Gestational alloimmune liver disease: a leading cause of neonatal acute liver failure

Sarah A. Taylor, MD

Assistant Professor of Pediatrics

Ann & Robert H. Lurie Children's Hospital of Chicago

Northwestern University Feinberg School of Medicine, Chicago, IL

NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

Ann & Robert H. Lurie Children's Hospital of Chicago™

Objectives

- Review differences between ALF in the neonate versus older children
- Overview of common etiologies of neonatal ALF
- Gestational alloimmune liver disease
  - Mechanism of disease
  - Clinical presentation and management
  - Prevention

Neonatal Acute Liver Failure

- Unique challenges applying definition of pediatric ALF to the neonate
- Distinct etiologies from ALF in older children
- Specific considerations in the treatment paradigm for neonatal ALF

Definition of **neonatal ALF**

INR of ≥ 2.0 with/without encephalopathy

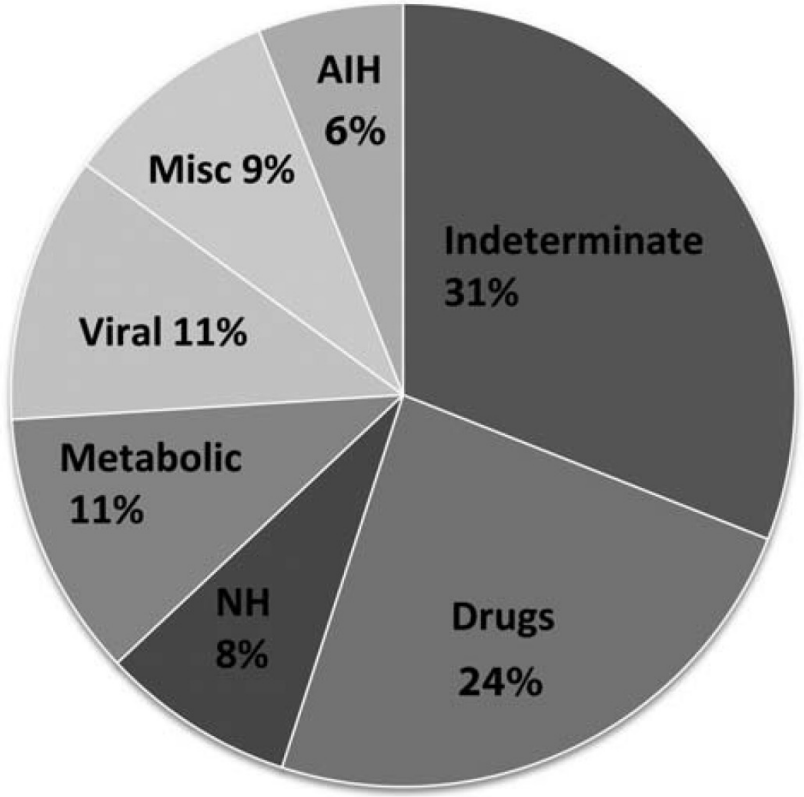
Hepatic encephalopathy is difficult to detect in the neonate

Grade	Mental Status	Asterixis	EEG
I	Euphoria/depression	Yes/No	Usually normal
	Mild confusion		
	Slurred speech		
	Disordered sleep		
II	Lethargy	Yes	Generalized slowing
	Moderate confusion		
III	Marked confusion	Yes	Grossly abnormal slowing
	Incoherent		
	Sleepy but arousable		
IV	Coma	No	Decreased amplitude and delta waves

Overall etiologies of pediatric acute liver failure

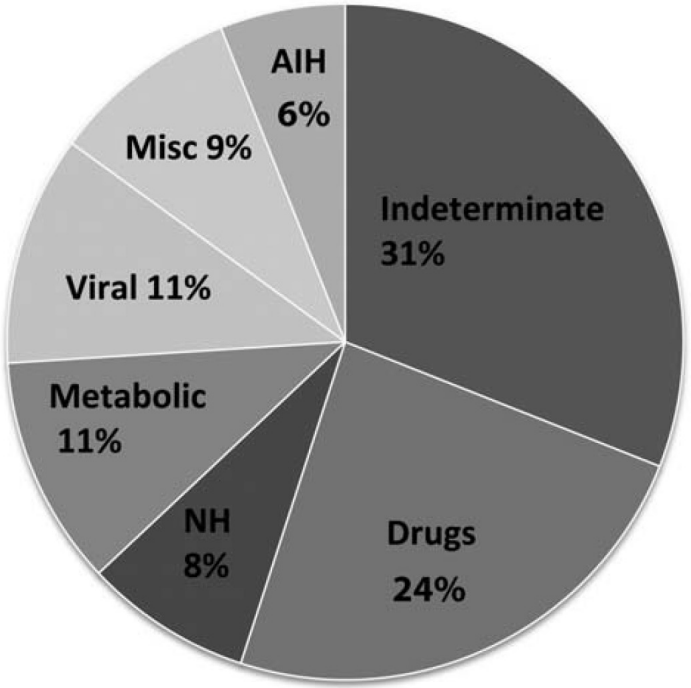
- Prospective multi-center study of 348 children from birth to 18 years with PALF (Squires et al. *J Pediatr* **2006**):
  - Indeterminate – 49%
  - Acetaminophen toxicity – 14%
  - Non-APAP drug-related hepatotoxicity – 5%
  - Metabolic disease – 10%
  - Autoimmune liver disease – 6%
  - Infectious – 6%
  - Non-APAP drug-related hepatotoxicity – 5%
  - Other diagnoses – 10%

PALF Etiology: Jain and Dhawan *Liver Transplantation* **2016**



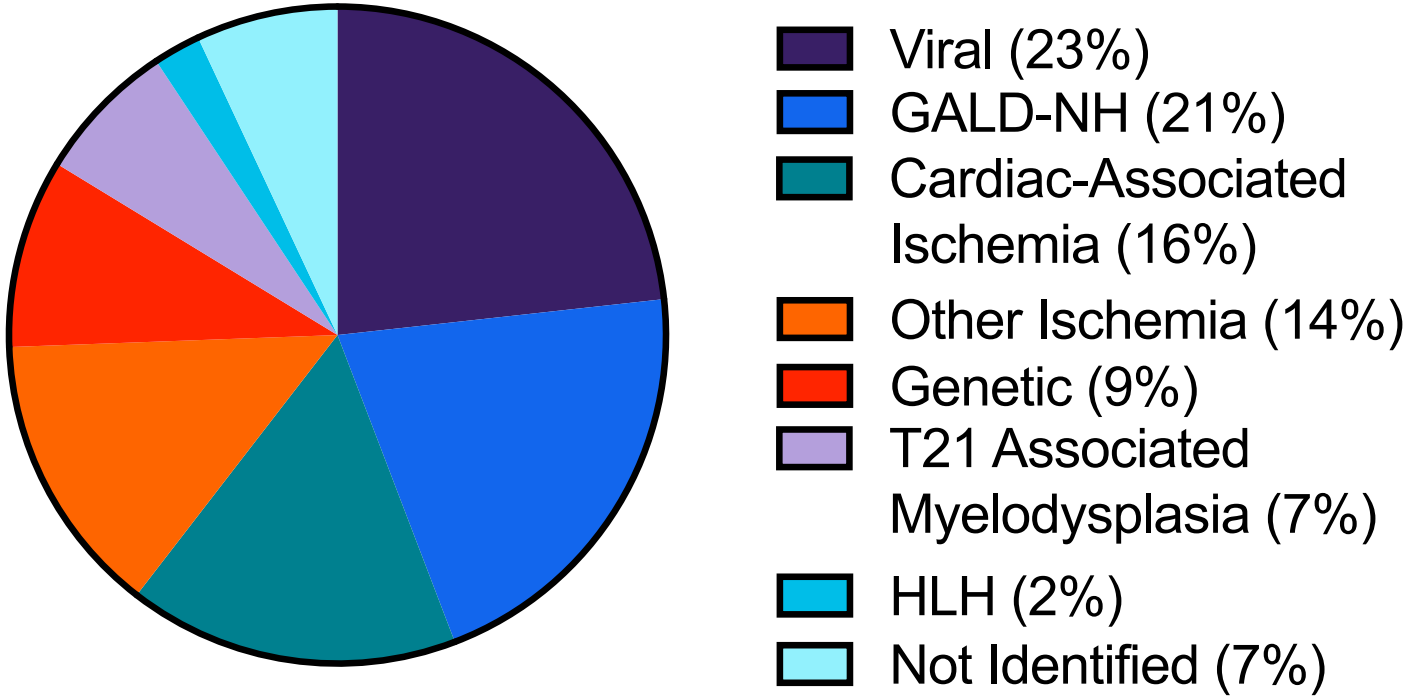
Age matters: distinct diagnoses, treatment, and outcomes within pediatric ALF

Overall PALF Etiology



*Jain and Dhawan *Liver Transpl* 2016

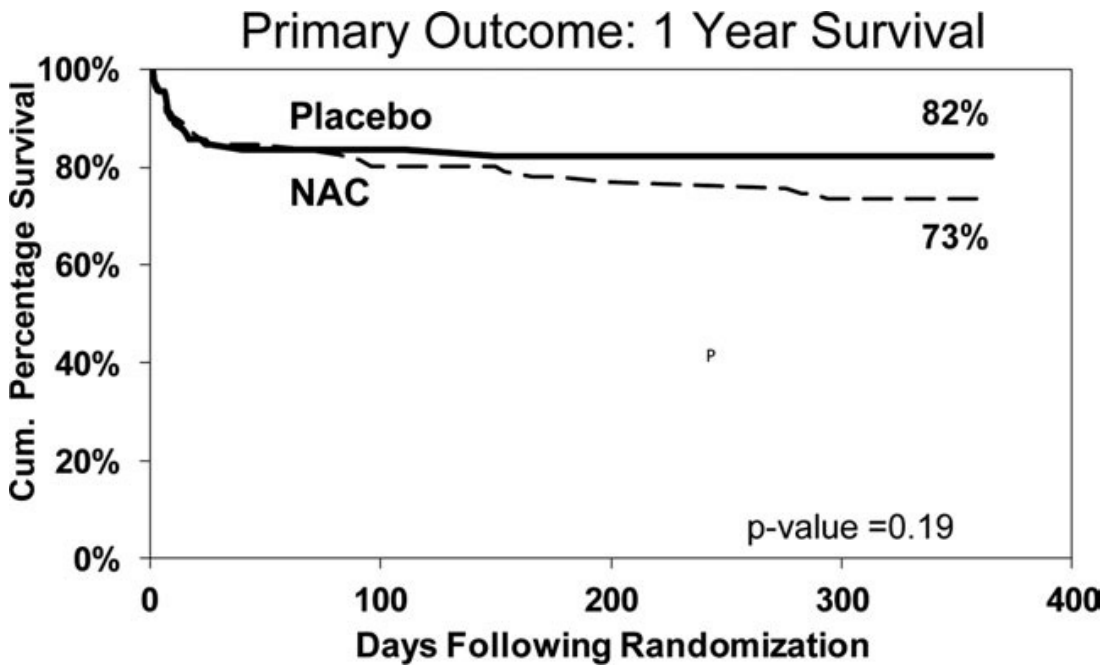
Neonatal ALF Etiology (Lurie Children's)



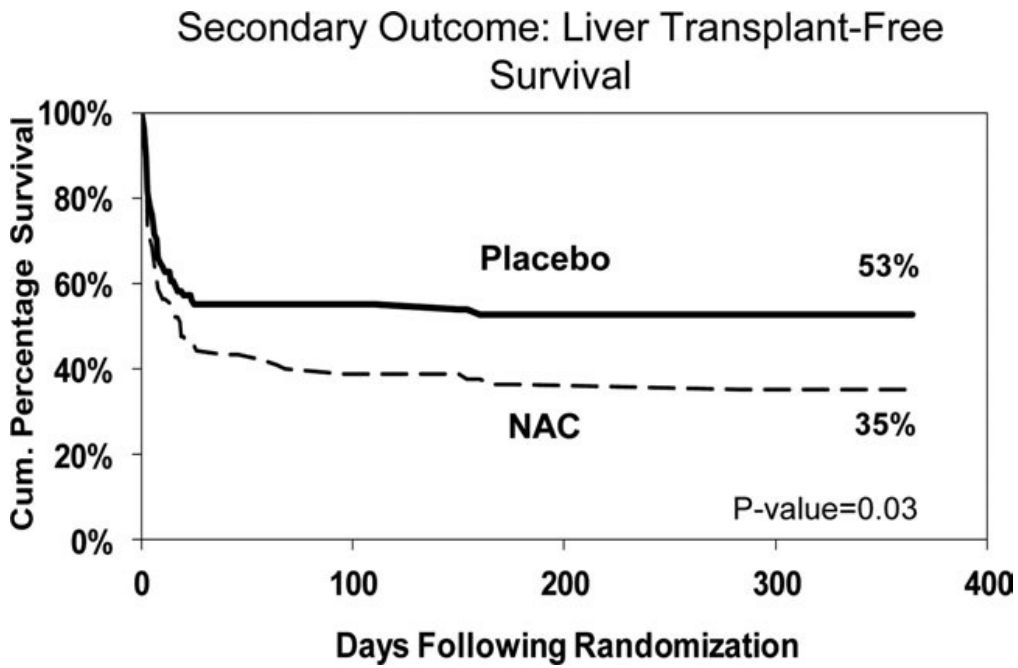
Total = 43

*Borovsky et al. *JPGN* 2021

Age matters: distinct diagnoses, treatment, and outcomes within pediatric ALF



No difference in 1-year patient survival



Children < 2 years: SNL of 29% with NAC vs 58% with placebo (p = 0.03)

