Pediatric Hepatology: Guidance For Your Daily Practice

Alexander Weymann, M.D.
Medical Director, Liver Center and Liver Transplantation
Nationwide Children's Hospital
Assistant Professor of Clinical Pediatrics
The Ohio State University College of Medicine
Columbus, Ohio

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

I have no financial relationship to disclose

Patient History 1

- 49 day old baby boy with CC: jaundice
- Jaundice since birth, worse over last 2 weeks
- 39 weeks EGA, NSVD, no phototherapy
- Discharged with a total bilirubin of 14 mg/dL; repeat 10 (a few weeks prior to admission)
- Otherwise well; no fever or rash
- EnfaCare 2 oz q 2 h; voiding & stooling
- Stools white or yellowish

Phone call from referring GI M.D.

Total bilirubin 7.7

Direct bilirubin 5.9

J Pediatr Gastroenterol Nutr. 2017 Jan;64(1):154-168

Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, McLin VA, Molleston JP, Neimark E, Ng VL, Karpen SJ

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

Background

- Cholestatic jaundice in infants is uncommon but potentially serious (hepatobiliary dysfunction)
- Early detection and accurate diagnosis are important for successful treatment and optimal prognosis
- Focus to identify infants with biliary atresia (BA)
- However, most cholestasis in this age group is not due to BA

Biliary Atresia

- Most frequent identifiable cause of *obstructive* jaundice in first 3 months of life
- Etiology unknown; prevalence 1:12,000 in US
- 16% have other anomalies with (10%) or without (6%) laterality defect (situs inversus)
- Kasai procedure: ≈70% success if before 60 days; <25% if after 90 days
- Optimal approach to early screening unclear

Recommendations

1. Any **formula-fed** infant noted to be **jaundiced after 2 weeks** of age [2.5-15%] should be evaluated for cholestasis with measurement of total and conjugated (direct) serum bilirubin (1A). Depending upon local practice, **breastfed** babies that appear otherwise well may be **followed clinically until 3 weeks** of age, at which time, if they appear icteric, should then undergo [measurement] of total and conjugated (direct) serum bilirubin.

Recommendations

2. Measurement of serum bilirubin should always be fractionated into unconjugated (indirect) or conjugated (direct) hyperbilirubinemia (1A).

3. Conjugated (direct) hyperbilirubinemia (> 1.0 mg/dL) is pathological and warrants diagnostic evaluation (1A).

History

- Prenatal Hx, NB screening, vitamin K
- Prematurity, NICU +/- complications, PN
- Onset of jaundice, stool color, urine color
- Maternal history: miscarriages, pruritus, liver dysfunction during pregnancy, fever or rash, drug/medication exposure
- Family history: consanguinity, siblings with liver disease, relatives with lung disease?

Family history	
Consanguinity	Increased risk of autosomal recessive disorders
Neonatal cholestasis in the parents or siblings	Cystic fibrosis, α-1-antitrypsin deficiency, progressive familial intrahepatic cholestasis, Alagille syndrome are all genetic conditions causing neonatal cholestasis
History of repeated fetal loss or early demise	Gestational alloimmune liver disease
Spherocytosis and other hemolytic diseases	Known to aggravate conjugated hyperbilirubinemia
Prenatal history	
Prenatal ultrasonography findings	Presence of choledochal cyst, cholelithiasis, bowel anomalies or concern for syndrome
Cholestasis of pregnancy	May be seen in heterozygotes for *PFIC* gene mutations; mitochondrial disorder
Acute fatty liver of pregnancy	Neonatal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency
Maternal infections	TORCH infections
Infant history	
Gestational age	Prematurity as a risk factor for neonatal hepatitis
SGA	Increased risk of neonatal cholestasis, congenital infections
Alloimmune hemolysis; glucose-6-P-dehydrogenase deficiency; hydrops fetalis	Increased risk of neonatal cholestasis
Neonatal infection	Urinary tract infection, sepsis related cholestasis, CMV, HIV, syphilis, etc
Newborn screen	Panhypopituitarism galactosemia, fatty acid oxidation defects, cystic fibrosis
Source of nutrition: breast milk, formula, PN	Galactosemia, hereditary fructose intolerance, PN-associated liver disease
Growth	Genetic and metabolic disease
Vision	Septo-optic dysplasia
Hearing	PFIC1, TJP2
Vomiting	Metabolic disease, bowel obstruction, and pyloric stenosis
Stooling	Delayed stooling: CF, panhypopituitarism; diarrhea: infection, metabolic disease
Stool color	Acholic stools: cholestasis, biliary obstruction
Urine characteristics: smell and color	Dark urine (conjugated hyperbilirubinemia), metabolic disease
Excessive bleeding	May indicate coagulopathy, vitamin K deficiency
Disposition: irritability, lethargy	Metabolic disease or sepsis, panhypopituitarism
Abdominal surgery	Necrotizing enterocolitis, intestinal atresia

CF = cystic fibrosis; CMV = cytomegalovirus; HIV = human immunodeficiency virus; PFIC = progressive familial intrahepatic cholestasis; PN = parenteral nutrition; TJP = tight-junction protein; TORCH = Toxoplasma gondii, other viruses, rubella, cytomegalovirus, and herpes simplex virus.

Physical examination

- General: poor growth, dysmorphic features?
- Skin: jaundice, rash, vascular malformations?
- Abdomen: protuberance/distension, visible veins, (firm) hepatomegaly, splenomegaly?
- Heart: murmur?
- Genitalia: hypoplastic male genitalia?
- Neurology: vigor, tone, fix and follow?

Assessment of general health	Ill appearance may indicate infection or metabolic disease, infants with biliary atresia typically appear well
General appearance	Dysmorphic features: Alagille syndrome in the neonate rarely exhibits characteristic facial appearance with a broad nasal bridge, triangular facies, and deep-set eyes. Typical facial features may appear at around 6 months of age, but are often nonspecific (69)
Vision/slit lamp examination	
Hearing	Congenital infection, storage disease, septo-optic dysplasia, posterior embryotoxon, cataracts
Congenital infections, PFIC1, TJP2, mitochondrial	
Cardiac examination: murmur, signs of heart failure	Congenital heart disease: Alagille syndrome, biliary atresia splenic malformation syndrome
Abdominal examination	Presence of ascites; abdominal wall veins, liver size and consistency, spleen size and consistency (or absence thereof), abdominal masses, umbilical hernia
Stool examination (crucial—the primary physician should make every effort to view stool pigment)	Acholic or hypopigmented stools suggest cholestasis or biliary obstruction
Neurologic	Note overall vigor and tone

PFIC = progressive familial intrahepatic cholestasis; TJP = tight-junction protein.

Recommendations

4. A thorough physical examination is crucial to the proper evaluation of the jaundiced infant. Attention to hepatomegaly, splenomegaly, and ill appearance warrants special considerations (1A).

5. Direct visualization of stool pigment is a key aspect of a complete evaluation of the jaundiced infant (1A).

Acholic stool

At this point:
Referral to Hepatologist

"…and what are THEY going to do??"

Tier 1: Aim to evaluate after cholestasis has been established in order to both identify treatable disorder as well as to define the severity of the liver involvement
Blood—CBC + differential, INR, AST, ALT, AP, GGTP, TB, DB (or conjugated bilirubin), albumin and glucose. Check α-1-antitryspin phenotype (Pi typing) and level, TSH, T4 if newborn screen results not readily available
Urine—urinalysis, culture, reducing substances (rule out galactosemia)
Consider bacterial cultures of blood, urine and other fluids especially if infant is clinically ill.
Verify results of treatable disorders (such as galactosemia and hypothyroidism) from newborn screen
Obtain fasting ultrasound
Tier 2: Aim to complete a targeted evaluation in concert with pediatric gastroenterologist/hepatologist
General—TSH and T4 values, serum bile acids, cortisol
Consideration of specific etiologies
Metabolic—serum ammonia, lactate level, cholesterol, red blood cell galactose-1-phosphate uridyltransferase, urine for succinylacetone and organic acids. Consider urine for bile salt species profiling
ID—direct nucleic acid testing via PCR for CMV, HSV, listeria
Genetics—in discussion with pediatric gastroenterologist/hepatologist, with a low threshold for gene panels or exome sequencing
Sweat chloride analysis (serum immunoreactive trypsinogen level or CFTR genetic testing) as appropriate
Imaging
CXR—lung and heart disease
Spine—spinal abnormalities (such as butterfly vertebrae)
Echocardiogram—evaluating for cardiac anomalies seen in Alagille syndrome
Cholangiogram
Liver biopsy (timing and approach will vary according to institution and expertise)
Consideration for consultations
Ophthalmology
Metabolic/Genetic (consider when to involve, especially when there is consideration for gene panels or whole exome sequencing)
Cardiology/ECHO (if murmur present or has hypoxia, poor cardiac function)
General pediatric surgery
Nutrition/dietician

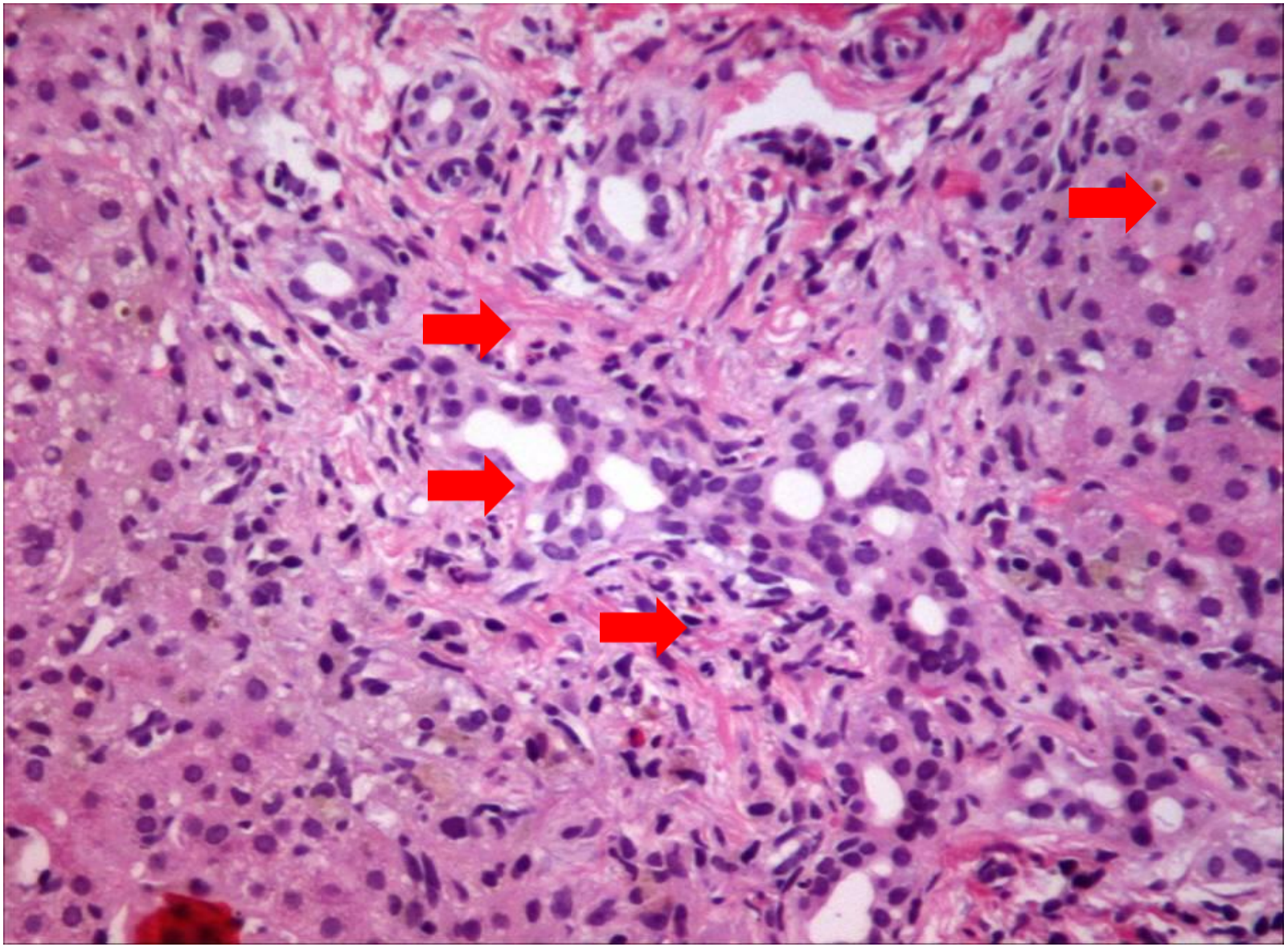
ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CBC = complete blood count; CFTR = cystic fibrosis trans-membrane receptor; DB = conjugated (direct) bilirubin; ECHO = echocardiogram; GGTP = gamma-glutamyl transferase; HSV = herpes simplex virus; ID = infectious diseases; INR = international normalized ratio; PCR = polymerase chain reaction; TB = total bilirubin; TSH = thyroid-stimulating hormone.

