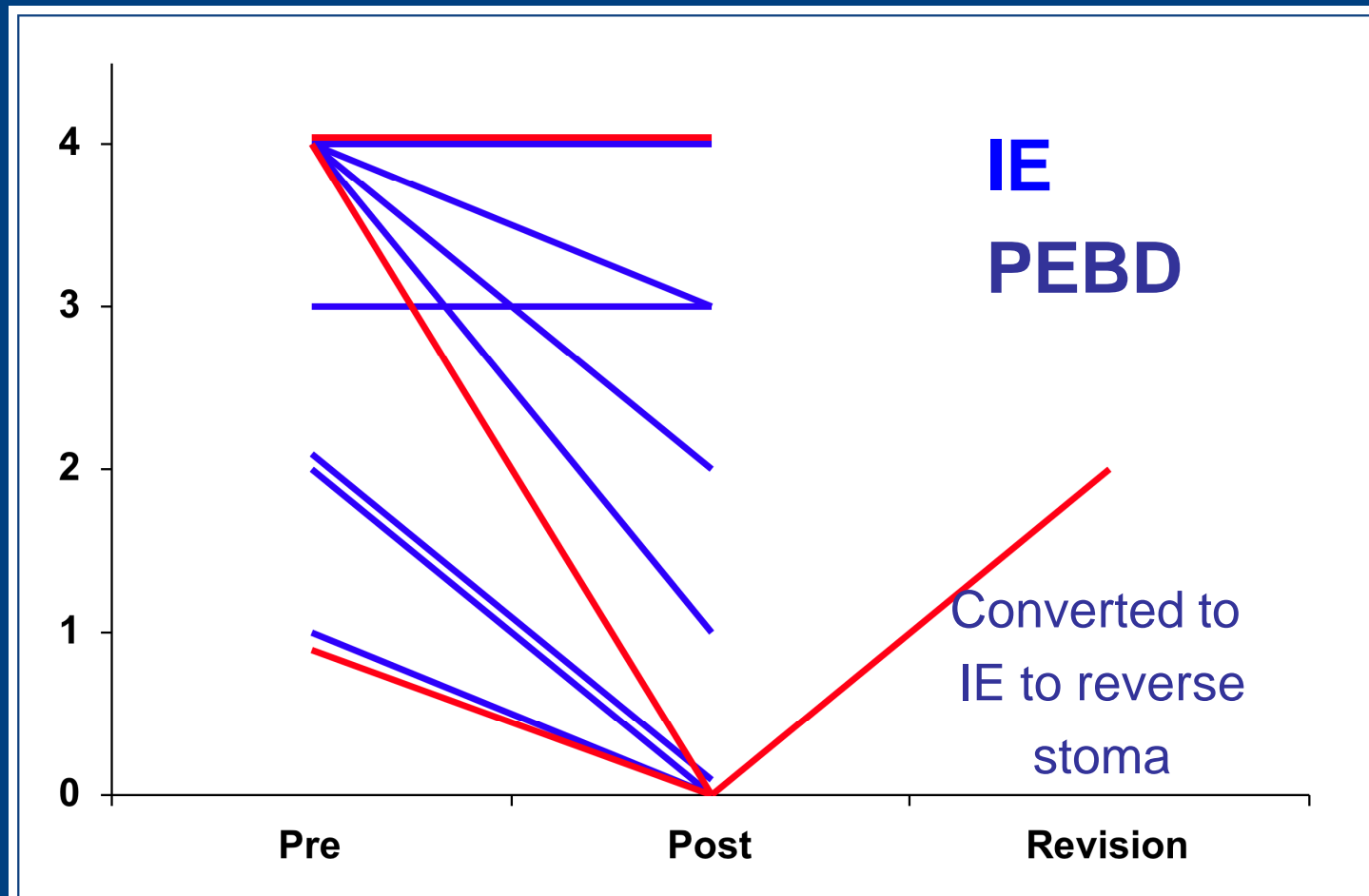
8 months Postop



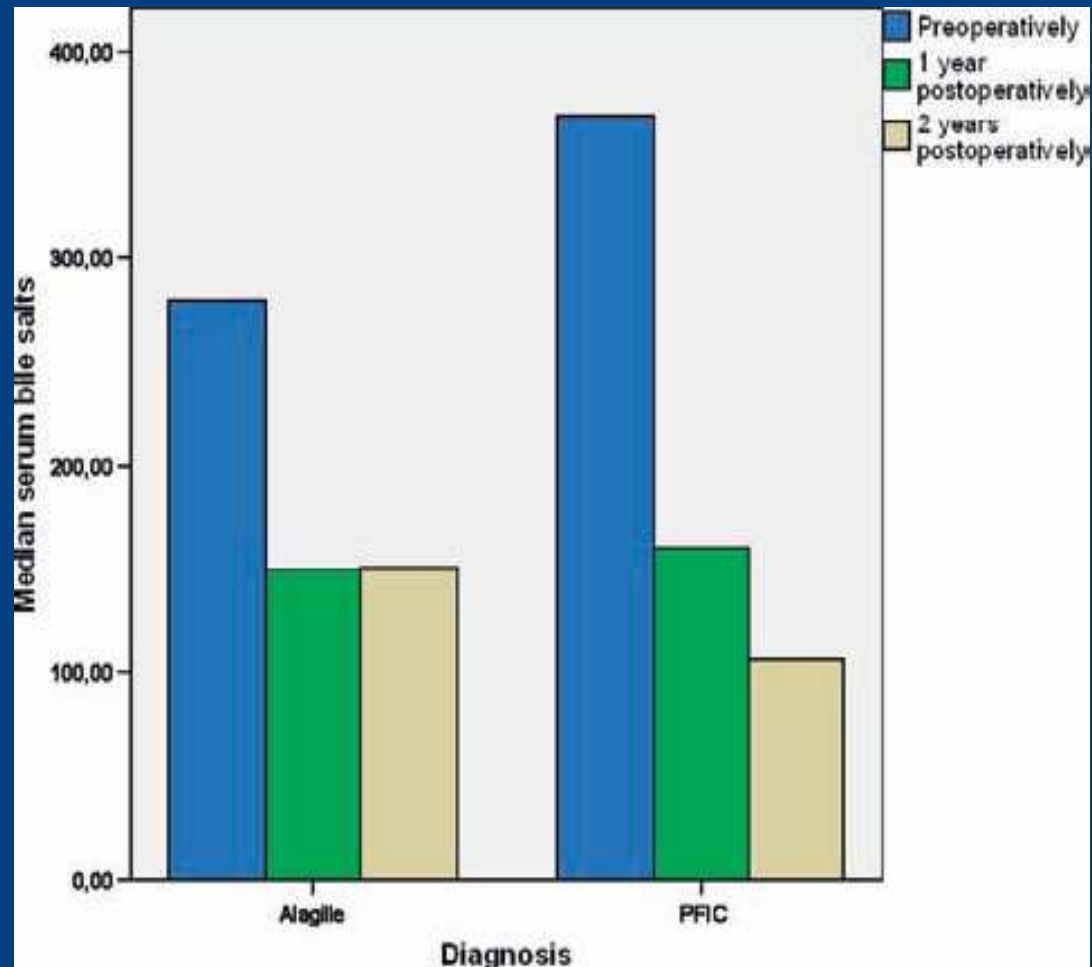
20 months Postop



Pre- and Post-Operative Pruritus Scores



Serum Bile Acids after Ileal Exclusion



Hyperlipidemia in Alagille Syndrome

- What is the nature of hyperlipidemia in AGS?
- Does it have any adverse effects in childhood or adulthood?
- Does hyperlipidemia affect the vasculopathy of AGS?
- Should it be treated? If so, how?