*Squires R et al, *Hepatology*, 2013

Variable etiologies and prognosis within infantile acute liver failure

Etiology	Present study (2007–2018) <3 mo (n = 42)	Sundaram et al (4) (1999–2009) <3 mo (n = 148)	Squires et al (3) (2000–2004) <3mo (n = 127)	Bitar et al (5), 1993 and 2012 <4 mo (n = 78)	Durand et al (2) (1986–2000) <12 mo, (n = 80)	Shanmugam et al (1) (1990–2003) Neonates (n = 60)	Nieto et al (6) (2003–2015) Neonates (n = 45)
Indeterminate	14 (33.3%)	56 (37.8%)	68 (54%)	5 (6.4%)	13 (16%)	3 (5%)	4 (8.9%)
Galactosemia	7 (16.7%)	12 (8.1%)	2 (2%)	11 (14%)	2 (2.5%)	4 (6.7%)	3 (6.6%)
Tyrosinemia 1	5 (12%)	3 (2%)	4 (3%)	3 (4%)	12 (15%)	0	0
NH	4 (9.5%)	20 (13.5%)	6 (5%)	7 (9%)	13 (16.2%)	22 (36.7%)	8 (17.8%)
Mitochondrial disease	3 (7.1%)	8 (5.4%)	9 (7%)	9 (11.5%)	17 (21.2%)	0	1 (2.2%)
HLH	4 (9.5%)	4 (12.3%)	2 (2%)	6 (8%)	3 (3.7%)	8 (13.3%)	2 (4.4%)
Infectious	0	26 (17.5%)	9 (7%)	13 (17%)	12 (15%)	14 (23.3%)	9 (20%)
Hypoxic/ischemic	0	6 (4%)	7 (6%)	15 (19%)	0	3 (5%)	13 (28.9%)
Others	TALDO (2) Niemann-Pick disease (1) UPS53 mutation (1) BASD (1)	NPD (3) UCD (1) OTC defect (1) Hemangioendothelioma (1) Leukemia (1)	NPD (1) UCD (1) HFI (1) FAO defects (4) Leukemia (1) Drugs (1)	TALDO (1) BASD (2) Donohue syndrome (1) Leukemia (1) Hypopituitarism (3)	Leukemia (1) Drugs (1) AIH (3) UCD (2) HFI (1)	5 (8.3%)	Liver hemangioma (1) Intrahepatic porto-systemic fistula (1) Neuroblastoma (1) Lactic acidosis (1) Citrullinemia (1)
Survival with native liver	15 (35.7%)	88 (59.5%)	66 (53%)	39 (50%)	19 (24%)	22 (36.7%)	27 (60%)
Survival post-LT (%)	4 (9.5%)	24 (16.2%)	33 (26%)	2 (2.5%)	12 out 23 (52%)	9 (15%)	1 (2.2%)
LT (%)	4 (9.5%)	24 (16.2%)	36 (29%)	6 (8%)	23 (29%)	13 (21.7%)	1 (2.2%)
Mortality (%)	23 (54.7%)	36 (24%)	26 (16%)	31 (40%)	38 (47%)	28 (46.7%)	17 (37.8%)

*Modified from Lone et al. *JPGN* 2020

Comparison between studies of neonatal ALF

Etiology – N (%)	Shanmugam et al 2011 (n = 60)	Nieto et al 2017 (n = 45)	Borovsky et al 2021 (n = 43)
Indeterminate	3 (5%)	4 (8.9%)	3 (7%)
Galactosemia	4 (6.7%)	3 (6.6%)	1 (2.3%)
Tyrosinemia	0	0	0
NH	22 (36.7%)	8 (17.8%)	9 (21%)
Mitochondrial	0	1 (2.2%)	1 (2.3%)
HLH	8 (13.3%)	2 (4.4%)	1 (2.3%)
Infectious	14 (23.3%)	9 (20%)	10 (23%)
Ischemia	3 (5%)	13 (28.9%)	13 (30%)
Others	5 (8.3%)	5 (11%)	5 (12%)
Outcome – N (%)			
Transplant-free survival	22 (36.7%)	27 (60%)	14 (33%)
Survival post-OLT	9 (15%)	1 (2.2%)	1 (2.3%)
OLT	13 (21.7%)	1 (2.2%)	2 (5%)
Mortality	28 (46.7%)	17 (37.8%)	28 (65%)

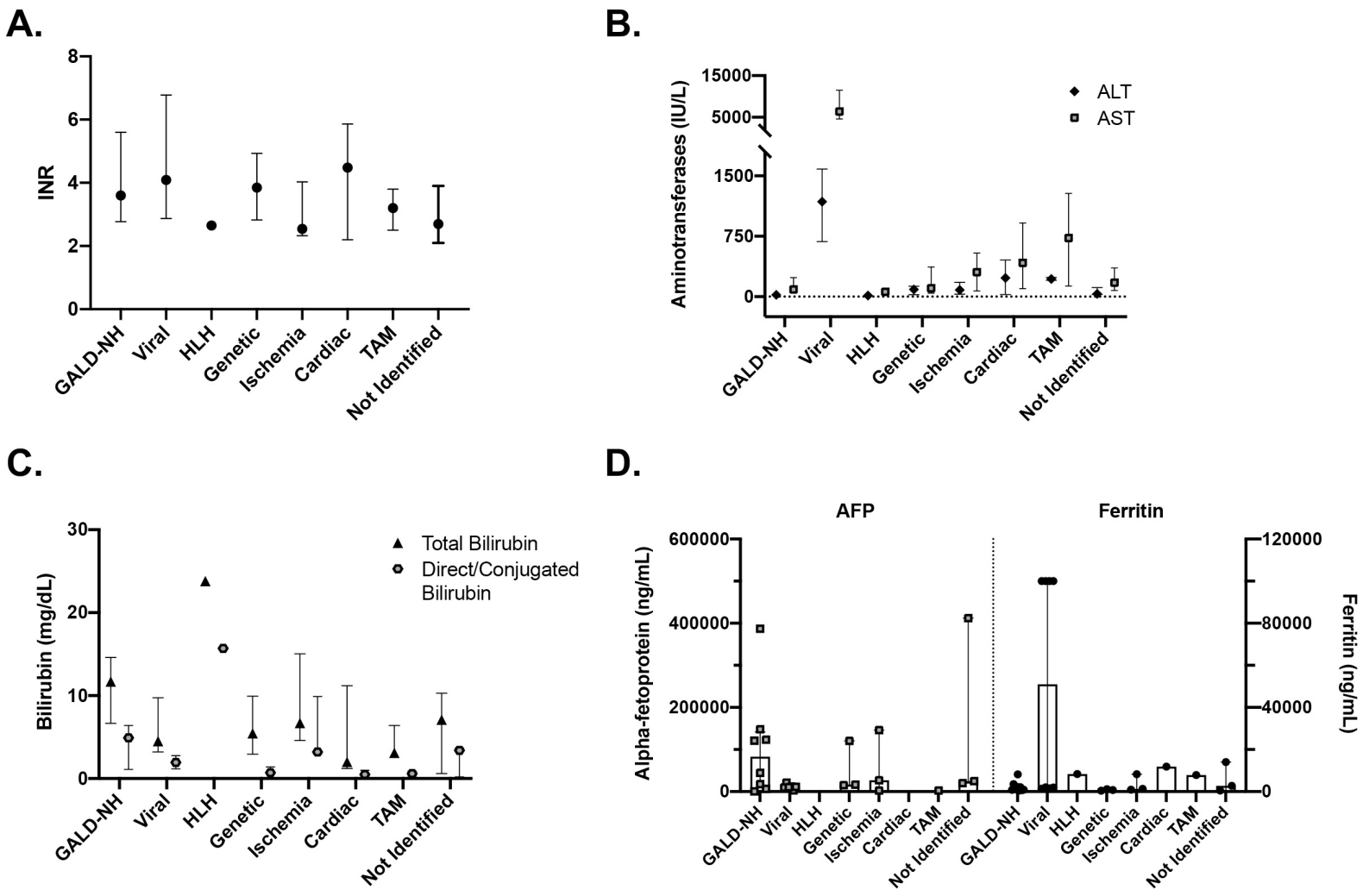
Clinical findings in neonatal ALF based on etiology

	GALD-NH	Viral Infection	HLH	Mitochondrial Hepatopathy
Age at presentation	Usually at birth and almost always < 3 days	Typically 5-14 days	Variable, sometimes at birth	Variable, often first weeks to months of life
Premature birth	Most (70%-90%)	Usual population incidence	Uncommon	Uncommon
History of maternal sibling death	Common	Almost never	Uncommon	25% risk in full siblings
Oligohydramnios	Most (70%-90%)	Rare	Rare	Uncommon (polyhydramnios seen)
Intrauterine growth restriction	Most (70%-90%)	Rare	Rare	Possible (20%-30%)
Multiorgan involvement	Renal tubular dysplasia	Common in HSV especially brain	Bone marrow	Central nervous system and heart
Ascites	Common (40%-60%)	Rare	Uncommon	Uncommon
Patent ductus venosus	Most (70%-90%)	Never	Never	Never
Hepatomegaly	Uncommon (10%-20%)	Common	Common	Common
Splenomegaly	Uncommon (10%-20%)	Common though often mild	Common	Uncommon
Hypoglycemia	Usual	Common	Common	Usual
Coagulopathy	Profound (INR, 4-10)	Moderate to profound	Moderate to profound	Moderate to profound
Metabolic acidosis	No	No	No	Yes
Cholestasis	Not at birth; increasing afterward	Minimal at presentation	Moderate to severe	Moderate
ALT	Typically low or normal and almost always < 100 IU/L	Typically high and often > 1000 IU/L	Typically high and often > 1000 IU/L	Typically high and often 100-500 IU/L
Ferritin	Almost always > 800 ng/mL and < 7000	Often very high (>20,000 ng/mL)	Very high (>20,000 ng/mL)	Variable elevation
Alpha-fetoprotein	Almost always high (> 80,000 ng/mL in term neonate); typically > 300,000 ng/mL	Almost always normal (< 80,000 ng/mL in term neonate)	Almost always normal (< 80,000 ng/mL in term neonate)	Variable elevation
Lactate:pyruvate molar ratio and ketone body ratios	Normal	Normal	Normal	Abnormal

*Taylor and Whitington. *Liver Tr* 2016

Laboratory findings in neonatal ALF based on etiology

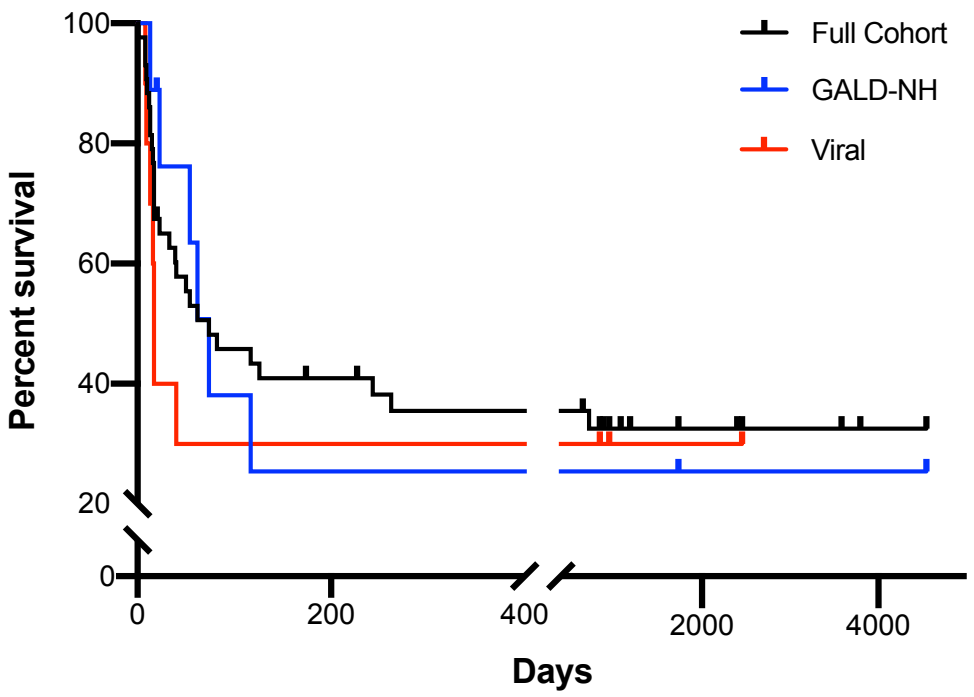
- Aminotransferase levels help distinguish GALD-NH from viral infection
- Variable elevation of AFP and ferritin across etiologies



*Borovsky et al. *JPGN* 2021

Neonatal ALF: how do we improve prognosis?