Histopathology

- “Cornerstone of workup”, 90-95% correct diagnosis by experienced pathologist (Russo et al., Clin. Gastroenterol. Hepatol.)

- Beware the “Great Impostors”: A1AT ZZ, CFLD, PNALD, Alagille syndrome, […]

Biliary Atresia



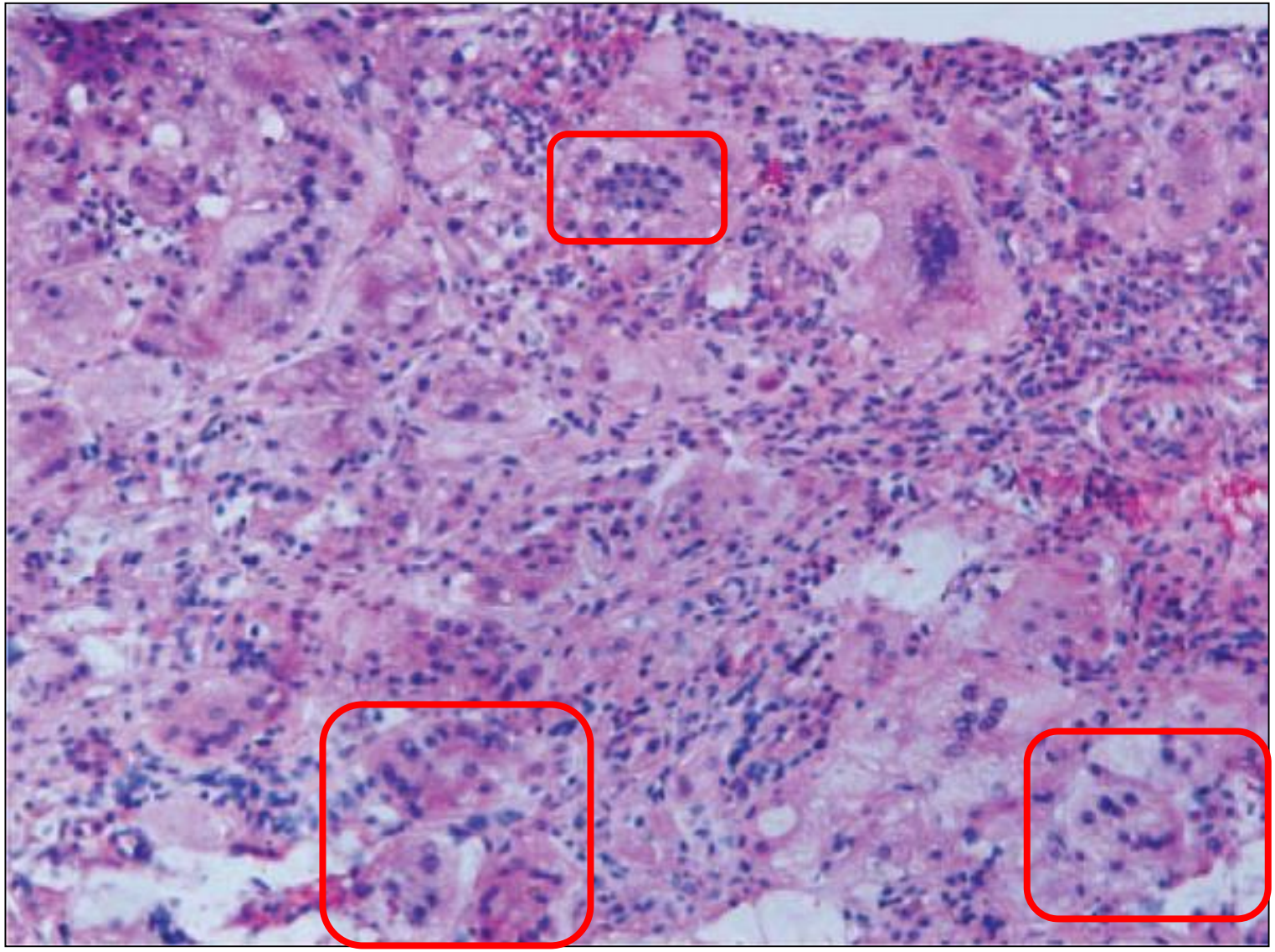
Recommendations

9. In the hands of an experienced pediatric pathologist, histopathological findings of bile duct proliferation, bile plugs, and fibrosis in an appropriately timed liver biopsy is the most supportive test in the evaluation of the infant with protracted conjugated hyperbilirubinemia (1B). *Diseases other than BA that can cause cholestasis* can be determined via histologic examination of the liver.

Neonatal Cholestasis: Other Causes

- Alagille Syndrome
- Cystic Fibrosis
- Alpha-1 Antitrypsin Deficiency
- Infections (UTI, CMV, others…)
- Endocrine Disorders (hypopituitarism, thyroid)
- Choledochal Cyst
- Progressive Familial Intrahepatic Cholestasis
- Bile Acid Synthesis/Metabolism Disorders

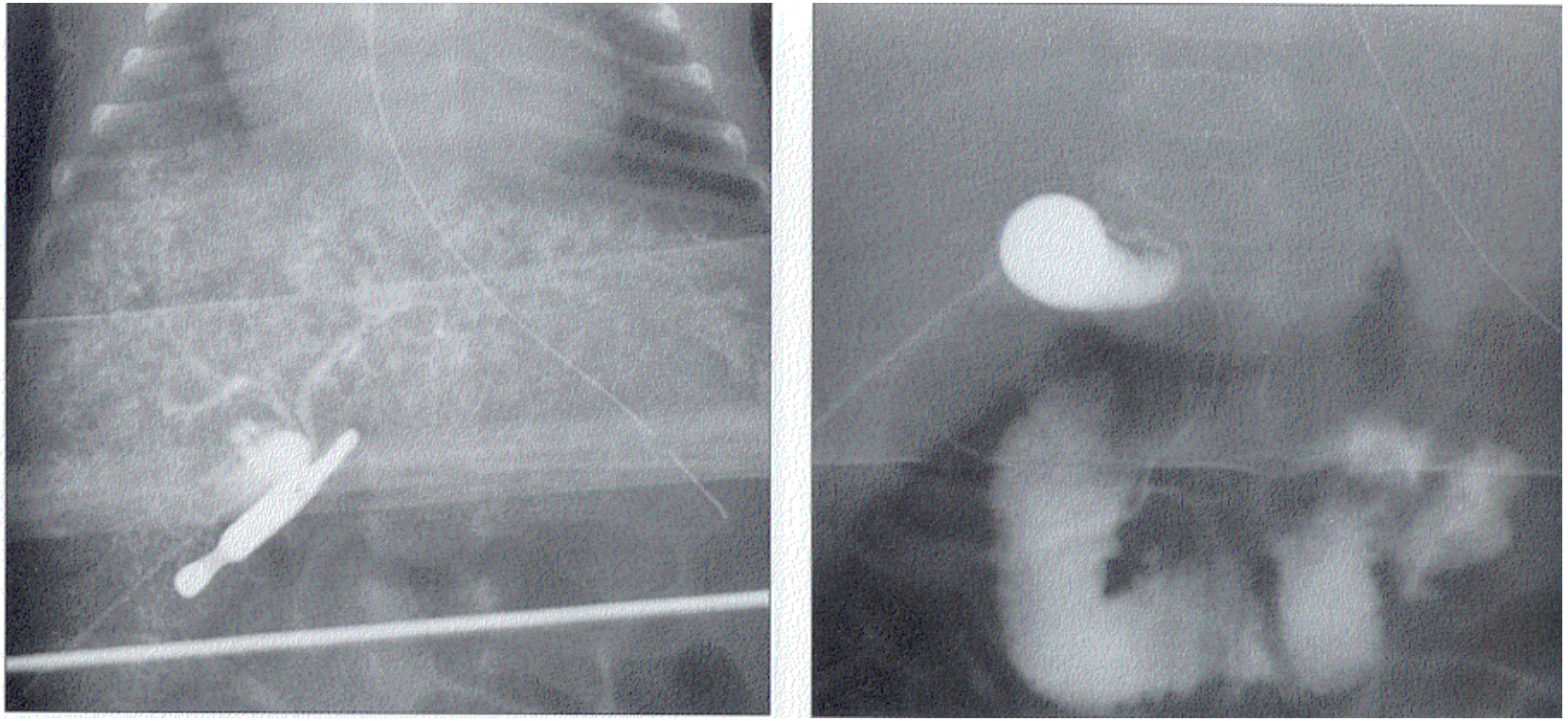
Idiopathic Neonatal Hepatitis



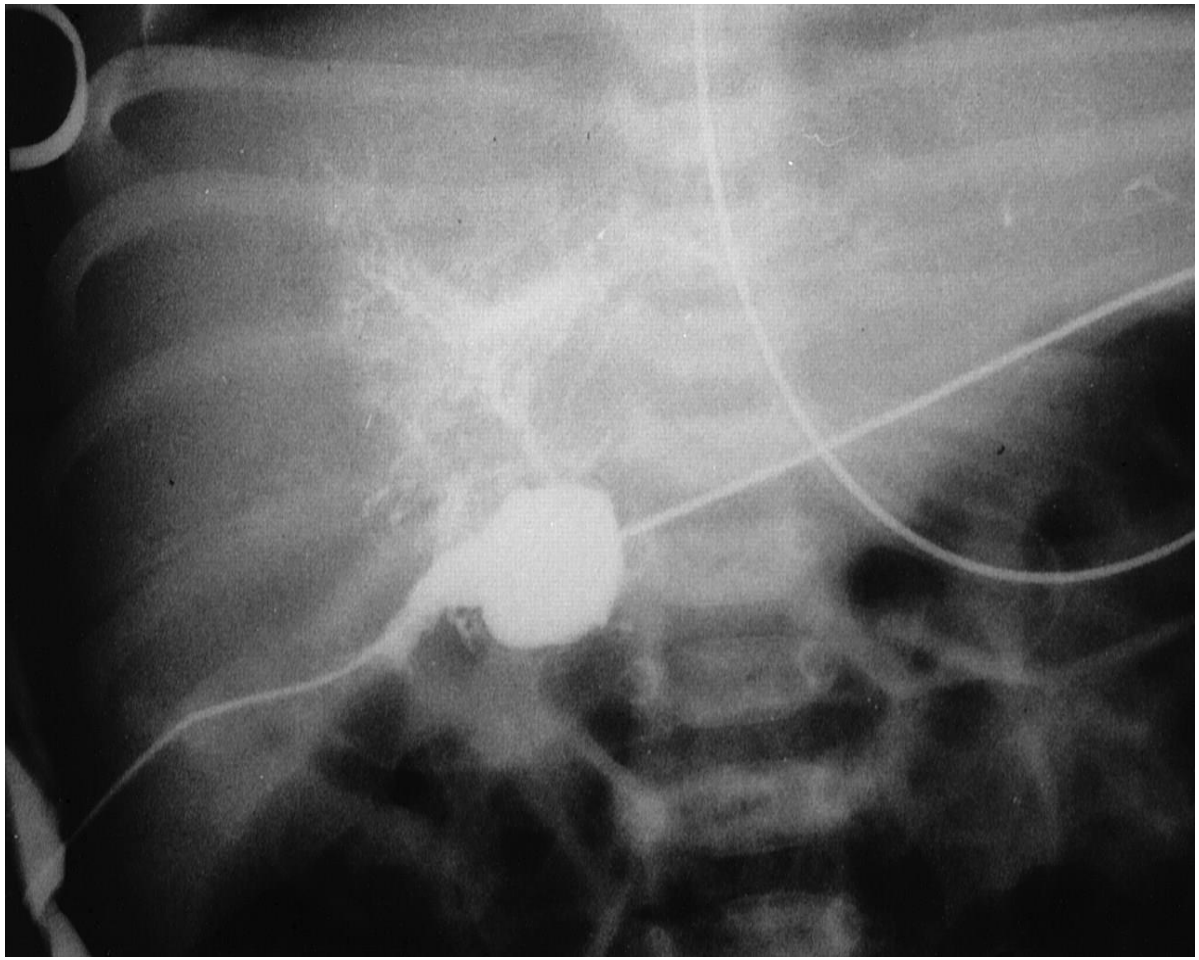
Recommendations

10. Evaluation by intraoperative cholangiogram and histological examination of the duct remnant is considered the gold standard to diagnose biliary atresia (1A).