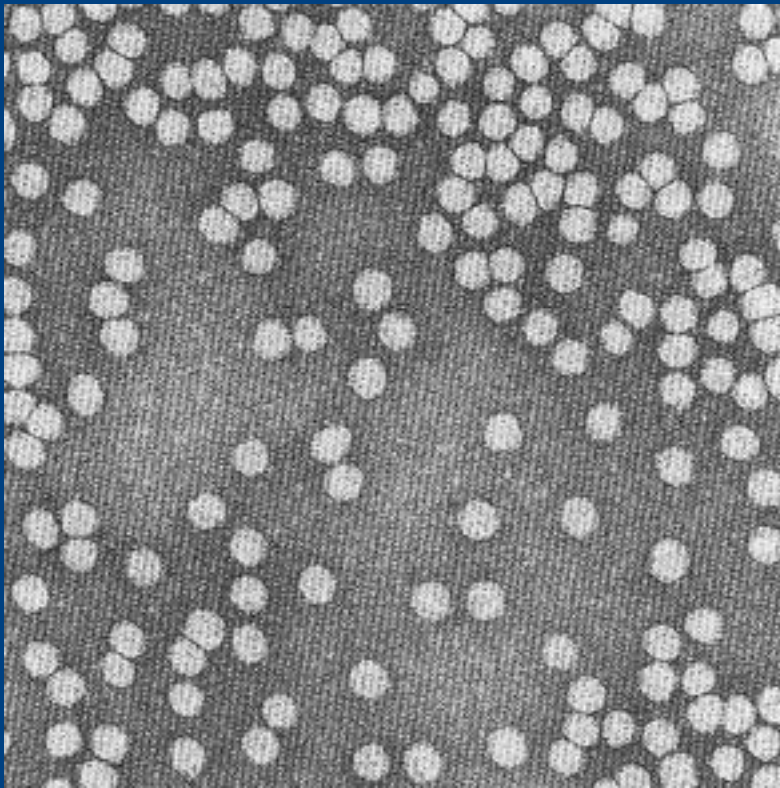
High Serum Cholesterol in Alagille Syndrome

- High cholesterol levels are seen in several types of cholestatic liver disease (AGS, PBC, bile duct obstruction, etc.)
- Often causes xanthomas on the skin
- Cholestasis results in several disturbances of lipid metabolism resulting in formation of an abnormal lipid particle in the blood, lipoprotein X

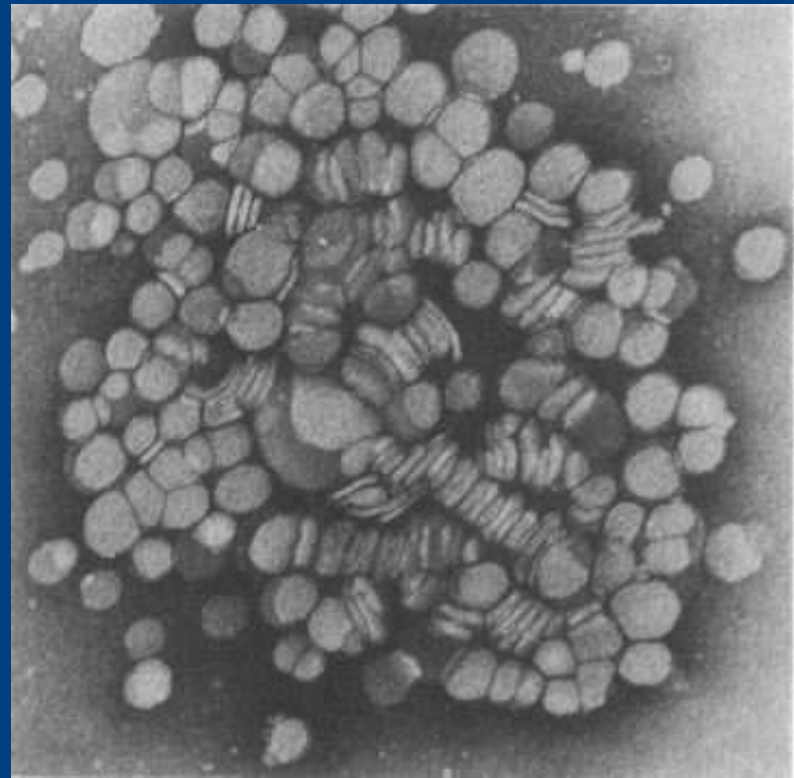
Normal Cholesterol Metabolism

- Liver is the “nerve center” for fat metabolism and makes most of the body’s cholesterol
- LDL particles transport cholesterol from the liver to tissues in the body by attaching to the LDL receptor
- LDL is “bad” when levels are too high and/or becomes oxidized and causes plaques to form in arteries resulting in reduced flow
- HDL is “good” and protects by transporting cholesterol back to the liver

Lipoprotein X



Normal LDL



Lipoprotein X

Lipoprotein X

- Formed by regurgitation of bile lipids into the blood from the liver
- Does not bind to the LDL receptor to deliver cholesterol to cells throughout the body as does normal LDL
- Increases liver cholesterol production by 5-fold
- Blocks normal removal of lipoprotein particles from the blood by the liver

Does Lipoprotein X Increase Cardiovascular Risk?