High mortality for neonatal ALF



Median survival: full cohort = 74 days, viral infection = 17 days, GALD-NH = 74 days (Borovsky et al 2021)

Strategies to improve prognosis

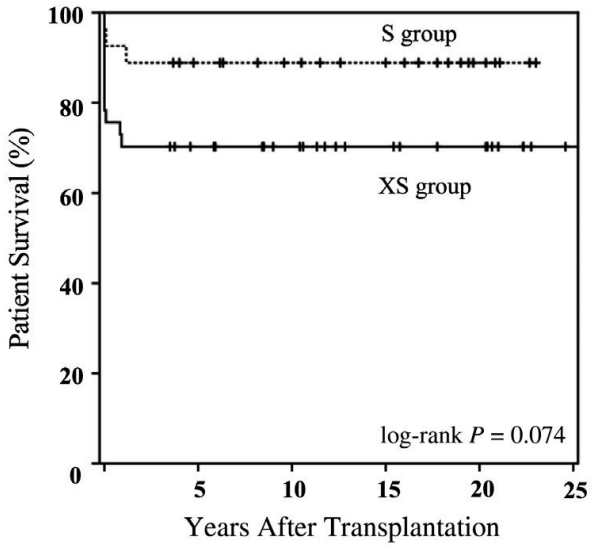
- Timely diagnosis and initiation of therapy
- Identification of prognostic indicators for transplant-free survival
  - Higher ALT in neonates at diagnosis is with worse prognosis (Nieto et al 2017)
  - Total bilirubin is associated with poor outcome in infants < 3 months (Lone et al 2020)
  - Higher AFP in neonates with SNL (Borovsky et al 2021)

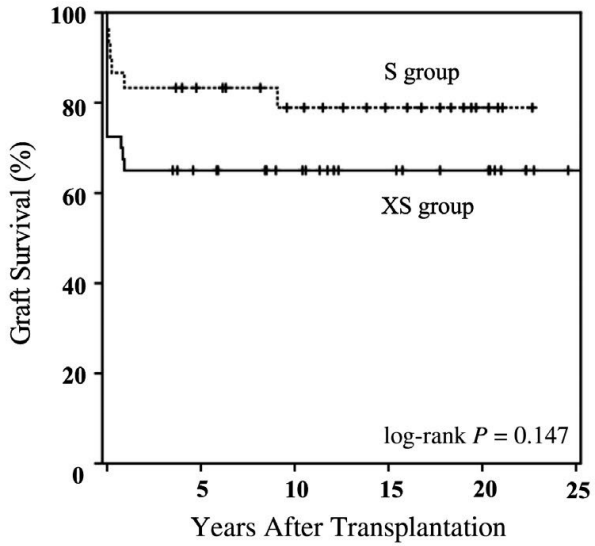
Outcomes for liver transplantation in infants

Challenges for liver transplant in the neonate

- Diagnostic considerations
- Technical challenges
- Tolerance of ABOI grafts
- Greater peri-op complications: ICU stay, intubation, infection, reoperation

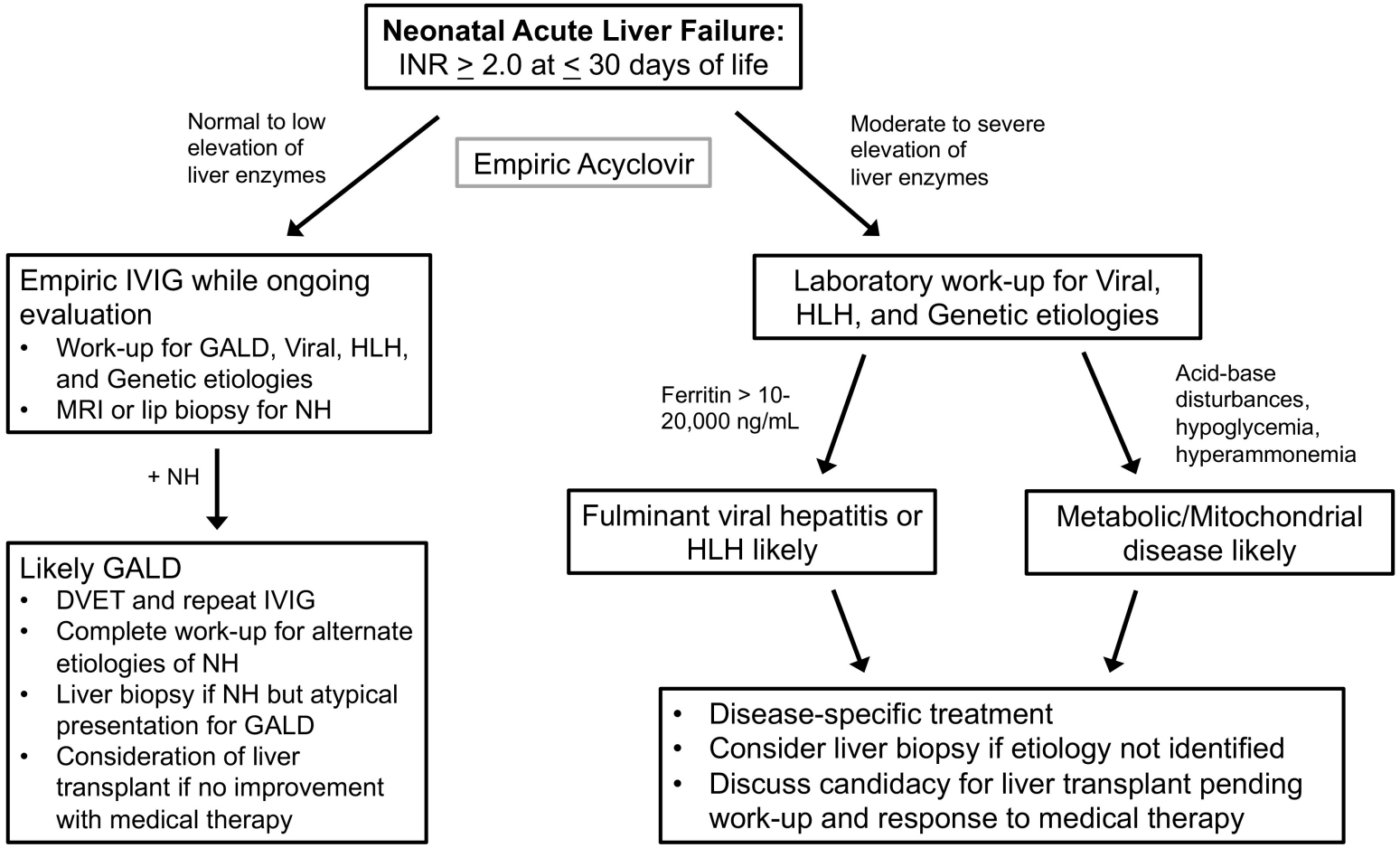
Similar outcomes for liver transplant in infants ≤ 3 months (XS, n = 37) as >3 to ≤ 6 months (S, n = 27)





*Yamamoto et al. *Liver Tr* 2019

Proposed algorithm for management of neonatal ALF



*Borovsky et al. *JPGN* 2021

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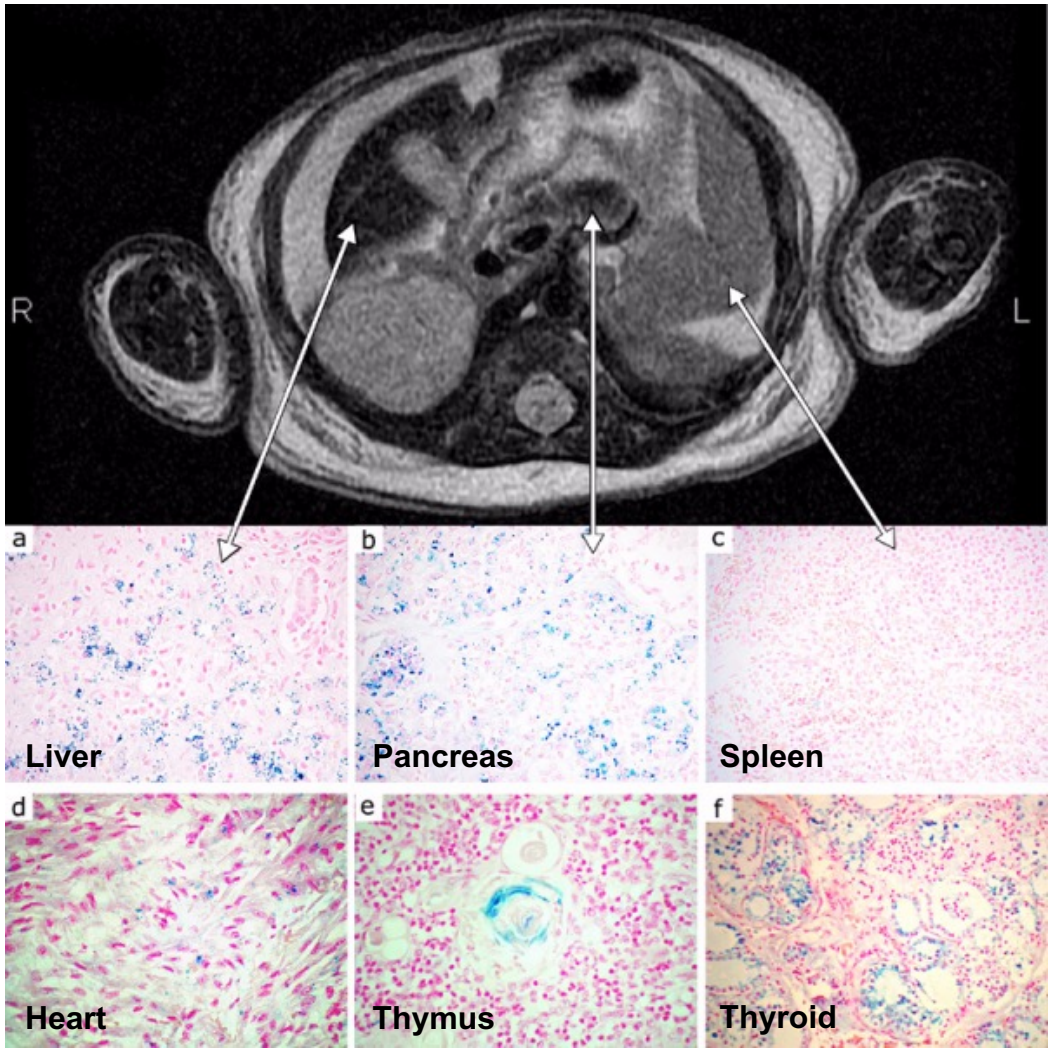
NH versus GALD

- **Neonatal hemochromatosis (NH):** phenotype of neonatal liver disease in association with extrahepatic siderosis

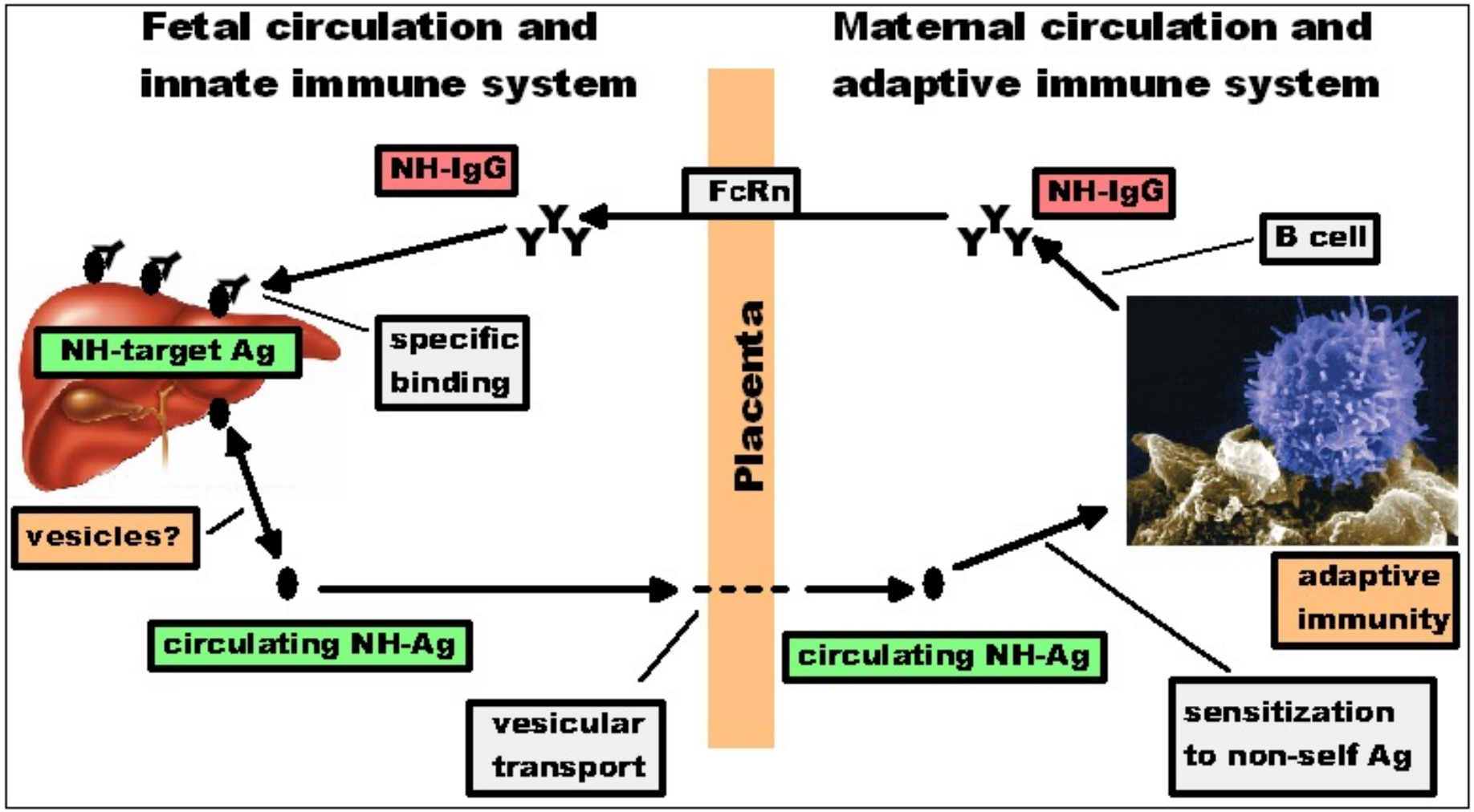
- **Gestational alloimmune liver disease (GALD):** maternal-fetal alloimmune disorder that is a leading cause of neonatal liver failure
  - Principal cause of NH
  - NH is the main phenotype of GALD
  - Estimated minimum incidence rate of 15 per million live births in the U.S.