Cholangiogram (normal)



Biliary Atresia (+ Choledochal Cyst)



Patient 1 - Physical Exam

- Well appearing baby boy
- Weight 4.82 kg (29%), Length 54 cm (6%)
- Mildly icteric conjunctivae
- Sacral mongolian spot; no other skin abnormalities
- Liver edge palpable 2-3 cm below the RCM
- Whitish-gray stool in diaper

Initial lab results

- **ALT 165, AST 189, AP 529, GGT 218**
- PT 12.1 / INR 0.84
- Albumin 3.9
- CBC: WBC 10.3, Hgb 10.0 (RDW 17%), Plts 522

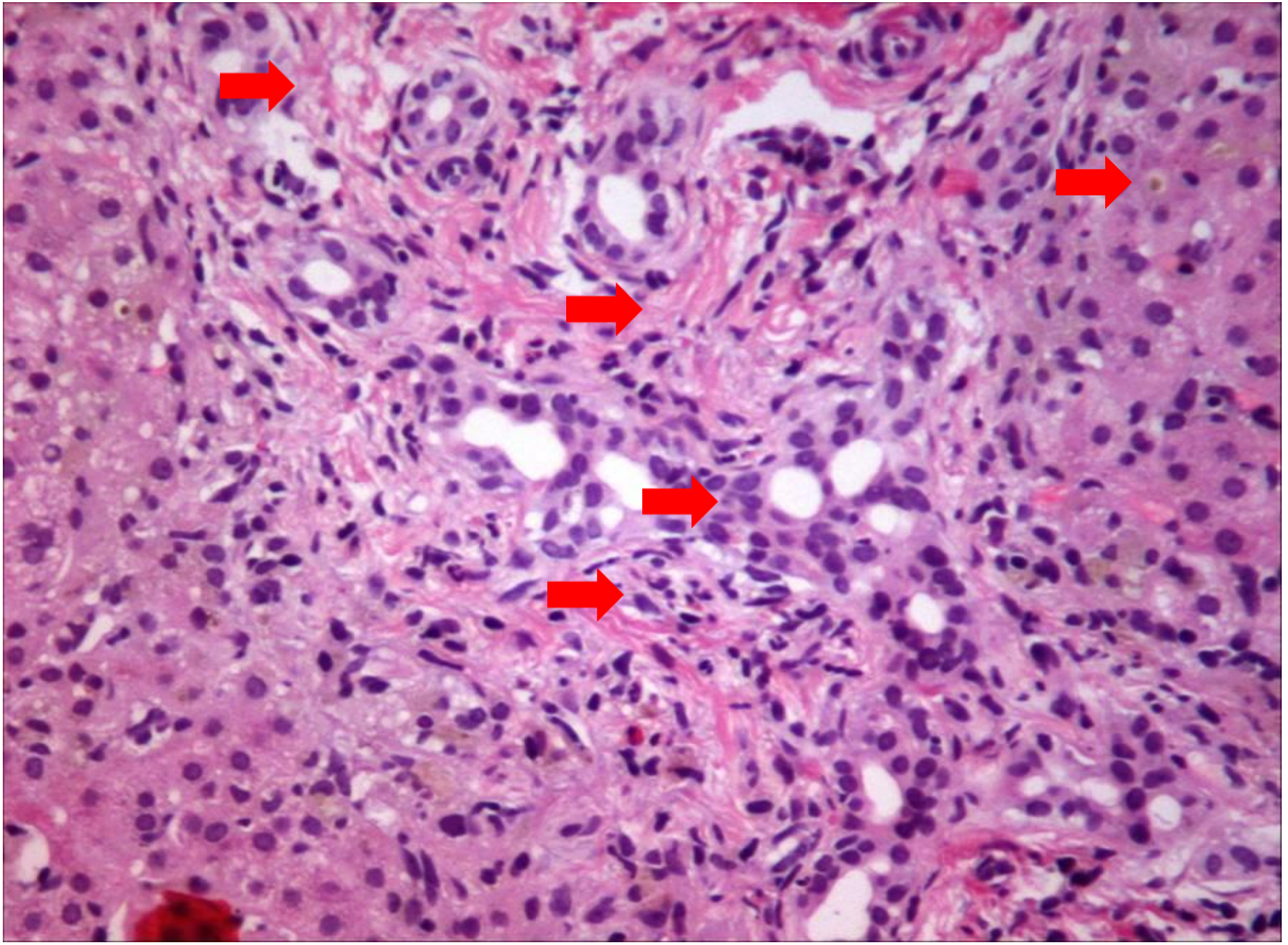
Other studies

- **Ultrasound**: “The liver is normal in size and echotexture. There is no intrahepatic duct dilation. The gallbladder is markedly hypoplastic measuring about 1 cm in length and 0.5 cm in diameter. *No definite common duct is seen in the porta hepatis*.”

- **Spine X-ray**: No definite butterfly vertebrae
- **Echocardiogram**: Structurally normal heart

Liver biopsy

Cholestasis with obstructive features: **bile plugs**, rosette formation, **ductular proliferation**, **portal edema** and **neutrophilic portal infiltrate**. **Fibrosis with portal expansion**. Giant cells and extramedullary hematopoiesis in the lobules.

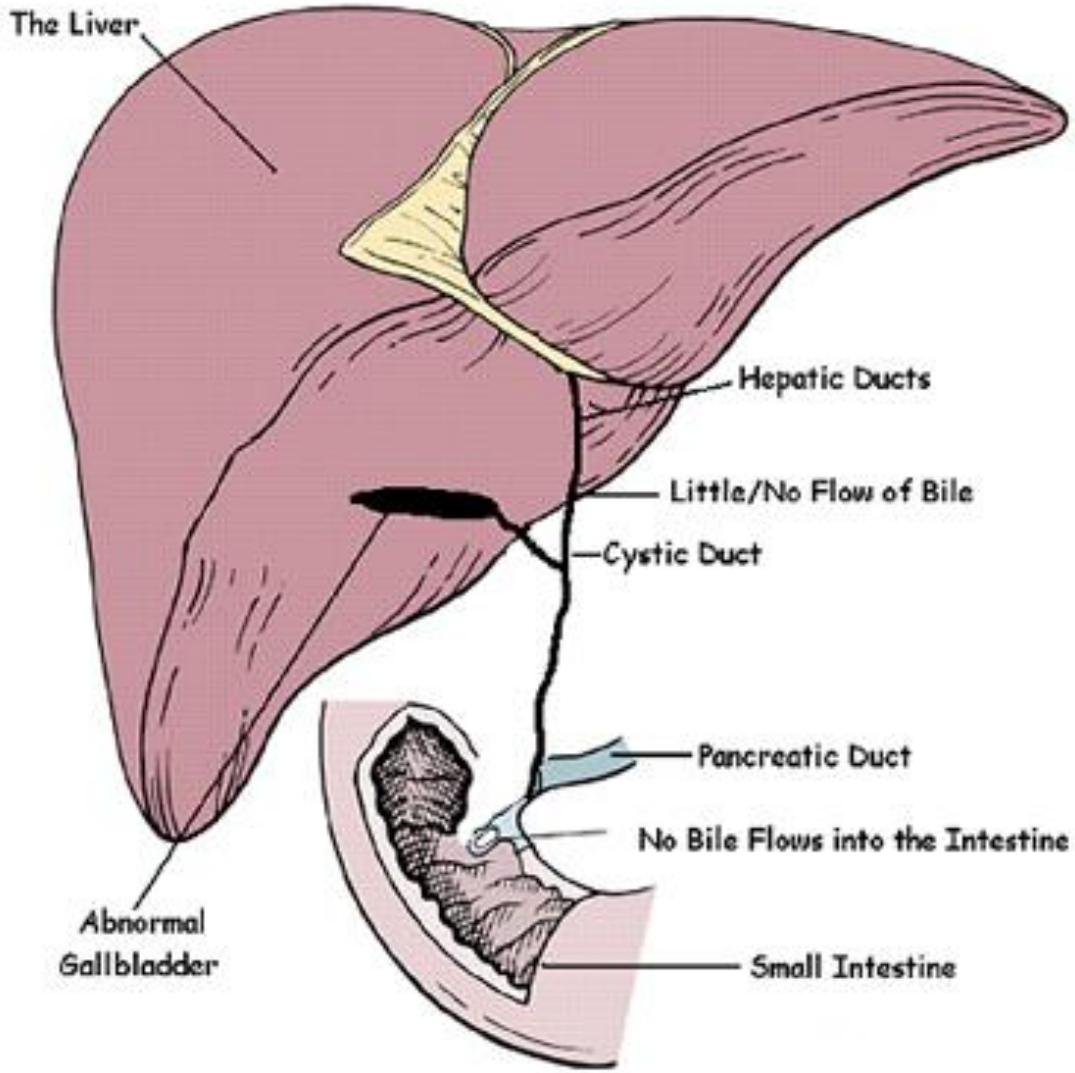


Surgical cholangiogram (DOL 60)

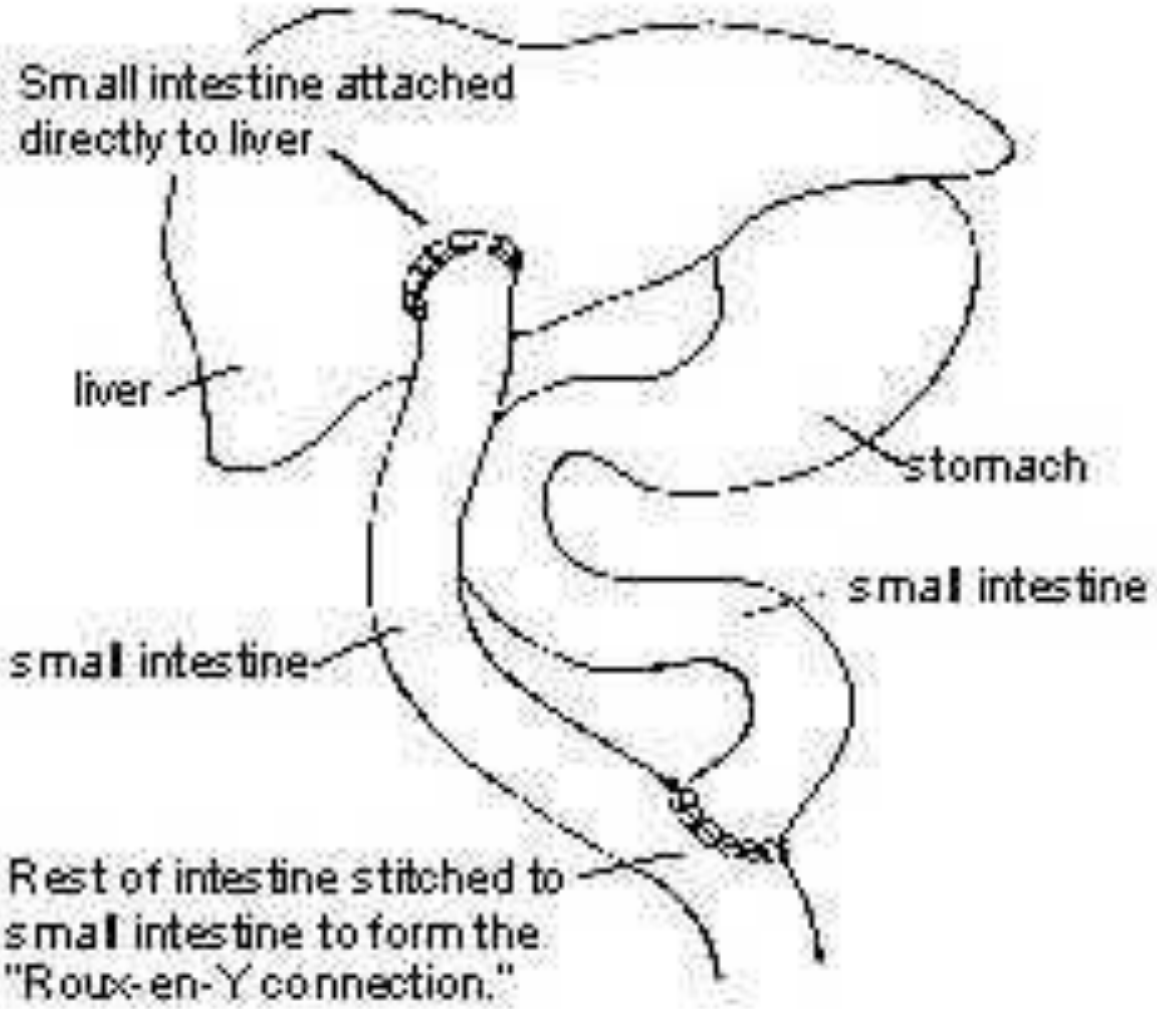
- **No opacification of intrahepatic or extrahepatic bile ducts** after injection of contrast
- After discussion with the hepatologist, the surgeon decided to proceed with a **Kasai procedure** (portoenterostomy)
- Baby was briefly admitted to the PICU and then recovered well on the surgical floor