- 312 adult PBC patients followed for a mean of 7.4 years had no increased incidence of atherosclerotic death compared to matched US population (Crippin et al, 1992)
- 400 Italian adult PBC patients followed for a mean of 6.2 years had no increase in atherosclerotic death compared to matched controls (Longo et al, 2002)

Does Lipoprotein X Increase Cardiovascular Risk?

- 596 Dutch PBC patients followed over a 14-year period had no association of death with cardiovascular risk. However, liver failure accounted for 70% of deaths (Van Dam et al, 1997)
- Lipoprotein X from PBC patients is resistant to lipid oxidation and protects normal LDL from oxidation (Chang et al, 2004)

Does Lipoprotein X Increase Cardiovascular Risk?

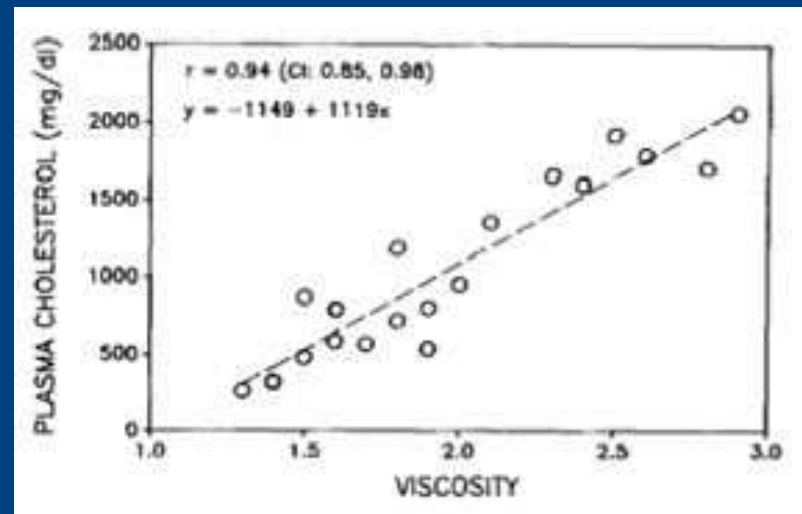
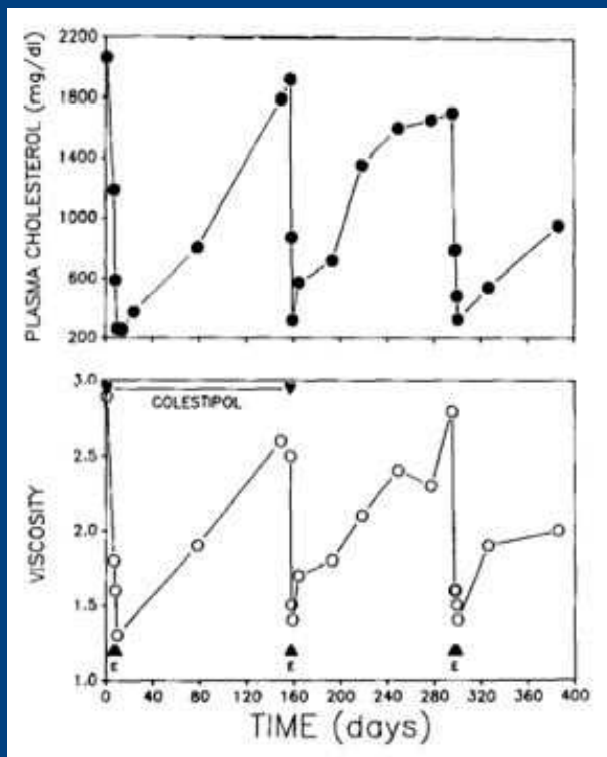
- Japanese AGS patients with elevated plasma cholesterol and lipoprotein X
 - Minimally elevated levels of oxidized LDL
 - Elevated HDL
 - Carotid artery wall thickness and wall stiffness not different from that of control children
- PFIC 1 and 2 patients
 - Normal plasma cholesterol and no lipoprotein X
 - High levels of oxidized LDL
 - Low HDL
 - Significantly increased carotid artery wall thickness and stiffness

Does Lipoprotein X Have Any Adverse Effects?