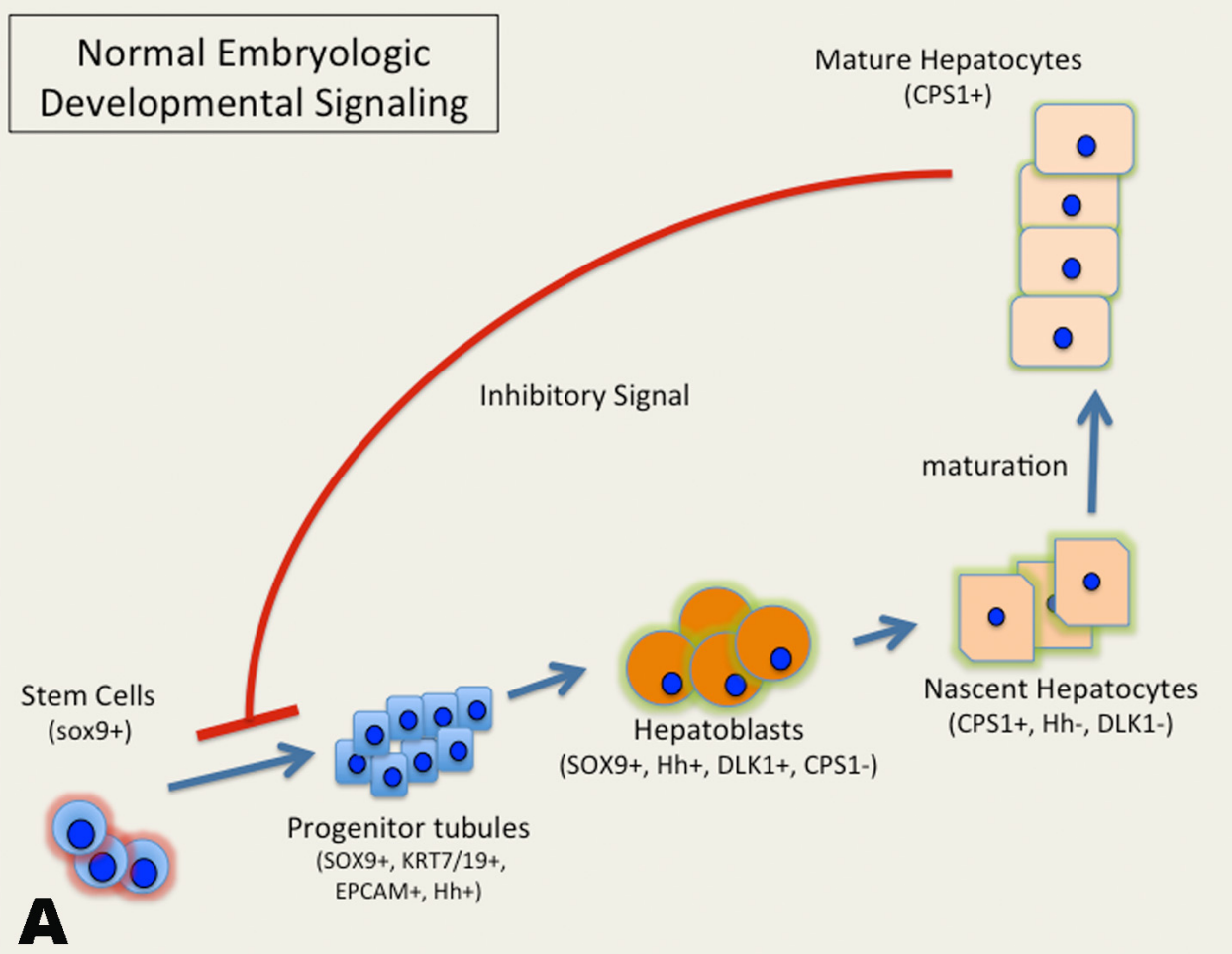
Evidence for an Alloimmune Mechanism of NH

- NH is congenital and familial but not hereditary:
  - High recurrence rate of lethal disease after the index case
  - Many women have several normal babies prior to the index case
  - Several women with affected offspring by different fathers
  - No sisters of affected women reported to have a baby with NH
  - Offspring of women who survived NH are unaffected

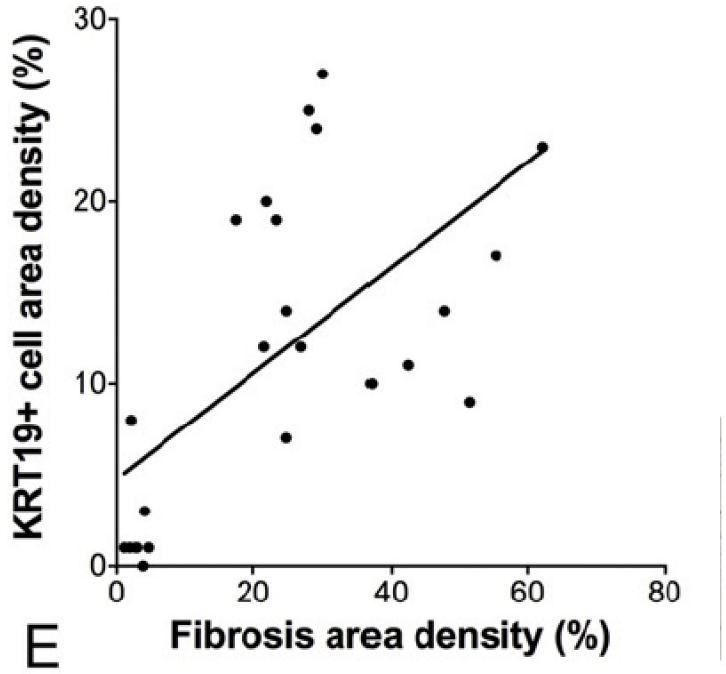
Proposed Mechanism of GALD-NH



Proposed Mechanism of GALD-NH

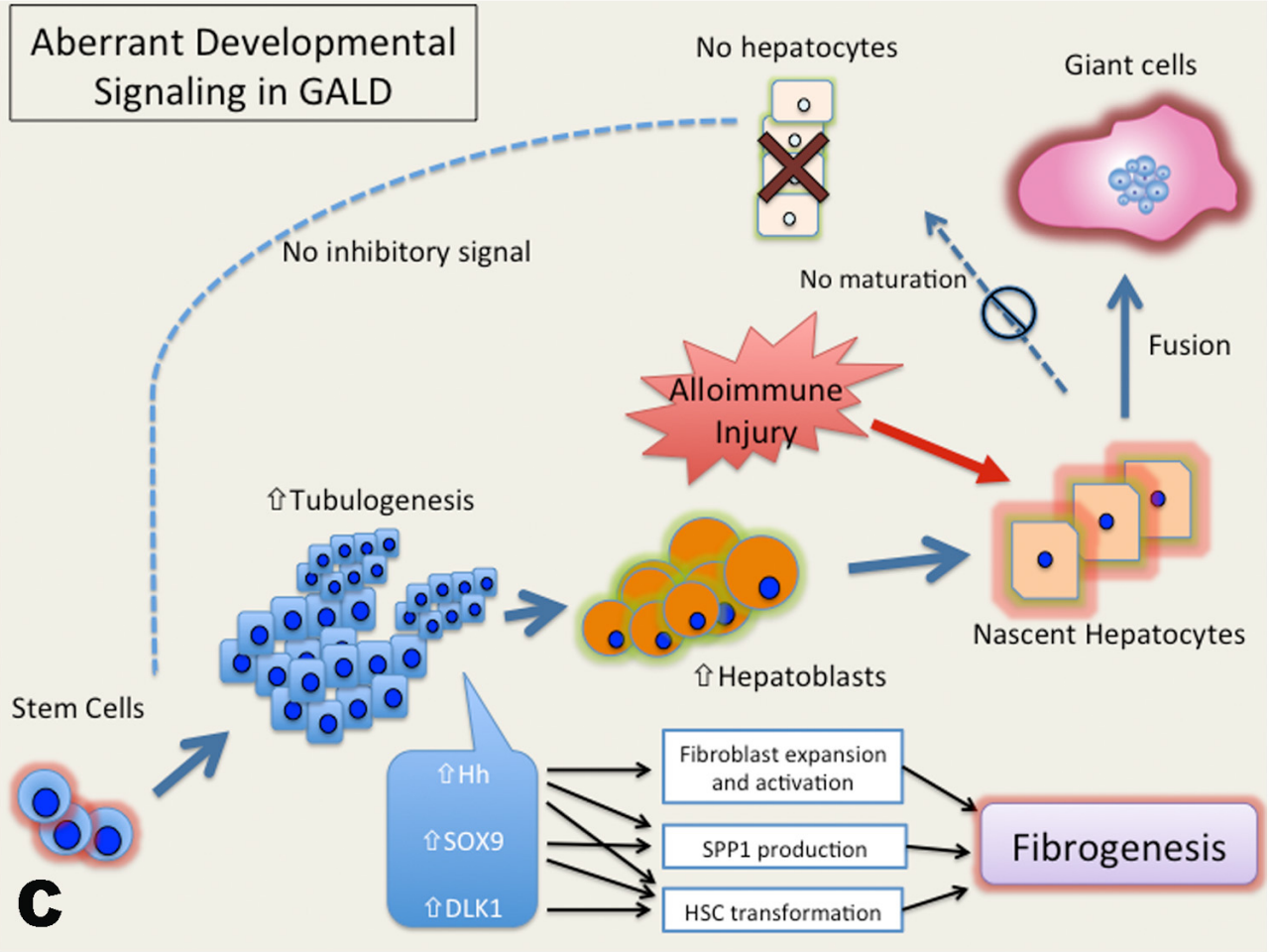


Tubule density correlates with fibrosis



*Asai et al. *Human Pathology* 2015.

Proposed Mechanism of GALD-NH



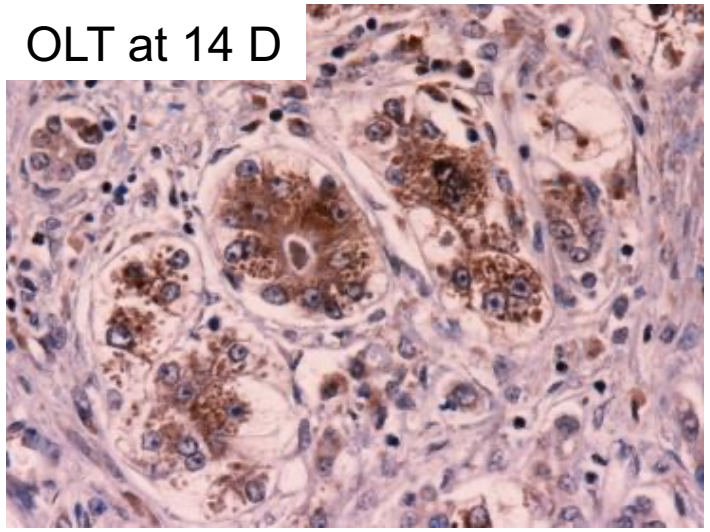
Aberrant signaling in GALD:

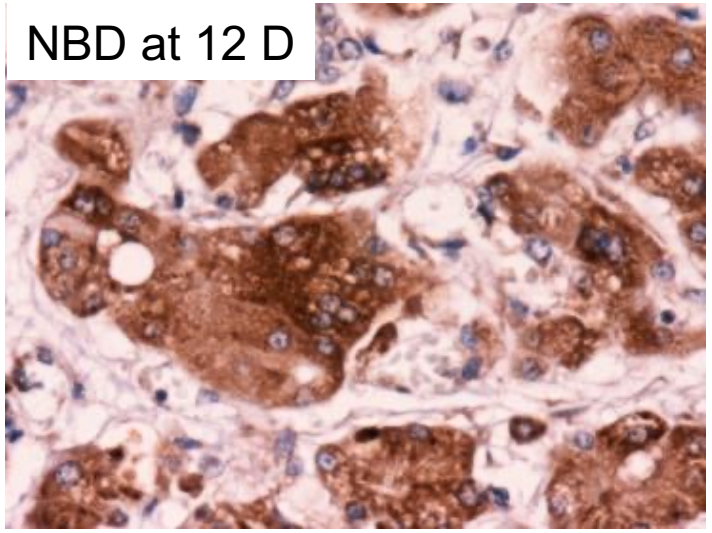
- Immune injury of nascent hepatocytes
- Excess parenchymal tubulogenesis
- Tubules exhibit active Hh signaling and produce osteopontin

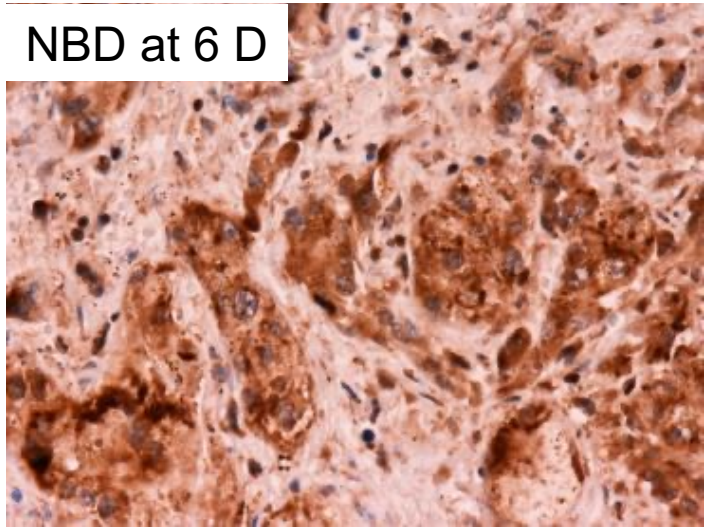
→ Prominent lobular fibrosis in GALD that correlates with density of tubules

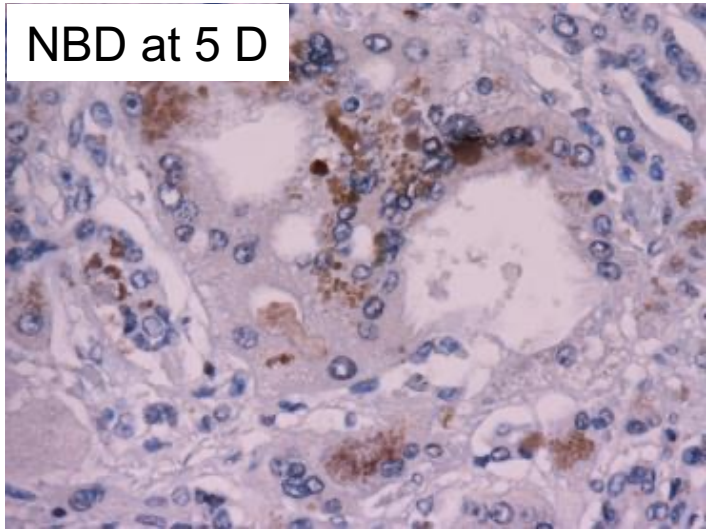
*Asai et al. *Human Pathology* 2015.