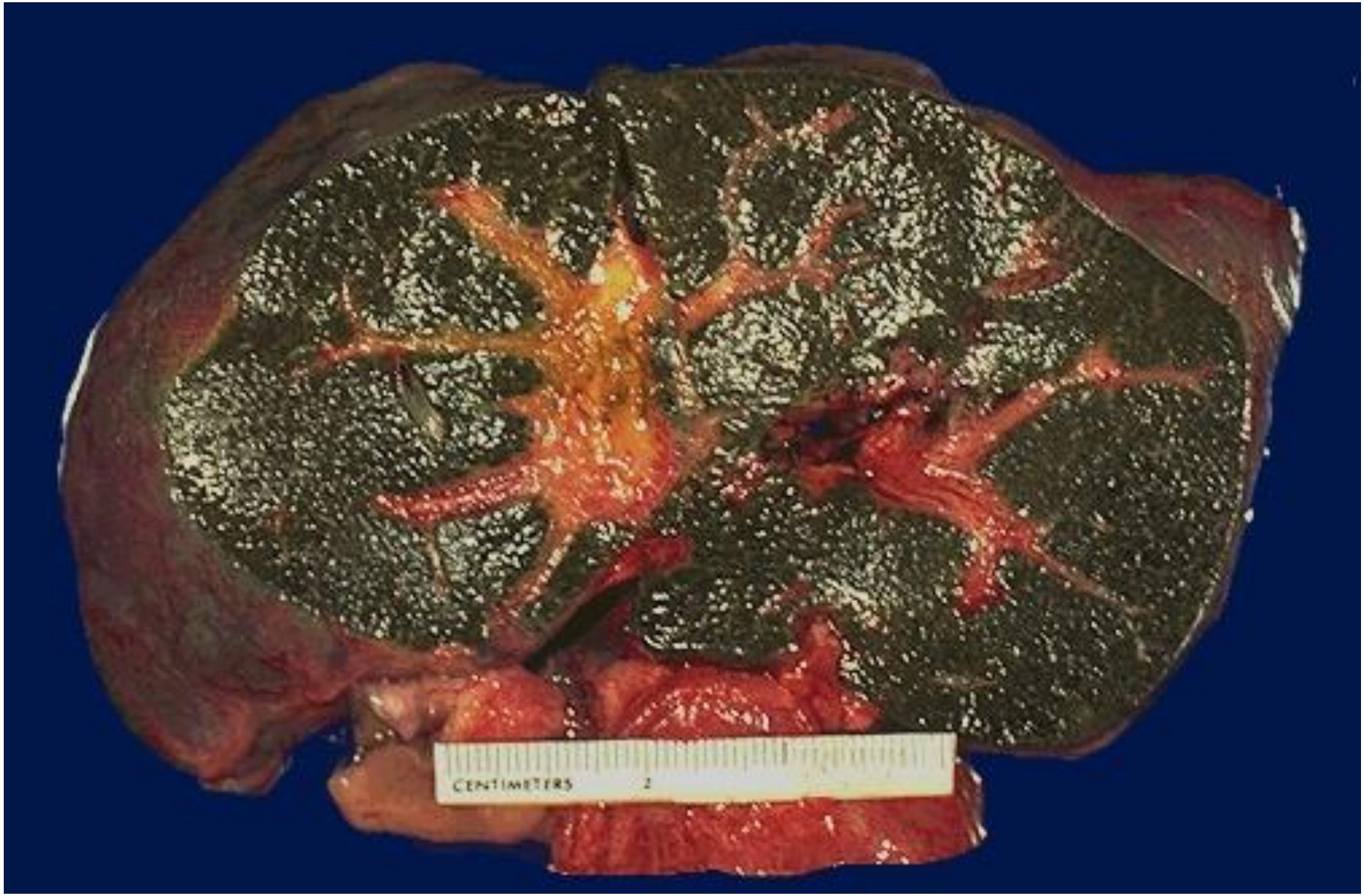
Biliary Atresia (BA)

- Most frequent indication for liver transplantation in children
- Progressive fibro-obliteration of the bile ducts of unknown cause
- Jaundice often the only sign or symptom
- Only treatment is the Kasai procedure: variable long-term outcomes


The Liver
Hepatic Ducts
Little/No Flow of Bile
Cystic Duct
Pancreatic Duct
No Bile Flows into the Intestine
Abnormal Gallbladder
Small Intestine

Kasai Procedure




CENTIMETERS

Liver Transplantation for BA

- Failure to resolve jaundice within 3 months
- Worsening nutritional status
- Recurrent cholangitis
- Deteriorating liver function
  - Increasing bilirubin
  - Refractory coagulopathy
  - Hypoalbuminemia
- Cirrhosis-related complications
  - Ascites, GI bleeding, Peritonitis

Patient History 2

- 7 y/o female with CC: **elevated serum transaminases**

11 weeks prior to referral:

- **ALT 218, AST 226, total protein 9.3, albumin 4.4,** bilirubin 0.9
- CMP two days later: similar results. Hepatitis A, B, C negative.
- We have no pertinent test results after that.

- **She is without complaints today, and dad denies any symptoms for her.** There has been no irritability, lethargy, impaired cognition, fatigue, sleep disturbance, jaundice, pruritus, abdominal pain, abdominal distension, nausea, vomiting, diarrhea, melena, hematochezia, pale stools, unexplained fever, prolonged bleeding or easy bruising. No skin lesions, mouth sores, leg swelling, joint swelling or joint pain.

Physical Examination

- **Weight:** 23 kg (50 lb 11.3 oz), **42 %ile** (Z= -0.21)
- **Height:** 115.3 cm (45.39"), **6 %ile** (Z= -1.59)
- **BMI:** 17.3 kg/m^2, **79.83 %ile** (Z= 0.84) based on CDC (Girls, 2-20 Years) BMI-for-age based on BMI available as of 2/14/2019.
-
- GENERAL EXAM: alert, no acute distress. **Well nourished.**
- EYES: **conjunctivae anicteric** and not injected
- MOUTH/THROAT: moist mucous membranes, **no ulcers**
- NECK: nontender, full range of motion, no mass, **no focal lymphadenopathy**
- CHEST: breath sounds clear and equal bilaterally, no respiratory distress, respirations easy and regular
- CARDIOVASCULAR: regular rate and rhythm, no murmur, no gallop
- ABDOMEN: **soft, flat, nontender, nondistended, no mass. Liver edge smooth, slightly firm, palpable approximately 2 cm below the right costal margin and approximately 5 cm below the xyphoid. Spleen tip slightly firm, palpable approximately 3 cm below the left costal margin.**
- EXTREMITIES: **no edema, clubbing,** or cyanosis
- SKIN: no jaundice, no significant lesions, **no rash, no bruising or petechiae**

Assessment and Plan

Problems:

1.) Elevated serum transaminases (ALT and AST)
2.) Elevated total protein and TP/albumin gradient
3.) Palpable, firm liver
4.) Palpable, firm spleen

Considerations:

1.) Autoimmune hepatitis (most likely)
2.) Alpha-1 antitrypsin deficiency
3.) Wilson disease
4.) Lysosomal acid lipase deficiency
5.) Other genetic/metabolic hepatopathy
6.) Malignancy

Disposition:

1.) Laboratory tests (see below)
2.) Abdominal ultrasound with ARFI and Doppler
3.) Further work-up to be determined, but will likely include liver biopsy

Laboratory

- **IGG 2,890 mg/dL (537 - 1,432)**
- **ANA SCREEN – Positive [speckled/homogeneous]**
- **ANA TITER – Greater than or equal to 1:1280**

- ANTI-SMOOTH MUSCLE TITER – <1:20
- LIVER/KIDNEY MICROSOMAL ANTIBODY 6.2 U (0.0 - 24.9)

- CERULOPLASMIN – 31 mg/dL (21 – 53)
- ALPHA-1-ANTITRYPSIN – 151 mg/dL (90 – 200)
- A-1-ANTITRYPSIN PHENOTYPE – M1M2
- FERRITIN – 79 ng/mL (7 – 142)
- ALPHA-1-FETOPROTEIN 1.5 ng/mL (<8.5)

Ultrasound

- **LIVER: Normal contour and echotexture** without focal mass or intrahepatic biliary ductal dilation.

- COMMON BILE DUCT: Normal in caliber, 2 mm in diameter.
- GALLBLADDER: Bile-filled, without gallstone or gallbladder wall thickening. The bile is anechoic. No pericholecystic fluid.
- ASCITES: None.

- **SPLEEN: 12.4 cm in length**, appears sonographically normal.

- Normal abdominal Doppler

- **Median SWS, RIGHT hepatic lobe: 1.58 m/s**
- **Mean SWS, RIGHT hepatic lobe: 1.55 m/s**

Histology

RIGHT LOBE OF LIVER SEGMENT V, NEEDLE BIOPSY:

- **MARKED INTERFACE HEPATITIS WITH PLASMA CELLS**
- **ADVANCED BRIDGING FIBROSIS WITH NODULAR PARENCHYMA (STAGE 4/4)**

Comment: In the setting of elevated serum antinuclear antigen (ANA), the histologic findings are compatible with autoimmune hepatitis.

Intense portal inflammation

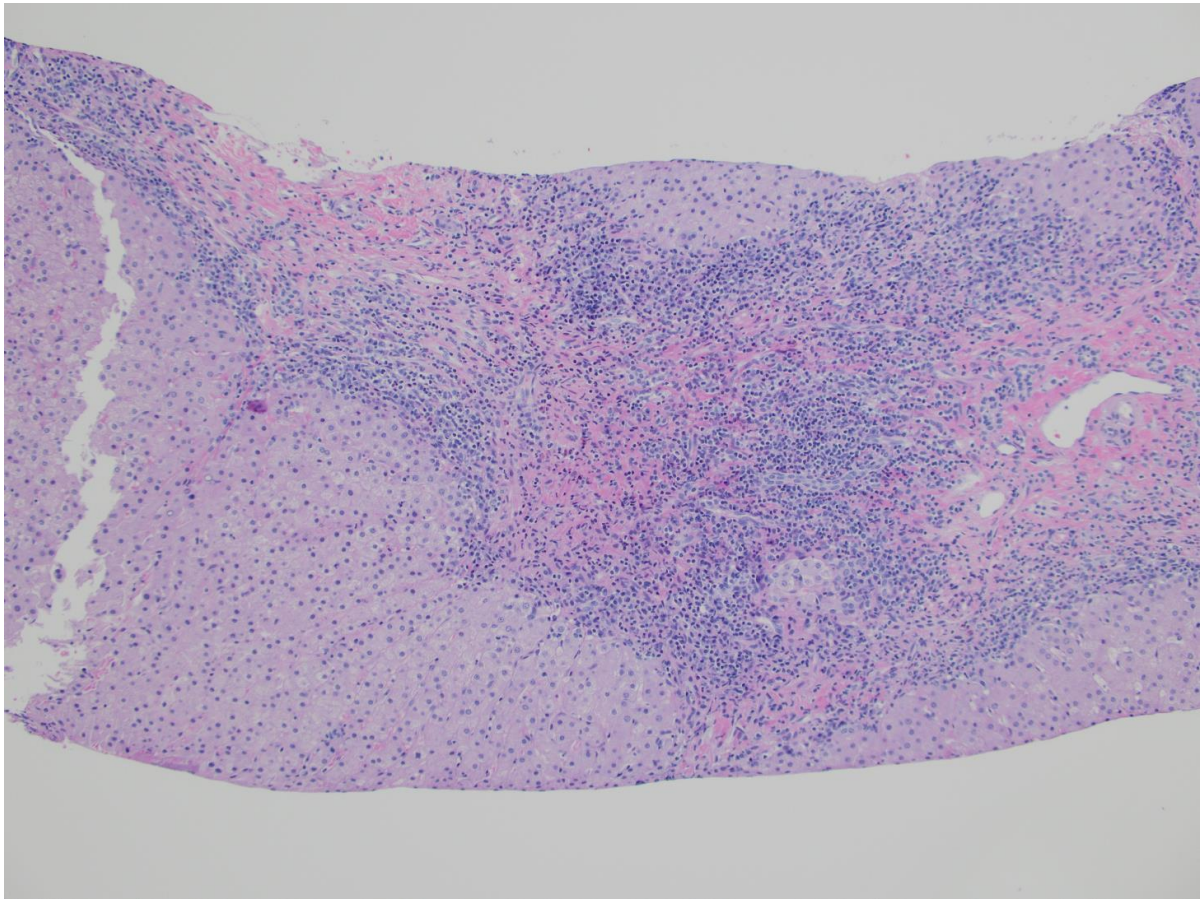


Image courtesy of Bonita Fung, M.D.