- Hyperviscosity syndrome
 - Caused by thickened blood due to high levels of red blood cells, abnormal proteins or lipoprotein X
 - Symptoms
 - Bleeding
 - Visual disturbances
 - Headache
 - Dizziness
 - Seizures
 - Not reported in Alagille syndrome, but is a potential risk at high lipoprotein X levels

Does Lipoprotein X Have Any Adverse Effects?

- Case report of adult PBC patient with hyperviscosity syndrome related to high lipoprotein X levels improved by plasma exchange to remove the lipoprotein X



Rosenson et al, 1990

AGS Vasculopathy

- Non-atherosclerotic vascular lesions occur in aorta, renal, celiac, hepatic, superior mesenteric, and subclavian arteries and the coronary ostia
- Most clinically significant are vascular lesions in the brain leading to hemorrhage
- Probably due to abnormal formation of blood vessels
- Although atherosclerotic injury not likely, the risk for injury in these vulnerable areas from hyperviscosity at high lipoprotein X levels is unknown

When To Treat?

- Severe cutaneous xanthomatosis
- Arbitrary total cholesterol levels above 1,500 mg/dl (?)
- Presence of known blood vessel lesions, especially in the central nervous system (?)
- CNS symptoms, especially those consistent with hyperviscosity syndrome (?)
- Family history of premature cardiovascular disease and heart attack (?)

How to treat?

- Treat the cholestasis
 - Ursodeoxycholic acid (URSO, Actigall)
 - Bile acid sequestrants
 - cholestyramine, colestipol, colesevelam
 - Generally poor compliance and effectiveness
 - Surgical
 - Partial external biliary diversion
 - Internal ileal bypass

Partial External Biliary Diversion

Table 2. Laboratory Values Before and After PEBD

Pt	Direct Bilirubin, mg/dL (<0.3) [*]			Bile Acids, $\mu\text{mol/L}$ (<10) [*]			Cholesterol, mg/dL (107-203) [*]			ALT, IU/L (2-30) [*]			GGT, IU/L (11-51) [*]		
	Pre-	Post-†	Last	Pre-	Post-†	Last	Pre-	Post-†	Last	Pre-	Post-†	Last	Pre-	Post-†	Last
1	0.3	0.3	0.3	129	34	39	284	277	277	188	495	495	406	183	183
2	4.5	3.1	3.0	78	22	7.5	774	419	232	484	440	175	1680	1272	499
3	7.9	8.4				54	1130	722	256		219	207	650	341	353
4		0.9	0.7	300	28	52	286	271	266	125	226	128		2076	599
5	2.7	3.5	3.6	159	94	23	617	295	350	127	158	176	741	232	311
6	0.4	1.0	0.8				168	283	283	88	85	153	551	586	673
7	1.8	0.5	0.3			6.2	1812	305	324	71	298	180	1139	947	674
8	0.2	0.1	0.2	16	7.8	7.8		207	201	131	479	273	333	592	363
9	0.8	0.9	0.9		57	44		511		687	181	212	370	134	166

^{*}Normal values.

†Between 6 months and 1 year post-PEBD.

How to Treat

- Statin therapy
 - Inhibits liver cholesterol production and lowers serum cholesterol level
 - May improve liver disease in PBC patients
 - Potential for liver toxicity and muscle injury
 - Most statins eliminated in bile from the liver, require careful dosing
- Transplant
 - Not indicated for hyperlipidemia alone

Summary

- AGS results in several complications related to cholestasis, retention of bile acids and disturbed lipid metabolism.
- Pruritus and xanthomas may be severe and debilitating but may be treated.
- Drug therapy, as well as surgical intervention with PEBD and IE, may be effective in many patients in reducing serum bile acids, cholesterol levels, pruritus, and skin xanthomas.
- Lipoprotein X in AGS probably does not contribute to atherosclerosis and may even be protective.

Summary

- Markedly elevated lipoprotein X levels may cause hyperviscosity syndrome and possibly compound AGS vasculopathy at high levels. This should be formally studied in AGS.
- Treatment of AGS dyslipidemia is controversial and no evidence-based guidelines exist, but consider specific therapy if:
 - Debilitating xanthomas
 - Extremely high cholesterol levels (> 1,500 mg/dl)
 - Definite vasculopathy, especially intracranial
 - Neurological symptoms
 - Concomitant primary hyperlipidemia (familial hypercholesterolemia)



Questions