MAC Expression in GALD-NH: Evidence for Complement-Mediated Injury

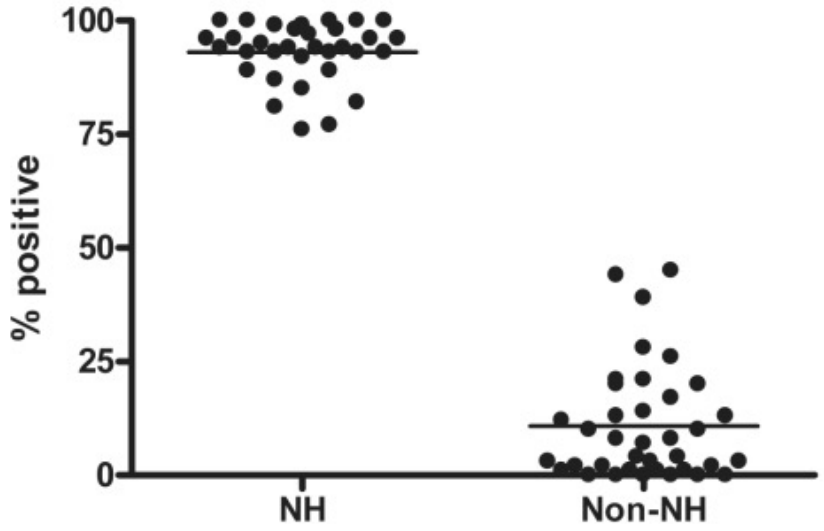








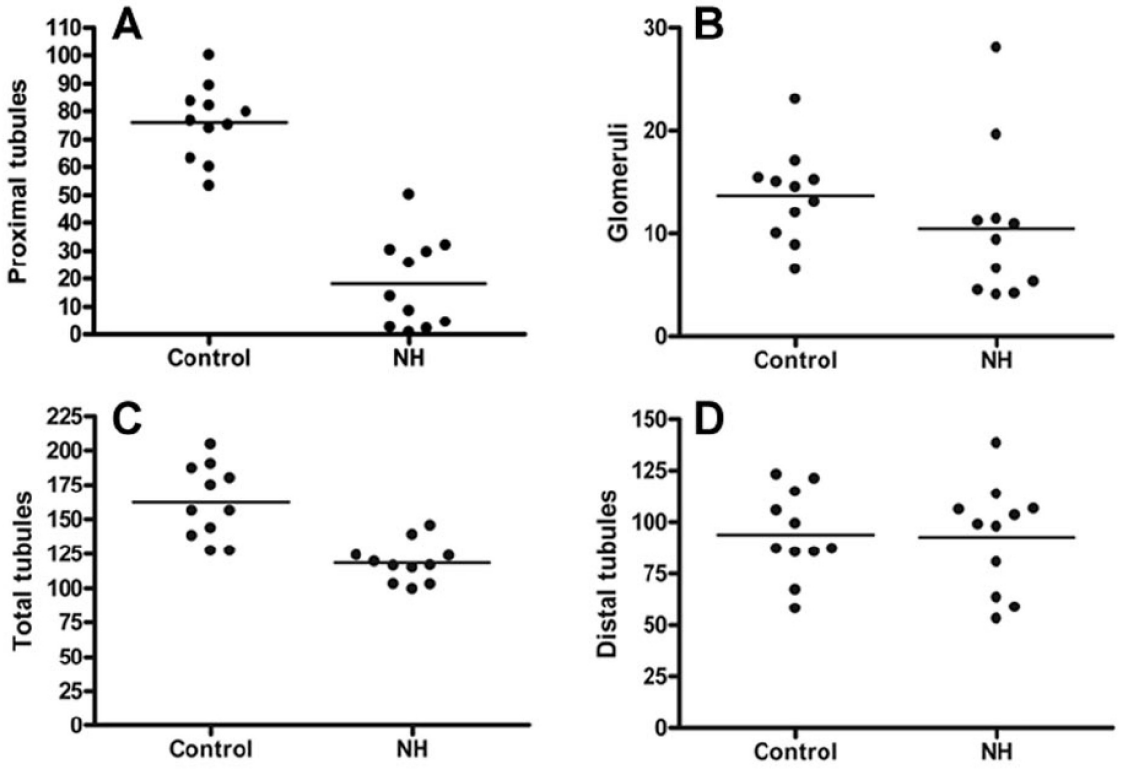
Increased expression of MAC in hepatocytes of NH vs. non-NH liver disease.



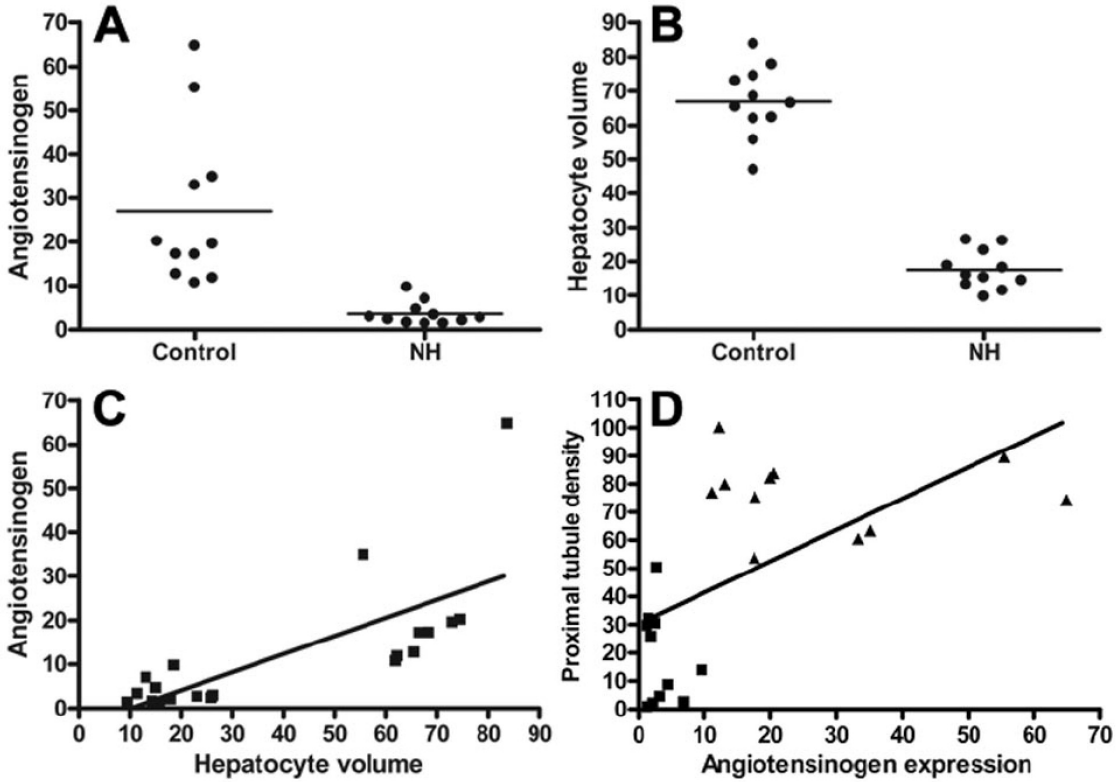
*Pan et al. *Hepatology* 2010.

GALD-NH: Renal Tubular Dysgenesis

Reduction of renal proximal tubules (PT) in NH



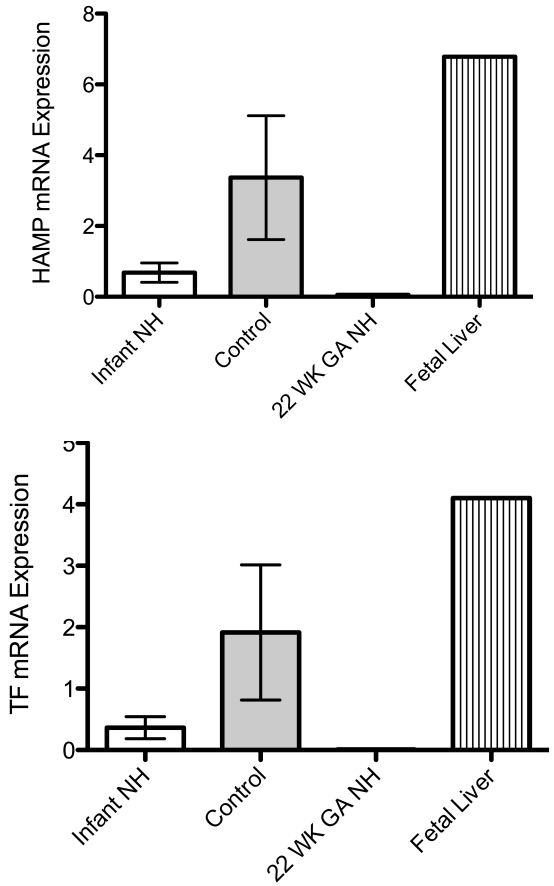
Reduced hepatic AGT correlates with hepatocyte volume and PT density



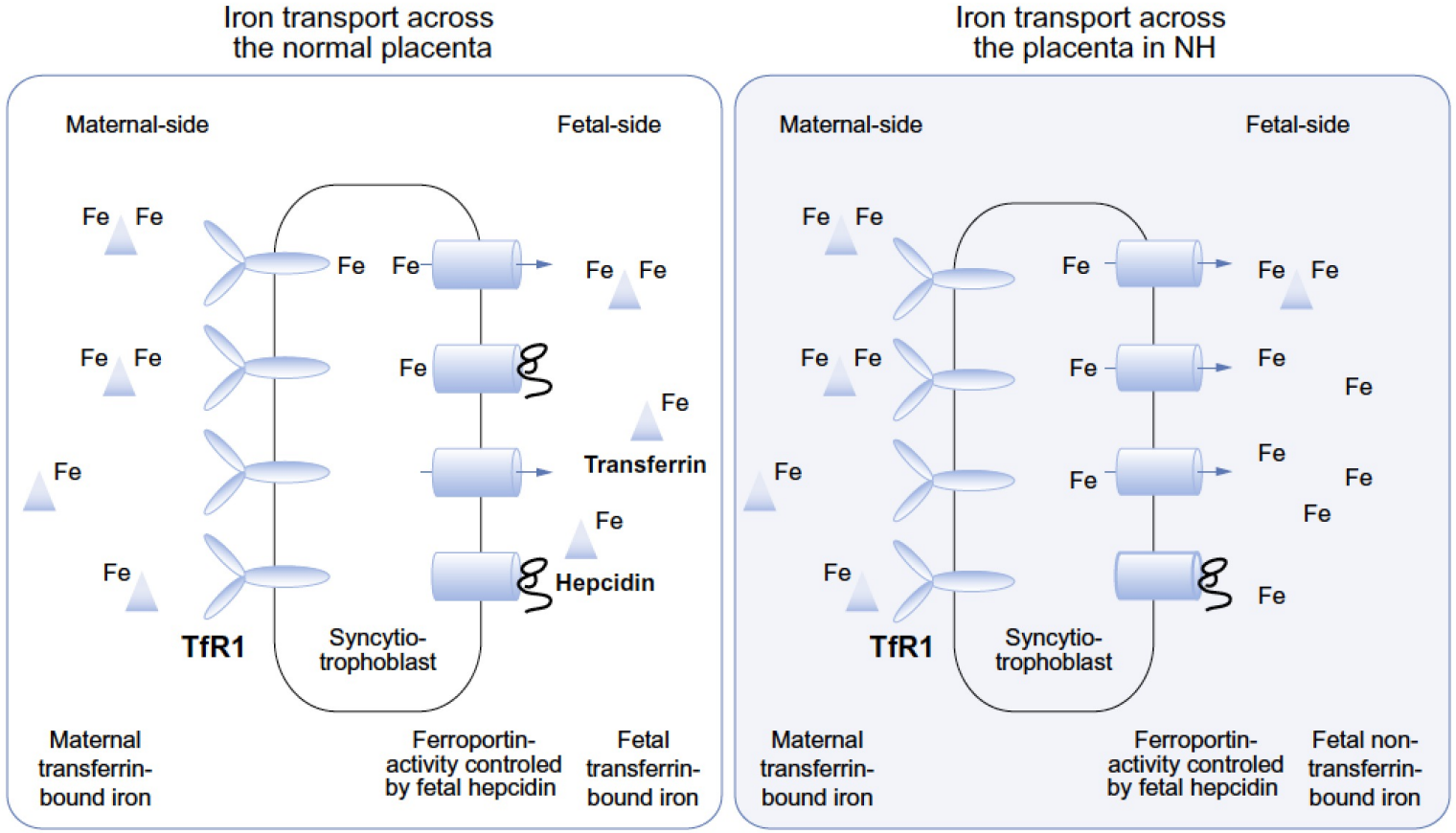
*Bonilla et al. *Pediatric Research* 2010.

GALD-NH: Extra-Hepatic Iron Deposition

Reduced liver *HAMP* (hepcidin) and *TF* (transferrin) lead to excess fetal NTBI



*Bonilla al. *J Hepatol* 2012.



*Zolleret al. *J Hepatol* 2012.

GALD-NH: Extra-Hepatic Iron Deposition

Excess NTBI uptake by ZIP14+/Ferroportin- tissues

→ **NH phenotype is the result of severe fetal liver injury**

Iron indices in GALD vs normal newborn

	GALD cases	Reference values	
	Mean ± SD (n)	Range or mean ± SD	[Ref.]
Ferritin (ng/ml)	2174 ± 1699 (20)	40-775 35-309	[23] [22]
Iron (µg/dl)	160 ± 63 (8)	72-203 118 ± 19	[23] [21]
Iron binding capacity (µg/dl)	174 ± 54 (7)	155-330 245 ± 50	[23] [21]
Binding saturation (%)	90 ± 13 (13)	49.9 ± 15.6	[21]

Expression of Zip14 and Ferroportin in extrahepatic tissues of GALD infants with siderosis

	Siderosis	ZIP14	Ferroportin
Pancreatic acinar cells	++	+++	+
Thyroid follicle epithelia	++	++	-
Hassall's corpuscles	++	++	+
Myocardium	+	++	++
Adrenal cortex	+	++	+
Renal tubular epithelium	+	+	+
Submucosal salivary glands	++	+++	-

*Bonilla al. *Journal of Hepatology* 2012.