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

Plasma cell infiltrate

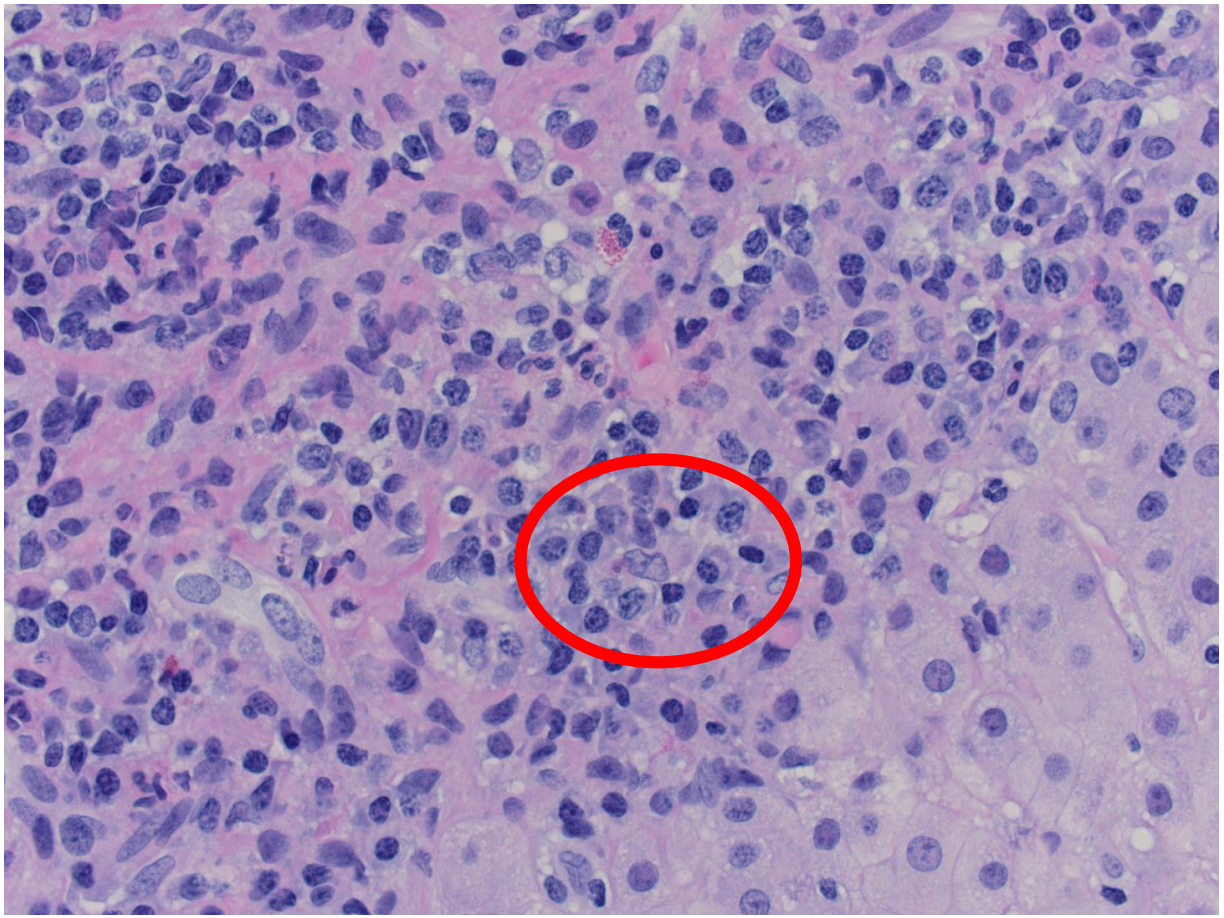


Image courtesy of Bonita Fung, M.D.

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

Interface hepatitis

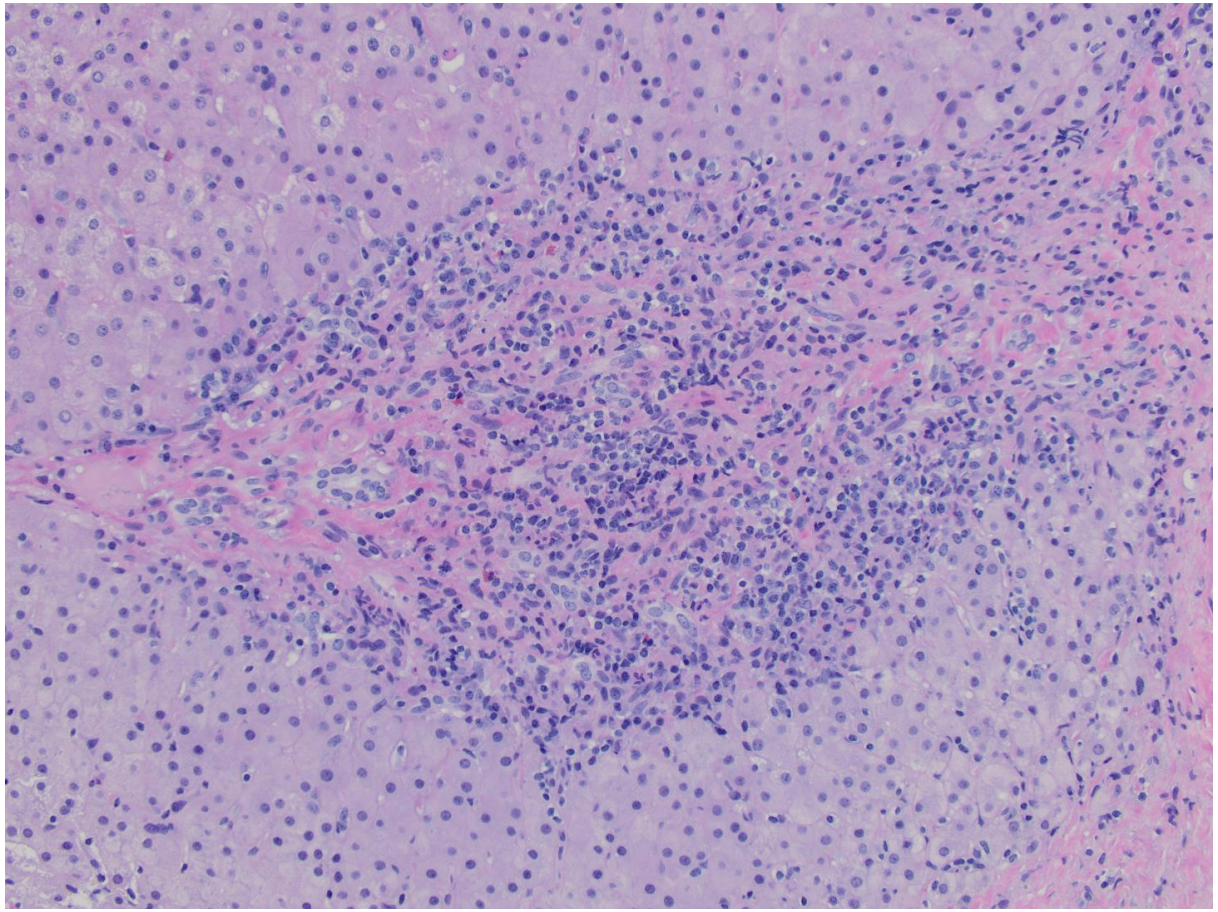


Image courtesy of Bonita Fung, M.D.

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

Cirrhotic nodules

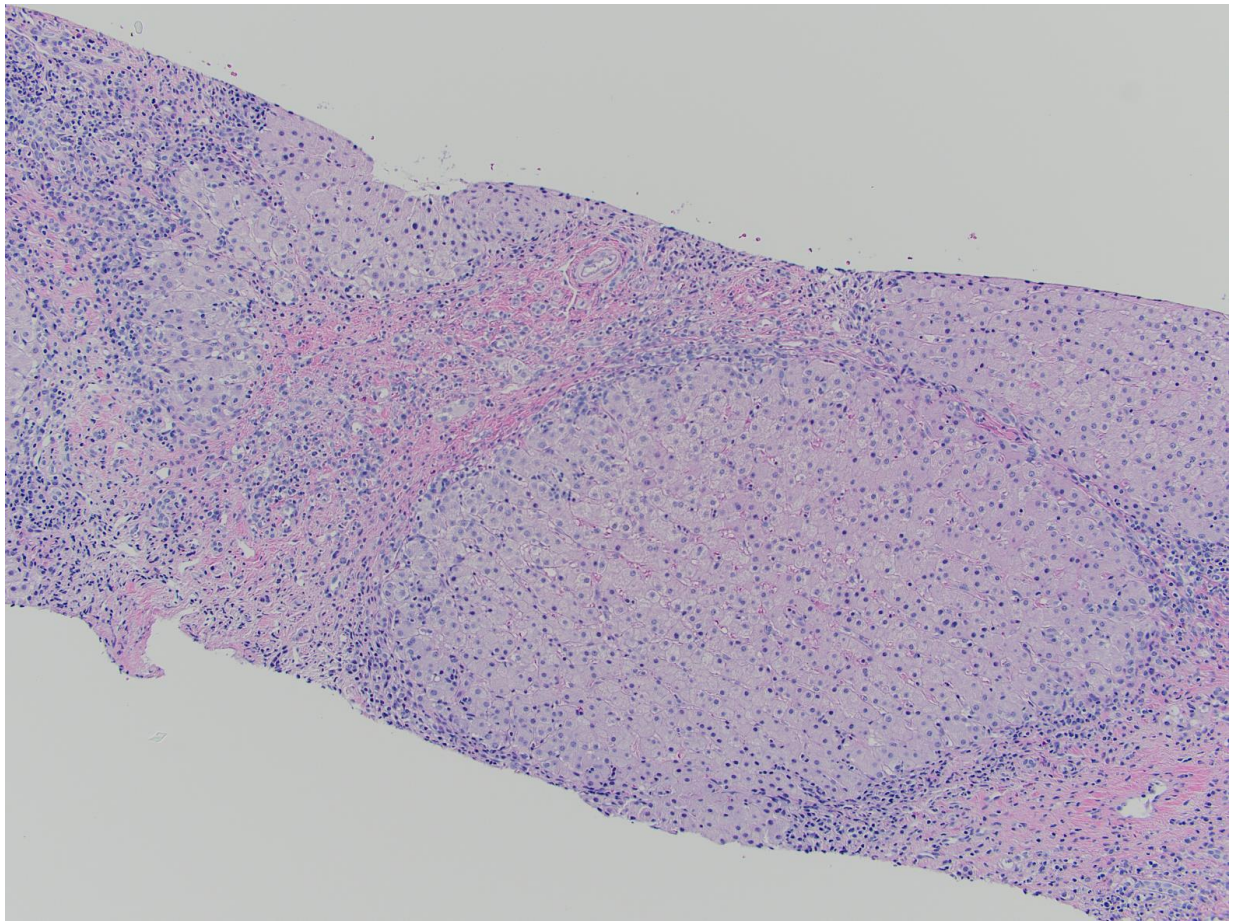


Image courtesy of Bonita Fung, M.D.

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

Bridging fibrous septae

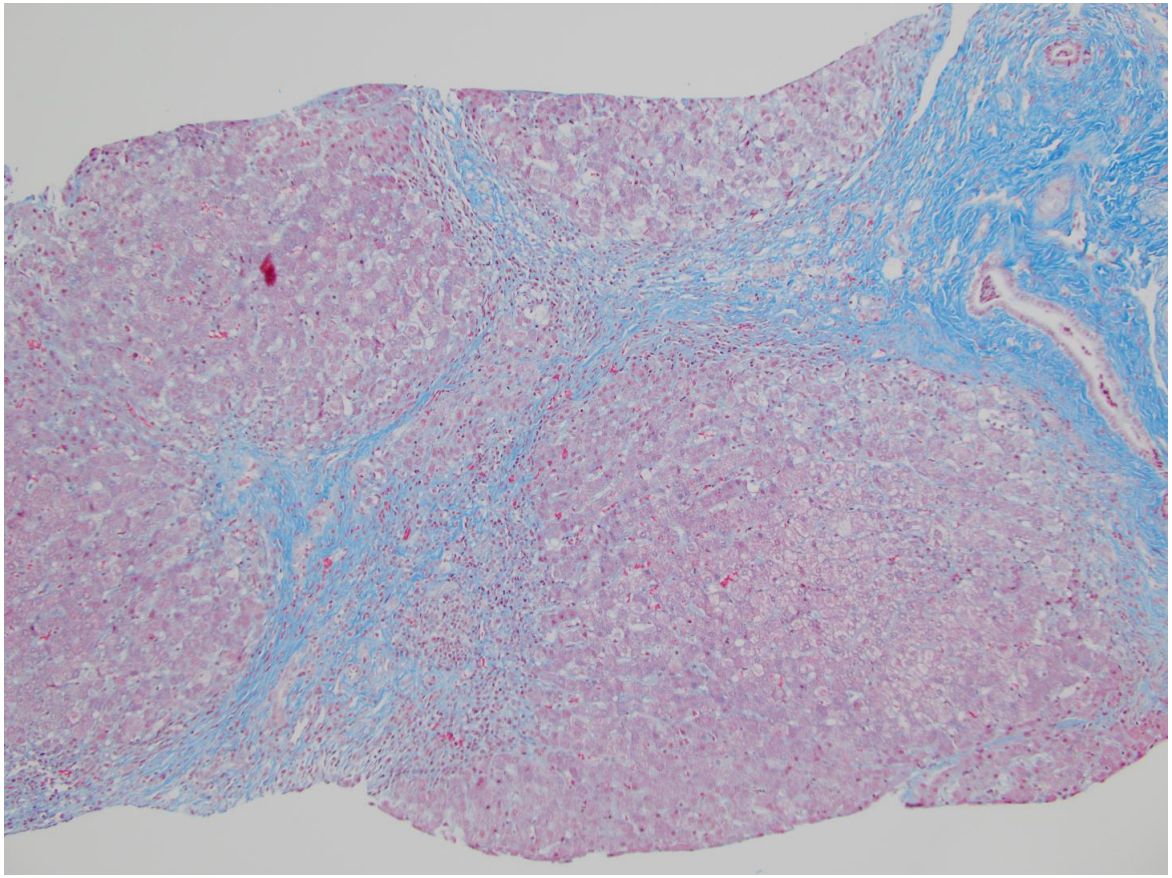


Image courtesy of Bonita Fung, M.D.