GALD in the Newborn: Clinical Presentation and Management Principles

GALD: Leading Cause of Neonatal Acute Liver Failure

- **Differential diagnosis of neonatal ALF:**
  - GALD
  - Infection
  - Hemophagocytic lymphohistiocytosis (HLH)
  - Mitochondrial DNA depletion syndromes
  - Toxic metabolic hepatopathies: tyrosinemia, galactosemia, hereditary fructose intolerance

- **Differential diagnosis of NH:**
  - GALD
  - Trisomy 21 with myelodysplasia*
  - DGUOK mutations
  - Delta-4-oxosteroid 5-beta reductase of bile acid synthetic defects
  - Congenital HLH*
  - Other myelodysplasia and congenital anemias*
  - Perinatal infection

*Iron also usually in the spleen.

GALD: Leading Cause of Neonatal Acute Liver Failure

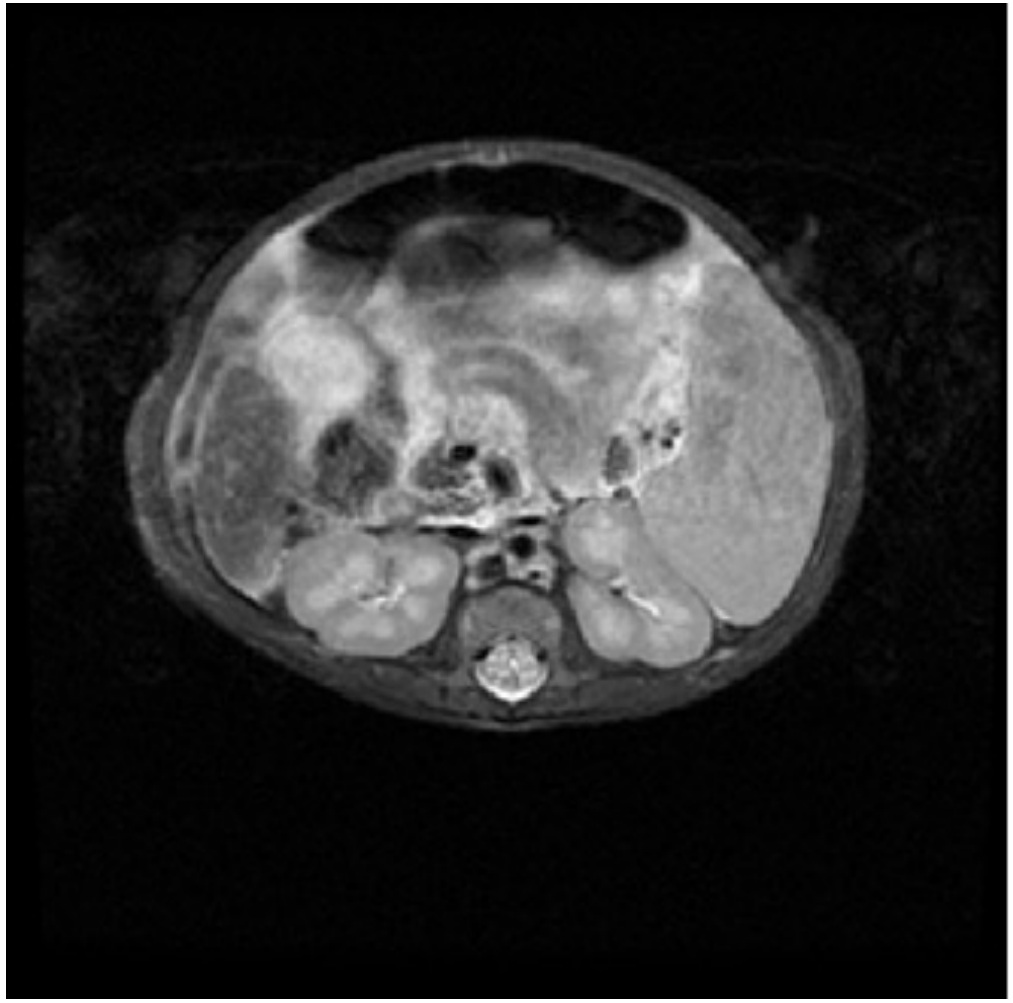
	GALD-NH	Viral infection	HLH	Mitochondrial hepatopathy
Age at presentation	Usually at birth and almost always < 3 days	Typically 5 – 14 days	Variable, sometimes at birth	Variable, often first weeks to months of life
Premature birth	Most (70-90%)	Usual population incidence	Uncommon	Uncommon
Multi-organ involvement	Renal tubular dysplasia	Common in HSV especially brain	Bone marrow	Central nervous system and heart
Ascites	Common (40-60%)	Rare	Uncommon	Uncommon
Hepatomegaly	Uncommon (10-20%)	Common	Common	Common
Splenomegaly	Uncommon (10-20%)	Common though often mild	Common	Uncommon
Metabolic acidosis	No	No	No	Yes
Cholestasis	Not at birth; increasing afterwards	Minimal at presentation	Moderate to severe	Moderate
ALT	Typically low or normal, often < 100 IU/L	Typically high and often > 1000 IU/L	Typically high and often > 1000 IU/L	Typically high and often 100-500 IU/L
Ferritin	Almost always > 800 ng/ml and < 7000 ng/ml	Often very high (>20,000 ng/ml)	Very high (>20,000 ng/ml)	Variable elevation
Alpha-fetoprotein	Almost always high; typically > 300,000 ng/ml	Almost always normal	Almost always normal	Variable elevation
Lactate:pyruvate molar ratio	Normal	Normal	Normal	Abnormal

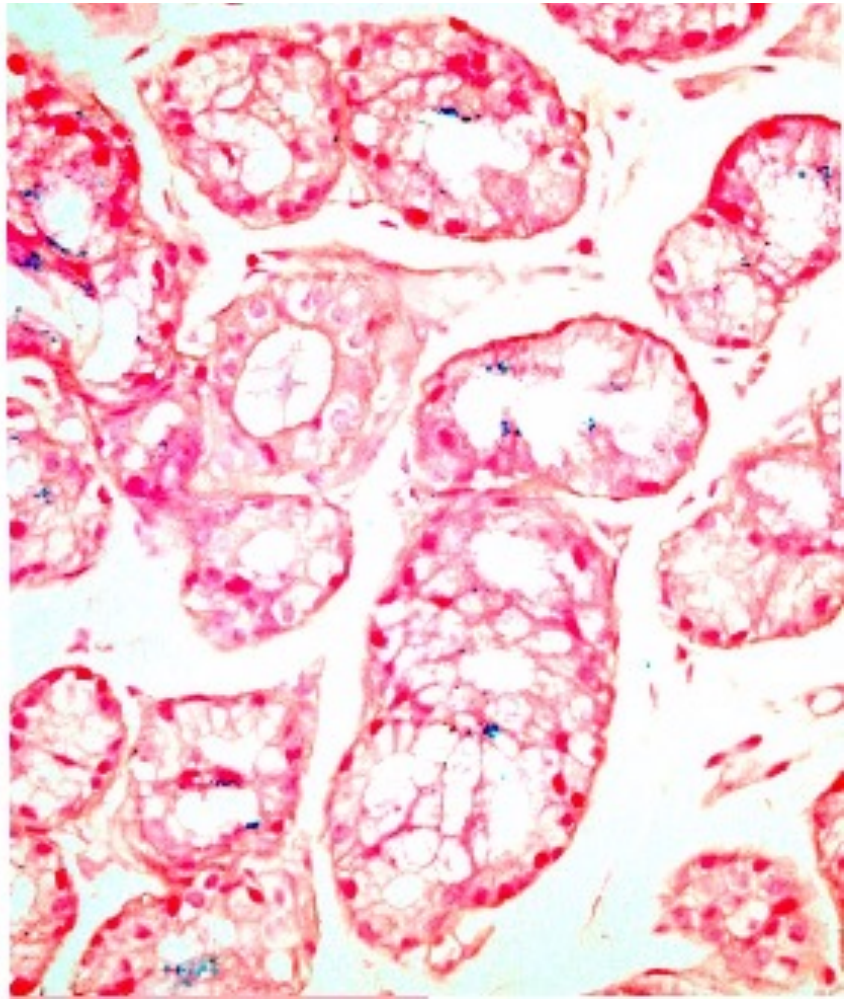
*Modified from: Taylor and Whitington. *Liver Transpl* 2016;22:677-685.

Laboratory Findings in GALD-NH

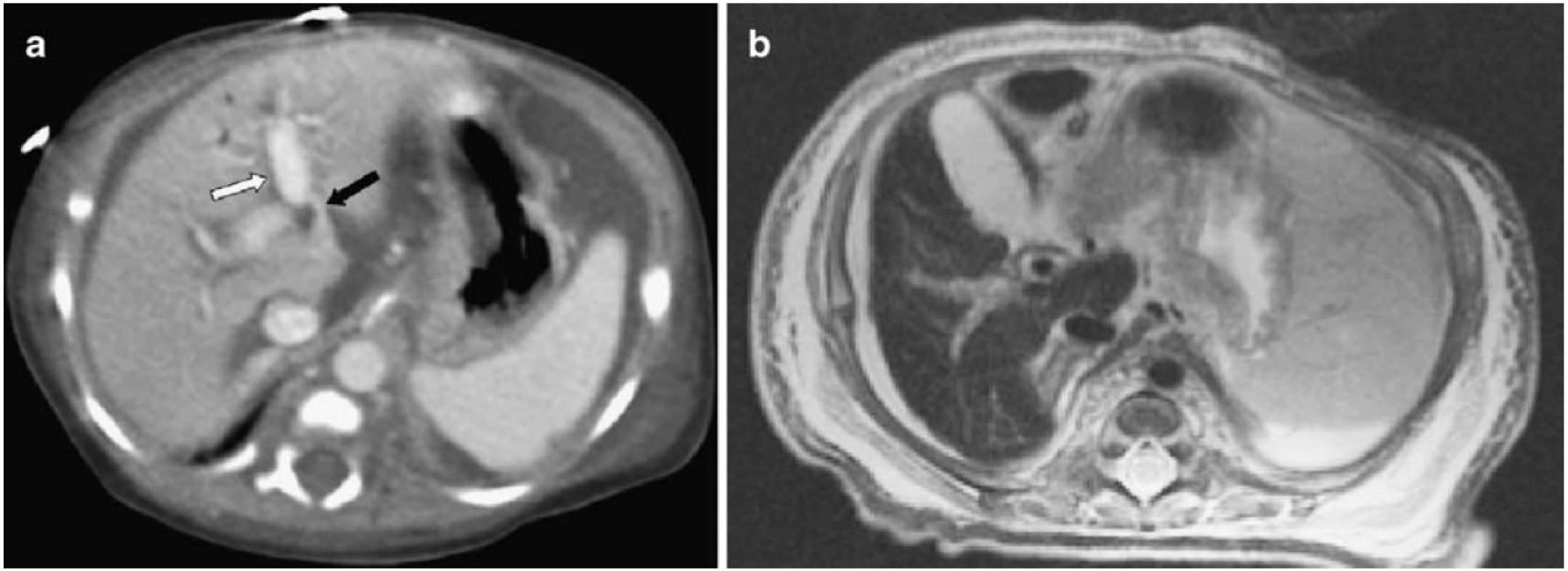
- Hypoglycemia
- Synthetic liver dysfunction
  - Median INR 4.1 (n = 22; 1st quartile 2.8, 3rd quartile 5.7)
  - Factors V and VII usually < 10%
  - Low albumin
- Elevated serum ferritin
  - Median 1,158 µg/L (n = 21)
- Elevated AFP: usually > 300,000 ng/ml
- Disproportionately low aminotransferases
  - Median ALT 62 IU/L (n = 18; 1st quartile 39, 3rd quartile 115)
  - Median AST 174 IU/L (n = 17; 1st quartile 61, 3rd quartile 294)

MRI and Buccal Biopsy to Demonstrate Extra-Hepatic Iron Deposition



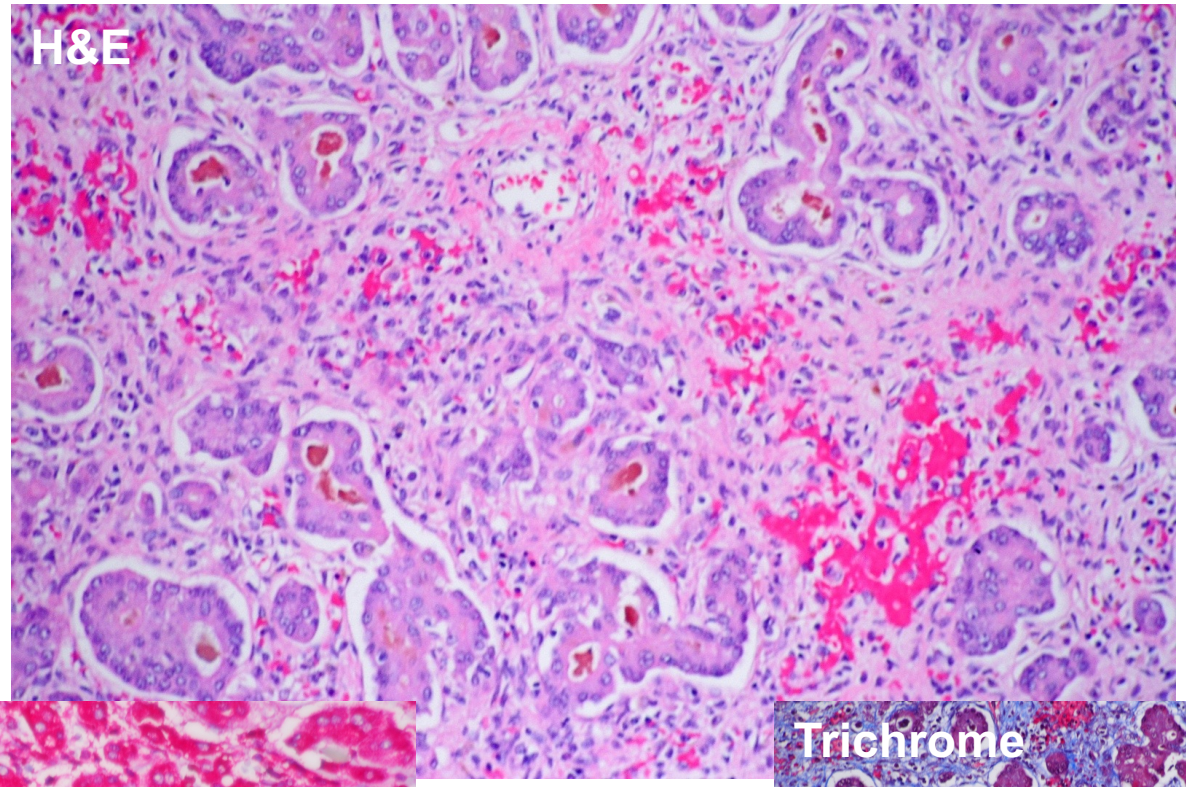


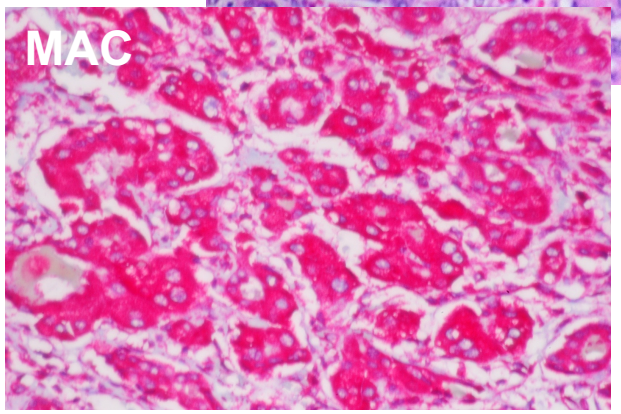
GALD-NH and Patent Ductus Venosus

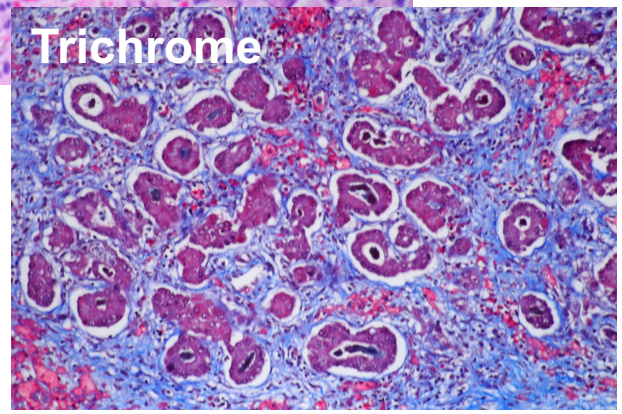


*Tsai et al. *Pediatr Radiol* 2009.

Liver Pathology in GALD

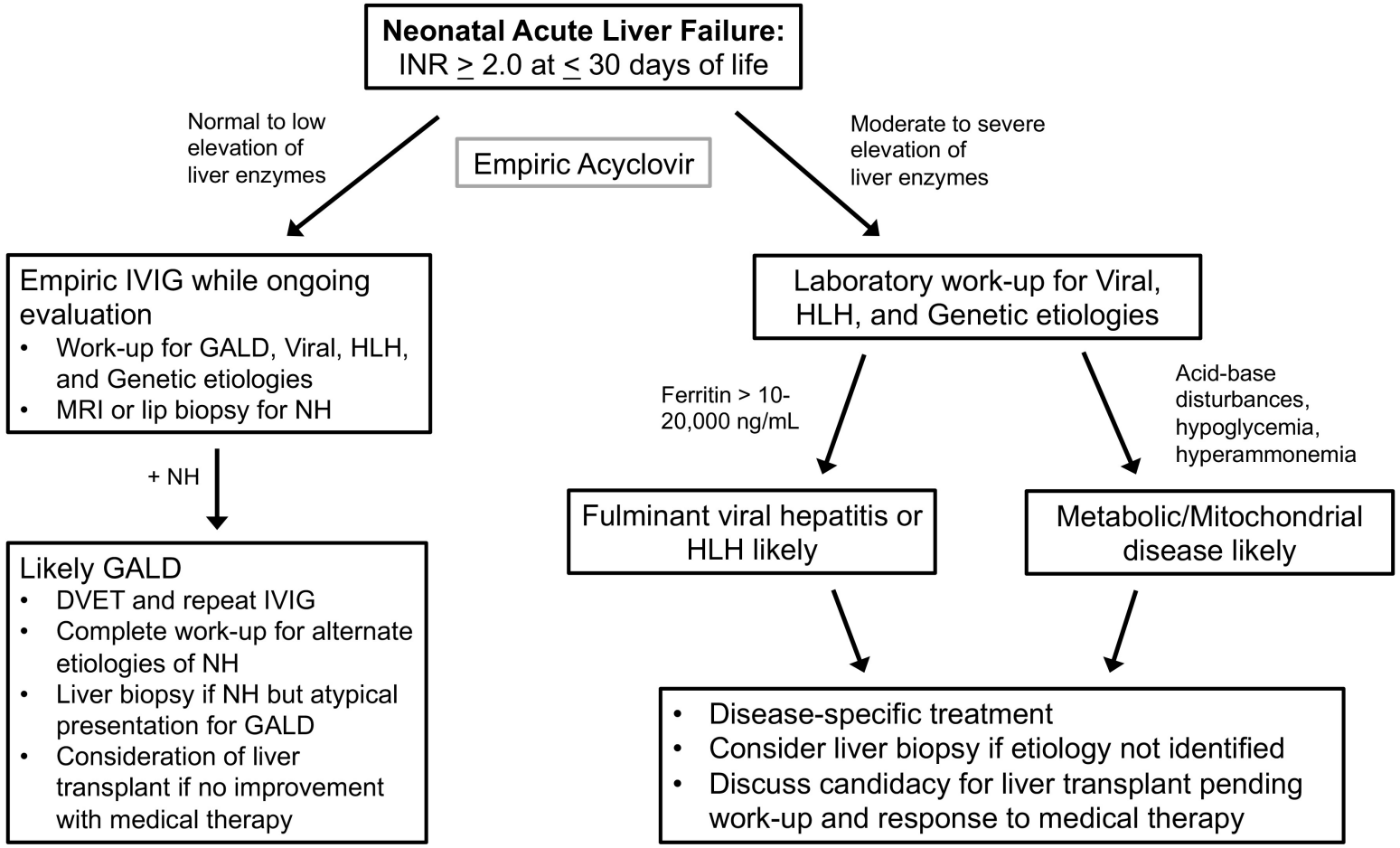






- Paucity of hepatocytes
- Remaining hepatocytes with giant cell or pseudoacinar transformation
- Parenchymal disease with ductular reaction
- Portal areas spared
- Pronounced lobular fibrosis, cirrhosis, possible regenerative nodules

Proposed algorithm for management of neonatal ALF



*Borovsky et al. *JPGN* 2021

GALD-NH Treatment: IVIG and Exchange Transfusion

Table II. Treatment of NH and outcome of subjects

Patient No.	Age at treatment (d)	ET	IVIG	Outcome	Age at discharge (d)	Current age (mo)
1	9	Yes	Yes	Death	-	-
2	14	Yes	Yes	OLT/Death	-	-
3	13	Yes	Yes	Alive	45	34
4	1	Yes	Yes	Alive	34	15
5	12	Yes	Yes	Alive	18	6
6	7	Yes	Yes	Alive	97	21
7	30	Yes	Yes	Alive	90	5
8	30	Yes	Yes	Alive	48	31
9	11	Yes	Yes	Alive	77	7
10	30	No	Yes	Alive	90	5
11	21	Yes	Yes	Death	-	-
12	22	Yes	Yes	OLT/Death	-	-
13	22	Yes	Yes	Alive	45	6
14	18	Yes	Yes	Alive	101	57
15	1	No	Yes	Alive	30	3
16	11	No	Yes	Alive	26	1

*Rand et al. J *Pediatr* 2009.

Table IV. Comparison of outcome with ET/IVIG therapy versus conventional therapy in historical controls

Outcome → Treatment ↓	Good	Poor	Total
DVET/IVIG	12 **(75%)**	4	16
Conventional	23 **(17%)**	108	131
Total	35	112	147

Fisher exact test, $P < .001$ for improved outcome with ET/IVIG therapy.

IVIG: displace maternal IgG and bind to circulating complement
DVET: remove maternal alloantibody in neonates' circulation

Liver Transplantation in NH

Outcomes of patients with LT for NH versus ALF between 1994-2013 in UNOS

	NH (N = 38)	ALF (N = 168)	p Value
Graft survival (%)			
30 days	81.6	86.3	0.46
1 yr	71.1	73.2	0.79
5 yr	68.4	63.1	0.54
Patient survival (%)			
30 days	89.5	91.1	0.76
1 yr	84.2	85.1	0.89
5 yr	81.6	80.4	0.86

*Sheflin-Findling et al. *Pediatr Transplant* 2015;19:164-169.

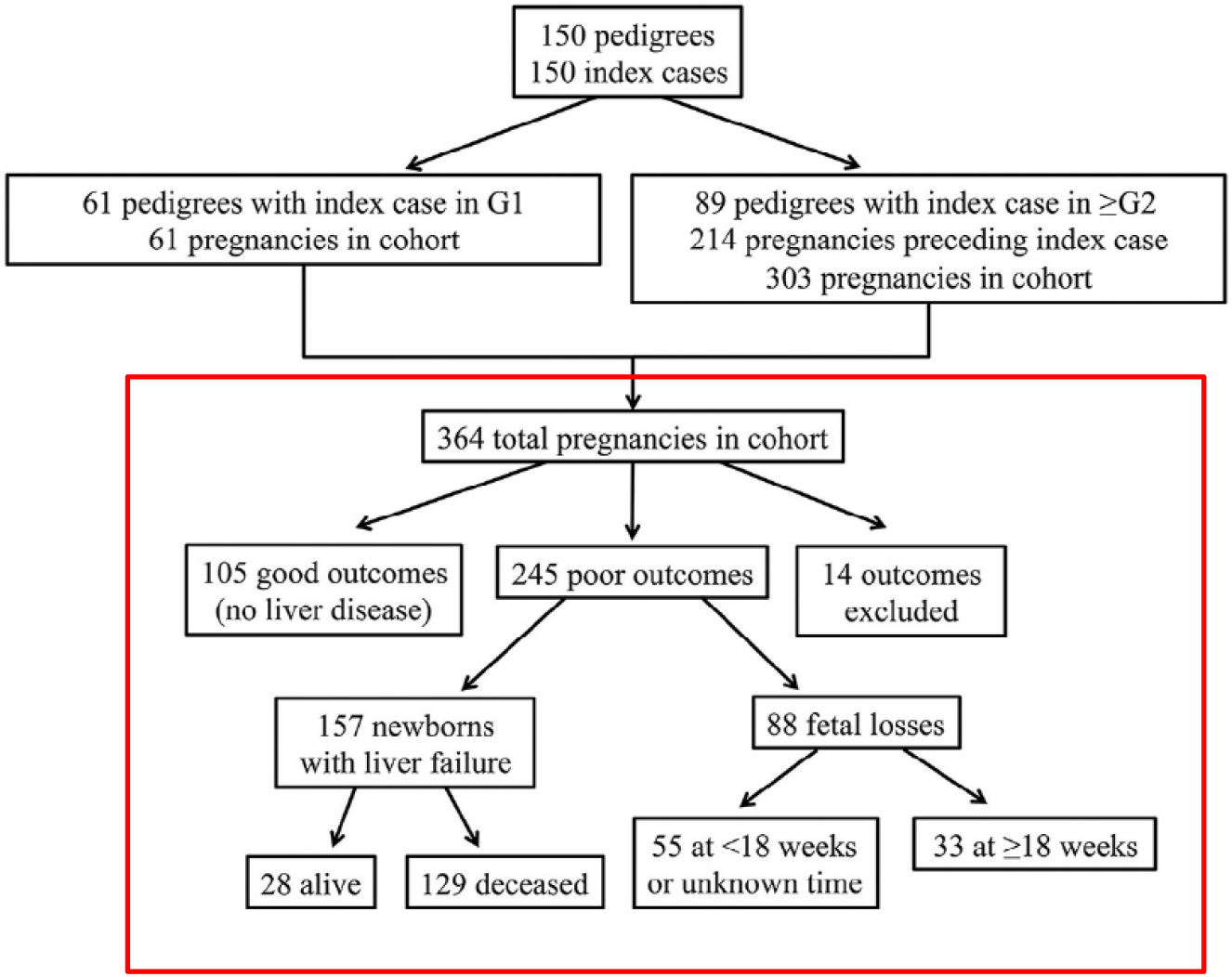
- Clinical characteristics:
  - NH infants transplanted at significantly lower weight: 3.85 kg vs 6.40 kg ($p<0.01$)
  - More infants with ALF listed as Status 1: 100% vs 86.5% ($p<0.01$)
- No difference in graft or patient survival for NH and ALF groups

Role for Liver Transplantation in GALD-NH

- Spontaneous recovery with medical treatment
  - IVIG and DVET remains first-line therapy
  - Supportive care for infants with coagulopathy but clinically stable
  - Improvement in INR can take weeks
  - Liver injury and fibrosis can reverse with time (Ekong et al. J Pediatr Gastroenterol Nutr 2008;46:329-22)

- Liver transplantation
  - Investigate mitochondrial hepatopathy prior to liver transplantation
  - Consider in GALD infants without signs of recovery
  - Unique challenges for liver transplantation in neonates