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

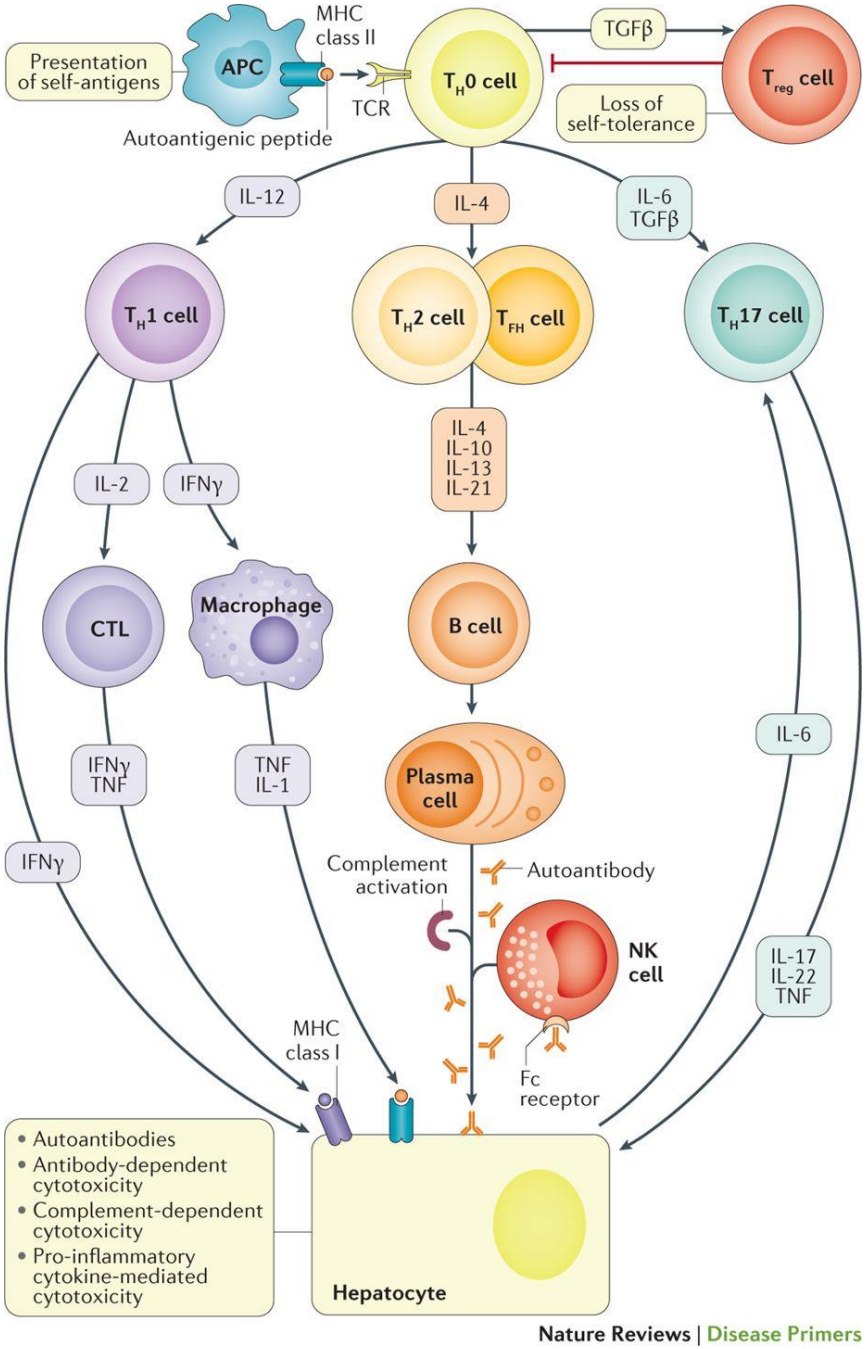
Clinical course

- Oral prednisone started, 2 mg/kg/day, with PPI
- TPMT activity and genotype confirmed as normal => mercaptopurine started at 1 mg/kg/day
- 4 weeks after starting treatment: ALT 49, AST 40 IU/L
- Transaminases subsequently normalized completely
- 6-MMP 1200-1434 pmol/8 × 108 RBC, 6-TG 160-195[1]
- Irritability and cushingoid facies initially; now resolved
- Currently on 3 mg prednisone and 20 mg 6-MP daily
- Doing well, is in good spirits and has no complaints

1 Sheiko et al., JPGN 2017;65: 80–85

Autoimmune Hepatitis: what is it?

- Progressive inflammatory hepatopathy; leads to end-stage liver disease if untreated
- Female preponderance, elevated serum IgG, positive autoantibodies, interface hepatitis on histology
- Presentation chronic, acute or fulminant
- May have coexisting autoimmune phenomena
  (arthritis, vasculitis, Sjögren syndrome, thyroiditis, glomerulonephritis, celiac disease, IBD, diabetes mellitus, AIHA, idiopathic thrombocytopenia…)



Mieli-Vergani et al., Nat Rev Dis Primers. 2018 Apr 12;4:18017

Autoimmune Hepatitis: Subtypes, terminology

- Type 1 Autoimmune Hepatitis
- Type 2 Autoimmune Hepatitis
- Autoimmune Sclerosing Cholangitis (ASC) / “overlap syndrome”
- De-novo Autoimmune Hepatitis following liver transplantation
- [Drug-induced Autoimmune Hepatitis (e.g. **minocycline**)]

Autoimmune Hepatitis: Type 1 vs. Type 2

Table 1
Differences between type 1 and type 2 autoimmune hepatitis

	Type 1 AIH	Type 2 AIH
Age at presentation	Usually pubertal age	May present very early in life, much younger than type 1
Prevalence	Much more common than type 2	<1/3 of cases with AIH
Clinical features and course	Usually chronic	Acute liver failure presentation more common
Autoantibodies	ANA, SMA	LKM, Anti-liver cytosol type1
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	No association	Association described
Histology	Cirrhosis more common	May have cell drop-out and necrosis in acute liver failure setting
Overlap with SC	Not uncommon	Very rare
Immunosuppression	May be weaned off	Need life-long immunosuppression

Kerkar N, Chan A: Clin Liver Dis. 2018 Nov;22(4):689-702

Simplified Diagnostic Criteria

Simplified diagnostic criteria (SDC)[125]

A pretreatment aggregate score of ≥7 defines definite AIH, whereas ≥6 defines a probable diagnosis

- Presence of autoantibodies:
  - ANA or SMA titres of ≥1:40 (+1 point) or ≥1:80 (+2 points)
  - Anti-LKM1 antibody titres of ≥1:40 (+2 points)
  - Anti-soluble liver antigen (anti-SLA) antibody positivity (+2 points)
- Immunoglobulin level:
  - IgG level greater than the ULN (+1 point)
  - γ-Globulin level of >1.1-fold the ULN (+2 points)
- Histological features
  - Compatible with AIH (+1 point)
  - Typical of AIH[c] (+2 points)
- Viral hepatitis: absent (+2 points) or present (0 points)

Mieli-Vergani et al., Nat Rev Dis Primers. 2018 Apr 12;4:18017

Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement

Giorgina Mieli-Vergani, Diego Vergani, Ulrich Baumann, Piotr Czubkowski, Dominique Debray, Antal Dezsofi, Björn Fischler, Girish Gupte, Loreto Hierro, Giuseppe Indolfi, Jörg Jahnel, Françoise Smets, Henkjan J. Verkade, and Nedim Hadžic

TABLE 4. Proposed scoring criteria for the diagnosis of juvenile autoimmune liver disease

Variable	Cut-off	Points AIH	Points ASC
ANA and/or SMA*	≥1:20†	1	1
	≥1:80	2	2
Anti-LKM-1* or	≥1:10†	1	1
	≥1:80	2	1
Anti-LC-1	Positive†	2	1
Anti-SLA	Positive†	2	2
pANNA	Positive	1	2
IgG	>ULN	1	1
	>1:20 ULN	2	2
Liver histology	Compatible with AIH	1	1
	Typical of AIH	2	2
Absence of viral hepatitis (A, B, E, EBV), NASH, Wilson disease, and drug exposure	Yes	2	2
Presence of extrahepatic autoimmunity	Yes	1	1
Family history of autoimmune disease	Yes	1	1
Cholangiography	Normal	2	−2
	Abnormal	−2	2

Score ≥7: probable AIH; ≥8: definite AIH. Score ≥7: probable ASC; ≥8: definite ASC. AIH = autoimmune hepatitis; ANA = anti-nuclear antibody; anti-LC-1 = anti-liver cytosol type 1; anti-LKM-1 = anti-liver kidney microsomal antibody type 1; anti-SLA = anti-soluble liver antigen; ASC = autoimmune sclerosing cholangitis; EBV = Epstein–Barr virus; IgG = immunoglobulin G; NASH = nonalcoholic steatohepatitis; pANNA = peripheral anti-nuclear neutrophil antibodies; SMA = anti-smooth muscle antibody; ULN = upper limit of normal.

*Antibodies measured by indirect immunofluorescence on a composite rodent substrate (kidney, liver, stomach).

†Addition of points achieved for ANA, SMA, anti-LKM-1, anti-LC-1, and anti-SLA autoantibodies cannot exceed a maximum of 2 points.

Autoimmune Hepatitis: Drugs and dosing

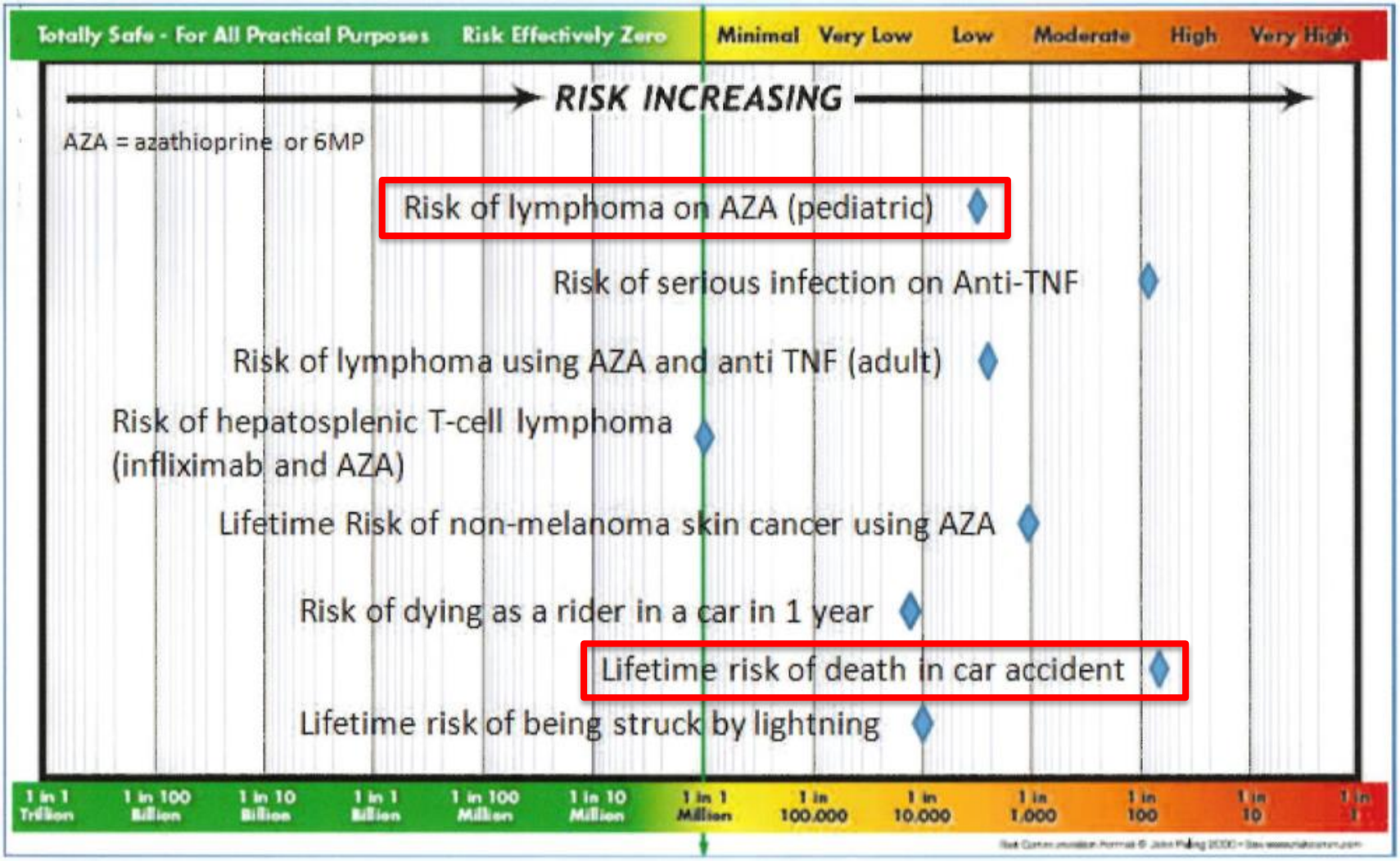
Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement

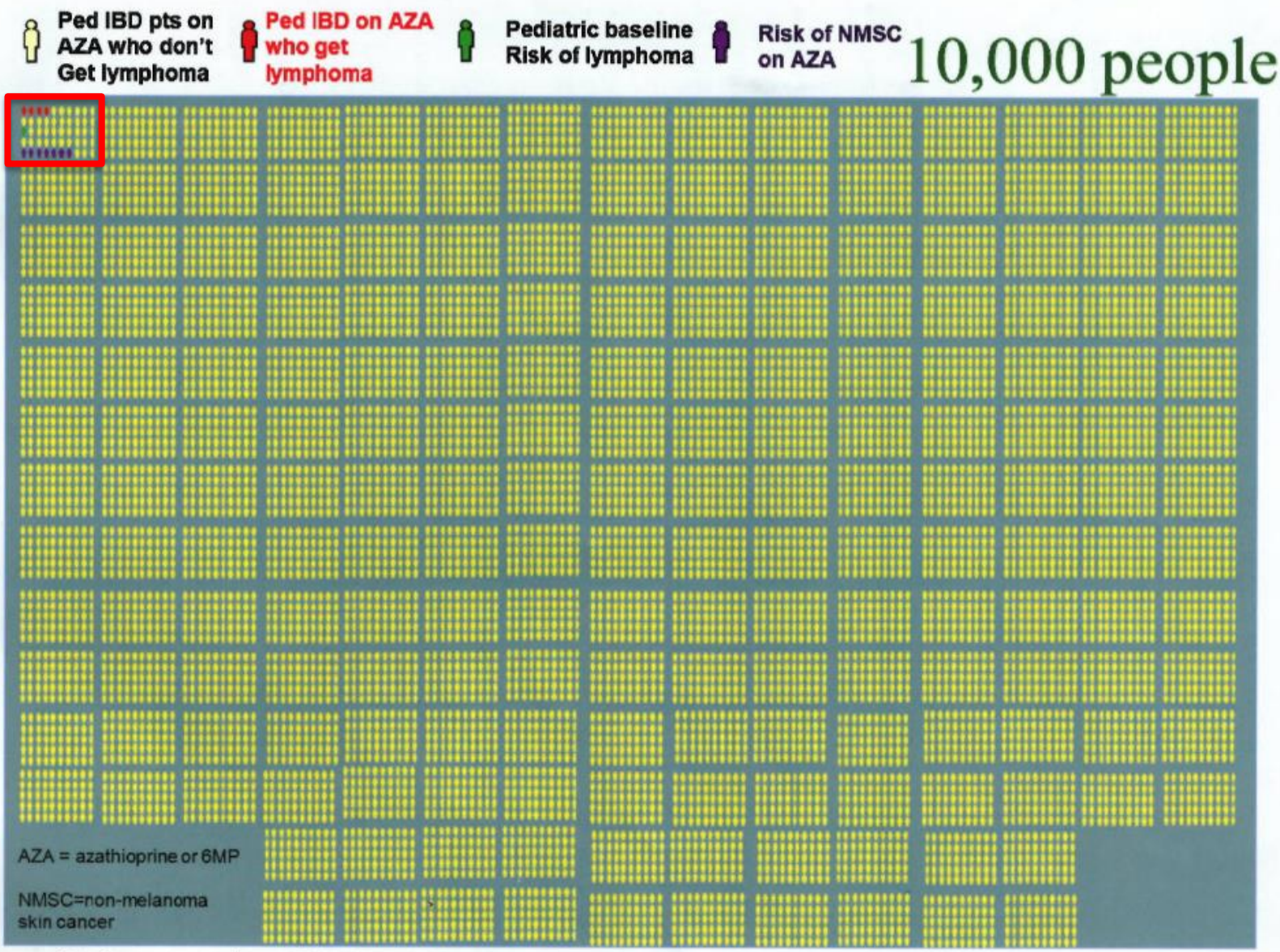
Giorgina Mieli-Vergani, Diego Vergani, Ulrich Baumann, Piotr Czubkowski, Dominique Debray, Antal Dezsofi, BjÖrn Fischler, Girish Gupte, Loreto Hierro, Giuseppe Indolfi, Jörg Jahnel, FranÇoise Smets, Henkjan J. Verkade, and Nedim HadŽic

(JPGN 2018;66: 345–360)

TABLE 1. Immunosuppressive treatment regimens for juvenile autoimmune liver disease

	Initial regimen		Maintenance					
AIH	Predni(so)lone	Azathioprine	Prednis(ol)one	Azathioprine	Azathioprine mono-therapy (in AIH-1)	Definition of remission	Treatment length	Before attempting treatment withdrawal
	2 mg · kg^{-1} · day^{-1} (up to 60 mg/daily) decreased weekly in parallel to transaminase levels decrease to a minimum maintenance dose of 2.5 to 5 mg daily	1–2 mg · kg^{-1} · day^{-1} added gradually if transaminase levels plateau or increase. Alternatively, added in all patients after 2 weeks of predniso(lo)ne treatment	0.1–0.2 mg · kg^{-1} · day^{-1} or 5 mg/day	1–2 mg/kg/day if required	1.2–1.6 mg/kg/day	Normal transaminase and IgG levels; - Negative or low titer (< 1:20) ANA/ SMA -negative anti-LKM-1/anti-LC-1	3 y Before considering suspension	Remission for at least 3 years + follow up liver biopsy showing no inflammatory changes


Totally Safe - For All Practical Purposes
Risk Effectively Zero
Minimal
Very Low
Low
Moderate
High
Very High
RISK INCREASING
AZA = azathioprine or 6MP
Risk of lymphoma on AZA (pediatric)
Risk of serious infection on Anti-TNF
Risk of lymphoma using AZA and anti TNF (adult)
Risk of hepatosplenic T-cell lymphoma (infliximab and AZA)
Lifetime Risk of non-melanoma skin cancer using AZA
Risk of dying as a rider in a car in 1 year
Lifetime risk of death in car accident
Lifetime risk of being struck by lightning
1 in 1 Trillion
1 in 100 Billion
1 in 10 Billion
1 in 1 Billion
1 in 100 Million
1 in 10 Million
1 in 1 Million
1 in 100,000
1 in 10,000
1 in 1,000
1 in 100
1 in 10
1 in 1



Risk Communication Format © John Pauling 2002

See www.riskcomm.com

Autoimmune Hepatitis: Second line treatments

- **Budesonide** [1,2,3,4]

- Mycophenolate mofetil
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Monoclonal antibodies (rituximab, infliximab)

- […]

1 Manns et al.: Gastroenterology. 2010 Oct;139(4):1198-206
2 Woynarowski et al.: J Pediatr. 2013 Nov;163(5):1347-53
3 Mohammad S: Scand J Gastroenterol. 2016;51(6):753-62
4 Lohse AW and Gil H: J Hepatol. 2011 Apr;54(4):837-9

Patient History 3

- CC: **elevated serum transaminases**; ?drug related.
- 13.5 y/o male with Tourette syndrome, OCD, ADHD, noted to have elevated AST and ALT.
- No fever, jaundice, pruritus, or bruising.
- Medication: Ziprasidone (Geodon); previously quetiapine (Seroquel) and clonidine (Catapres).
- Family History: Noncontributory

Clinical Data

- PE: Obese, NAD. 107.5 kg (+ 5 SD). Anicteric. No jaundice, hepatomegaly, splenomegaly, clubbing, palmar erythema, spider angioma, hematoma, petechiae, or prominent skin veins

- Labs: AST 171, ALT 351

- Tests of liver function (Bilirubin, albumin, PT): normal

Further Diagnostic Testing

- **Repeat serum transaminases: AST 202, ALT 326**
- CPK, PT, albumin, NH3, bilirubin, alkaline phosphatase – normal
- Hepatitis B and C serologies, immunoglobulins, autoantibodies, ceruloplasmin, α1AT phenotype – all normal or negative
- Ultrasound: diffusely increased echogenicity, consistent with **fatty infiltration**
- Biopsy: **Steatosis** with **steatohepatitis**: acute and chronic inflammation, fibrosis

Non-Alcoholic Steatohepatitis (NASH)

- Morphological pattern of liver injury similar to that seen in alcoholic liver disease (but without history of alcohol exposure)
- Increasingly recognized as a common cause of elevated transaminases in asymptomatic individuals, including children
- Classic description in 1980 (Ludwig et al.)
- Can progress to cirrhosis!
- NASH is the 2nd most common cause in the USA for adults to receive liver transplantation (expected to be the most common one by 2020)

Terminology

Non-Alcoholic Fatty Liver (NAFL)

Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-Alcoholic Steatohepatitis (NASH)

NAFLD: Risk Factors and Coexisting Conditions

- Male gender
- Ethnicity (Asian, Hispanic)
- Obesity / visceral adiposity
- Insulin resistance - Type II diabetes mellitus, hyperglycemia, glucose intolerance
- Hyperlipidemia, especially hypertriglyceridemia
- Polycystic ovary syndrome
- Obstructive sleep apnea

NASH: Diagnosis

- Clinical
  - Asymptomatic (or nonspecific symptoms such as mild RUQ discomfort/pain, fatigue)
  - Usually no stigmata of chronic liver disease

- Laboratory
  - Transaminases elevated, often to 2-4 x ULN
  - Normal liver synthetic function
  - Negative evaluation for other etiologies

Imaging

- Echogenic liver on **ultrasound** (compared to kidney)
- Decreased radioopacity compared to spleen on **CT scan**
- Bright liver tissue on T1 weighted **MRI**

- ***Ultrasound***
  - Sensitivity 60-94%, specificity 73-93%
  - Operator- and machine dependent
  - Influenced by body habitus and by liver fibrosis/inflammation
  - Current guidelines do NOT recommend US as screening test

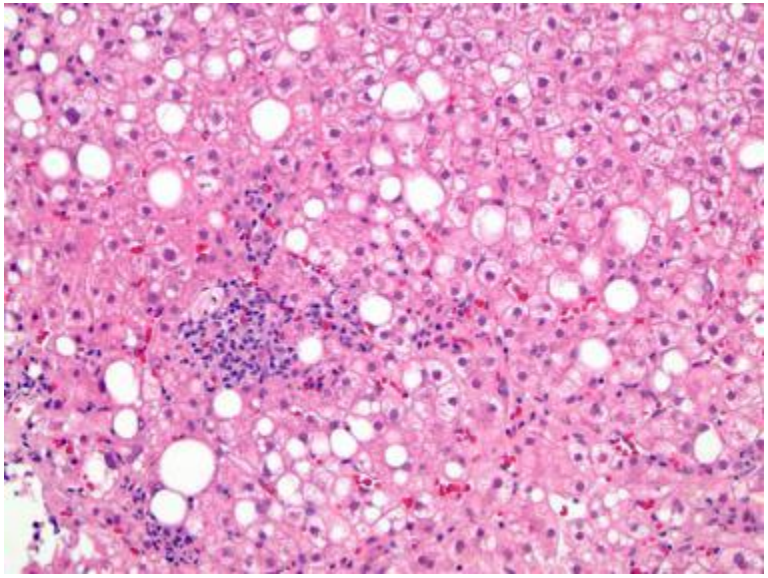
- ***MRI***
  - Operator independent, reproducible

Histology

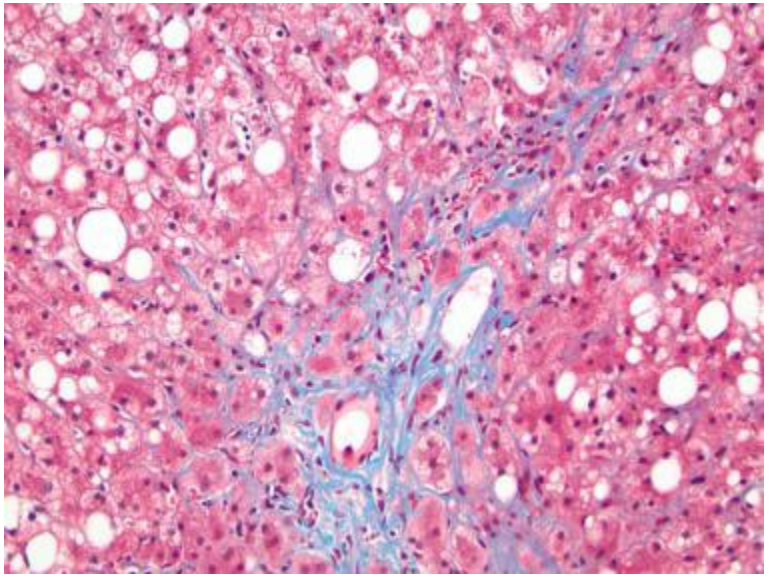
- **Macrovesicular**/microvesicular steatosis (lobular/patchy or diffuse)
- Portal and/or lobular chronic inflammation
- +/- ballooning degeneration
- Hepatocellular necrosis
- Variable degree of fibrosis (portal vs. sinusoidal); may progress to cirrhosis
- Scoring system (NAS score):

  Kleiner, Brunt et al., *Hepatology* 2005

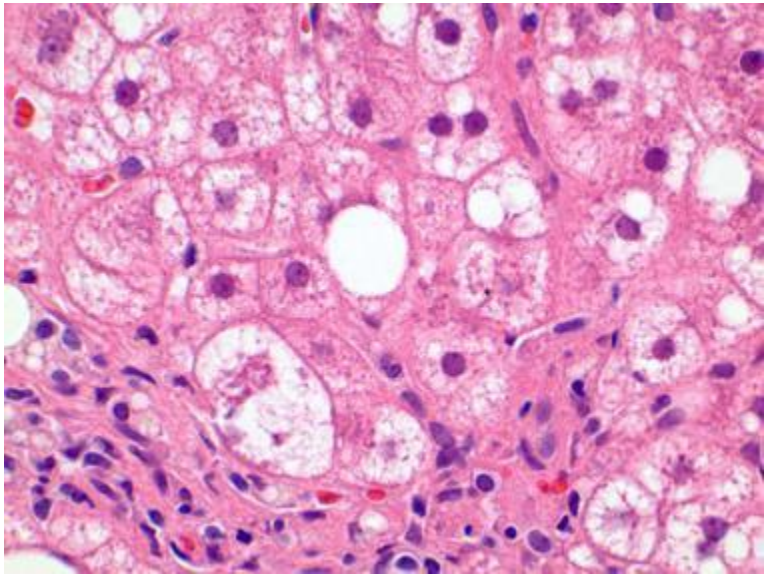
Steatosis and Chronic Inflammation



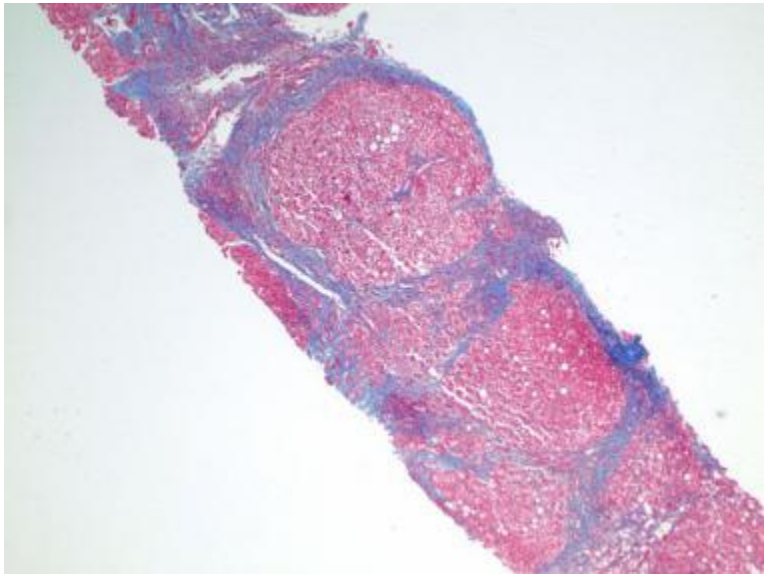
Portal, Pericellular and Perivenular Fibrosis



Ballooned Hepatocytes



Bridging Fibrosis and Cirrhosis



https://emedicine.medscape.com/article/2038493-overview

Screening for NAFLD: Problematic!

- Serum transaminases not reliable: can be normal despite evidence of fatty liver
- Uncertainty of appropriate reference ranges for ALT [ULN 22 for girls, 25 for boys? SAFETY study - Schwimmer et al. *Gastroenterology* 2010; 138(4): 1357–1364]
- Sensitivity and specificity of imaging not quite clear
- False-positive test leads to invasive procedure
- Limited Rx options = ?benefit of early detection

NAFLD: Treatment

- **Moderate and sustained weight loss**
  - **Normalization of biochemical & radiographic abnormalities in children with NASH has been shown to occur with weight loss**

- Pharmacologic therapies with no proven benefit in children: Antihyperlipidemic drugs (clofibrate, gemfibrozil), Ursodeoxycholic acid (ursodiol), Betaine, Metformin, DHA / fish oil, Probiotics (Lactobacillus GG and VSL), Pioglitazone

- Vitamin E in biopsy-proven NASH: **TONIC** trial Lavine JE et al., *JAMA* 2011;305:1659-1668) showed improvement in histology, but not in ALT; concerns about safety of long-term, high-dose vitamin E have since been raised based on data from adult trials; not recommended

JPGN 2017;64:319-334

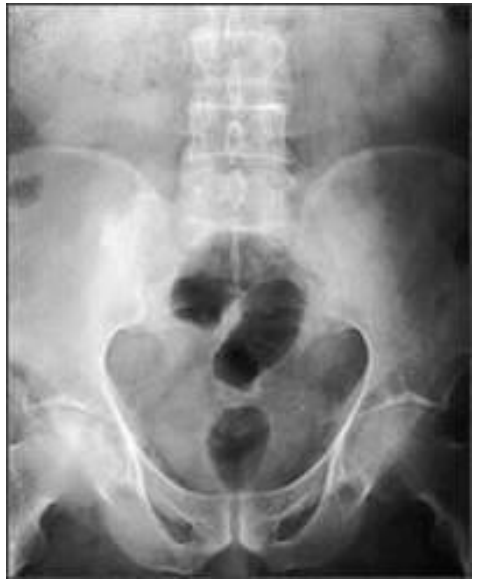
CLINICAL GUIDELINES

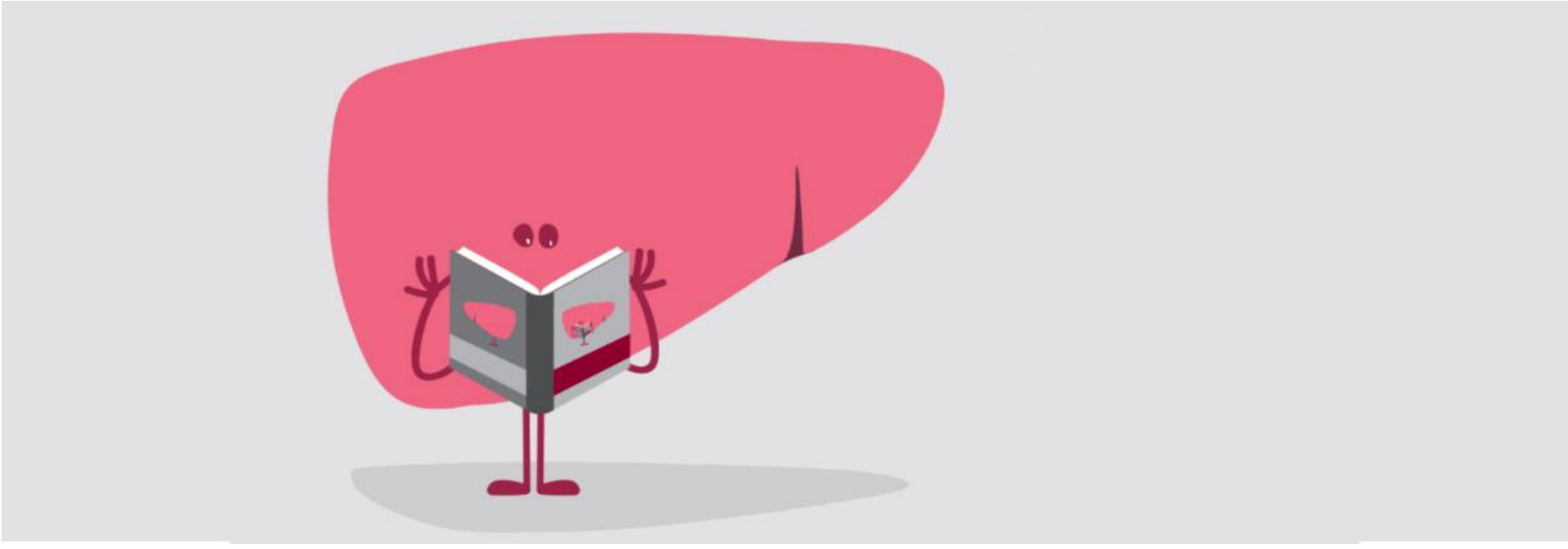
NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

*†Miriam B. Vos, ‡§Stephanie H. Abrams, ‡§Sarah E. Barlow, ||Sonia Caprio, ¶#Stephen R. Daniels, **††Rohit Kohli, ‡‡§§Marialena Mouzaki, ||||¶¶Pushpa Sathya, ##***Jeffrey B. Schwimmer, ¶#Shikha S. Sundaram, and **††Stavra A. Xanthakos

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

Questions?





Liver Transplantation at Nationwide Children's Hospital

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

Timeline of NCH Liver Transplant Program

- **March 2016**: **W. Kenneth Washburn**, M.D. (Director, Division of Transplant Surgery, Abdominal Transplant Program and Liver Transplantation at NCH)
- **12/06/2016**: **Stephen Sales**, MBA (Service Line Administrator, Abdominal Transplantation)
- **04/09/2017**: **Micheal Markham**, RN, BSN (Liver Transplant Nurse Coordinator)
- **07/19/2017**: **Monique Goldschmidt**, M.D. (Transplant Hepatologist and Assistant Medical Director, Liver Center and Liver Transplantation)
- **09/04/2017**: **Alexander Weymann**, M.D. (Transplant Hepatologist and Medical Director, Liver Center and Liver Transplantation)
- **09/11/2017**: **Brittany Morrow**, RN, BSN, CPN (Liver Transplant Nurse Coordinator)
- **11/02/2017**: **Preliminary approval by United Network for Organ Sharing (UNOS)**; final approval January 2018
- **11/21/2017**: **Approval by Ohio Solid Organ Transplant Consortium (OSOTC)**
- **05/25/2018**: **First pediatric liver transplant patient listed at NCH**
- **07/21/2018**: **First pediatric liver transplant performed at NCH**

Liver Transplant Leadership

Kenneth Washburn, MD

Director of Abdominal Transplantation

for OSU-WMC and NCH

Surgical Director of NCH

Liver Transplant program

Liver Transplant Physicians

- Carol Potter, MD – Hepatologist
- Cheryl Gariepy, MD – Hepatologist
- Monique Goldschmidt, MD – Transplant Hepatologist; Associate Medical Director
- Alexander Weymann, MD – Transplant Hepatologist; Medical Director







Liver Transplant team

- Sylvester Black, MD – Liver Transplant Surgeon
- Jane Choi, PharmD – Liver Transplant Pharmacist
- Amy Krick, LCSW – Liver Transplant Social Worker
- Jodi Timmons – Patient Financial Counselor
- Rose Schroedl, PhD – Clinical Psychologist
- Liver Transplant Dieticians – Lauren Kuhn, RD and colleagues
- Monica Ardura, M.D. and colleagues (Host Defense Team – Transplantation/Immunosuppression Infectious Diseases)
- Samantha Gee, M.D. and Maria Estrada, M.D. – PICU liaison
- Candice Burrier, M.D. – Transplant Anesthesiologist








What have we done so far?

- Transplanted 1 patient
- Evaluated or considered/pre-evaluated 14 patients
- 2 patients actively listed

- Created protocols, order sets, policies, guidelines, patient materials
- External consulting firm to prepare for CMS survey

- Education for nurses, residents, fellows and faculty