GALD: Fetal and Infant Morbidity and Mortality

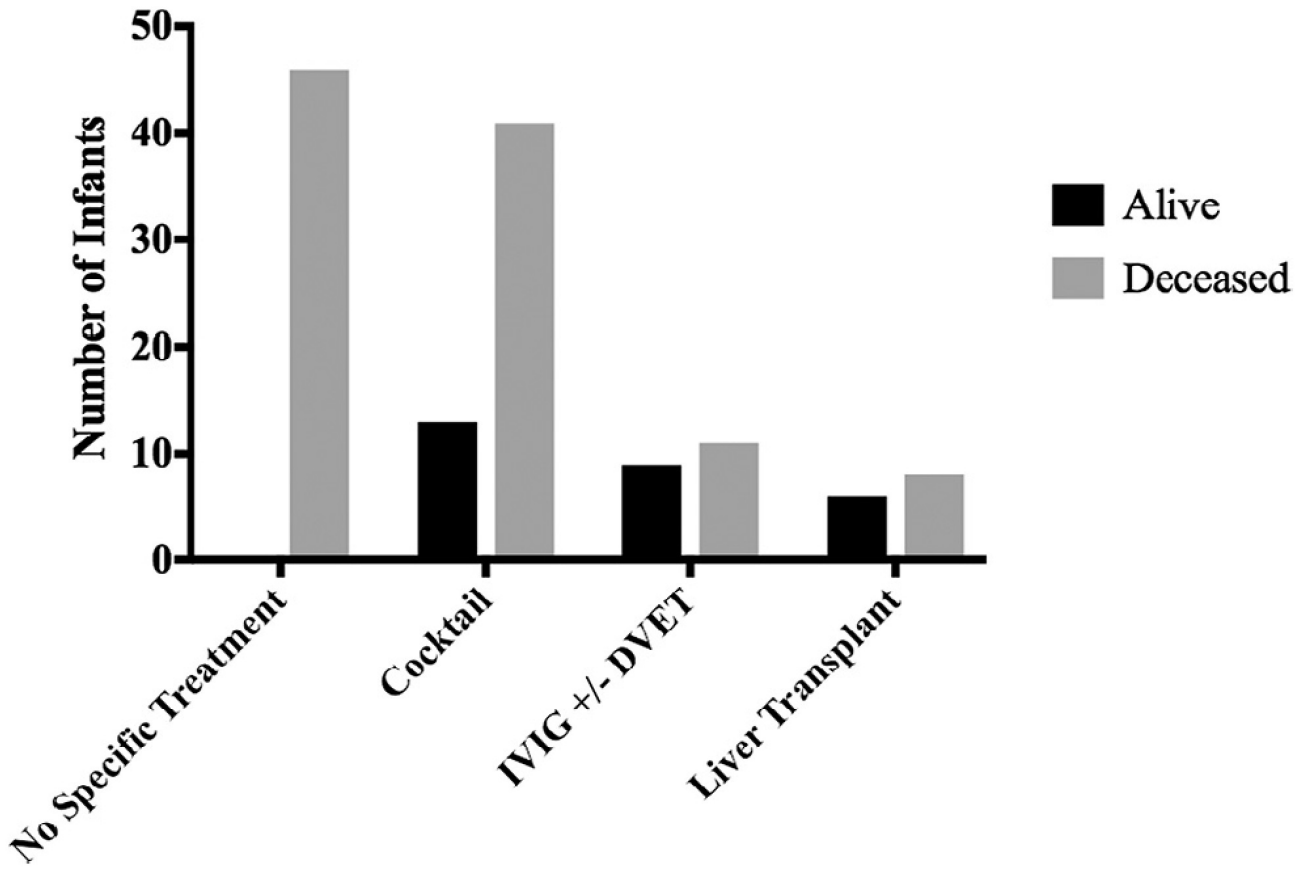


150 Pedigrees affected by GALD between 1997 and 2015

- First poor outcome in G1 in 60% of pedigrees
- High rate of fetal loss (25% of gestations)
- Poor outcome of affected live-born infants: 82% mortality
- Per-pregnancy repeat occurrence rate of 95%

*Taylor et al. *J Pediatr* 2018.

GALD: Outcomes of Live-born Infants by Treatment



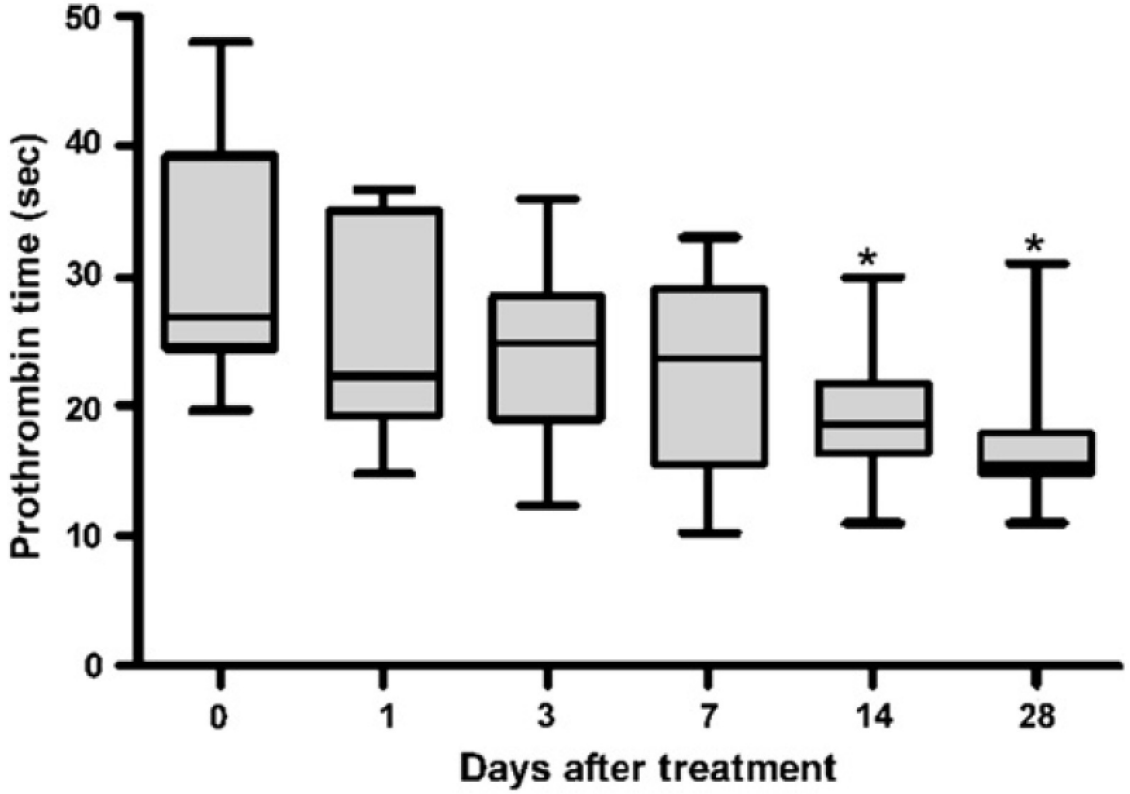
- General treatment strategies:
  - IVIG/DVET
  - Supportive care
  - Avoid maternal breast milk

- Outcome by treatment:
  - No disease specific treatment or cocktail (n = 100): 13% survival
  - IVIG/DVET(n = 9): 45% survival
  - Liver transplant (n = 14): 43% survival

*Taylor et al. *J Pediatr* 2018.

Recovery From GALD May be Protracted

Improvement in PT after IVIG/DVET can take weeks



*Rand et al. J *Pediatr* 2009;155:566-571.

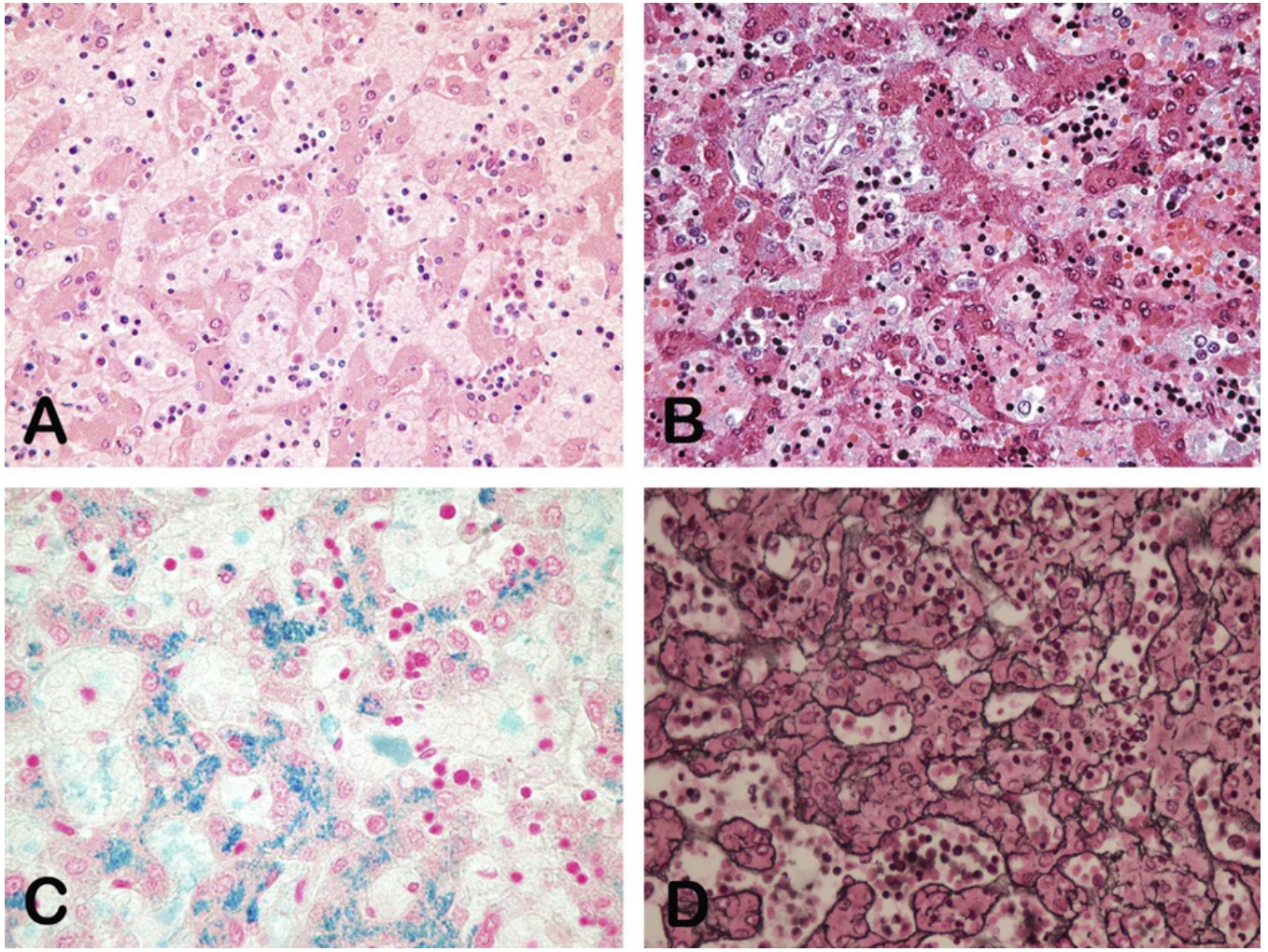
GALD Spectrum of Disease

- Subacute chronic hepatic injury with cirrhosis and liver failure at birth is the most common presentation
- Rarely fetal liver failure that may lack NH
- Disparate clinical presentation in twins (Ekong et al. *Pediatrics* 2005)

GALD Spectrum of Disease: Acute Fetal Demise

A. H&E with necrotic hepatocytes
B. Minimal fibrosis by tricrome
C. Positive iron stain
D. Reticulin staining without evidence of collapse

Liver injury in a 22-week gestation stillbirth



*Whitington et al. *J Pediatr* 2011.

Prevention of GALD: Gestational Treatment with IVIG Improves Outcomes

Preventative Gestational IVIG Based on Alloimmune Mechanism of Disease

- Pooled Human Immune Globulin 1 gm/kg IV at 14 and 16 weeks and weekly from 18 weeks
- Time and duration based on physiology of IgG transport and observations regarding NH
- High rate of poor outcomes in G1 suggests sensitization is early in pregnancy
- Only gestational alloimmune disease known to affect a solid organ

Gestational Treatment with IVIG Improves Outcomes

Mother	Neonate	Gestational age at birth, weeks	Ferritin, µg/L	AFP, µg/L	INR	ALT, IU/L	Treatment
M1	N1	40	227	NA	1·4	22	None
M2	N2	40	1250	118 000	1·1	12	Vitamin E
M3	N3	36	1730	130 390	1·2	17	Chelation/antioxidant
M4	N4	40	12 690	558 600	2·4	52	Chelation/antioxidant
M4	N5	40	13 304	230 280	2·2	28	Chelation/antioxidant
M5	N6	32	301	451 300	1·9	6	Chelation/antioxidant
M6	N7	40	142	NA	NA	NA	None
M7	N8	40	160	129 000	1·2	NR	None
M8	N9	38	202	583	1·0	10	None
M9	N10	40	187	100 820	1·0	20	None
M10	N11	37	1355	156 000	1·5	50	Vitamin E
M11	N12	39	1800	670 000	1·4	47	Chelation/antioxidant
M12	N13	38	15 948	182 690	2·1	37	Chelation/antioxidant
M13	N14	36	372	45 950	2·1	27	Chelation/antioxidant
M14	N15	38	1239	242 333	1·0	22	Vitamin E
M15	N16	39	186	NA	NA	43	None

NA=results not available; NR=reported only as within normal range.

Table 2: **Findings and treatments of neonates born after gestational IVIG therapy**

*Whitington and Hibbard. *Lancet* 2004.

Gestational IVIG Treatment Increases Healthy Live Offspring *AND* Reduces Fetal Loss

Table 1. Comparison of outcomes of pregnancies with antenatal IVIG therapy versus untreated gestations

Pregnancies in 151 women	Untreated pregnancies[a] (% of total untreated cohort)	Treated pregnancies[b] (% of total treated cohort)	Total (% of total)
Unaffected living offspring	105 (30)	177 (94)[c]	282 (52)
Affected living offspring	157 (45)	9 (5)	166 (31)
Fetal loss	88 (25)	2 (1)[d]	90 (17)
Total	350	188	538

[a] Spontaneous abortion at >18 weeks of gestation qualified as affected. [b] Spontaneous abortion after initiation of therapy qualified as affected. [c] Improved outcome with IVIG treatment (Fisher exact test $p < 0.0001$). Twins counted as one outcome. [d] Reduced fetal loss (qualified and unqualified) with IVIG treatment (Fisher exact test $p < 0.0001$). IVIG, intravenous immunoglobulin.

*Whitington et al. *Fetal Diagn Ther* 2018.

Gestational Treatment with IVIG: Post-partum Neonate Evaluation

- 94% of treated gestations result in healthy offspring (Whitington et al. *Fetal Diagn Ther* 2018)

- Testing for clinically significant liver disease in newborn on DOL1:
  - INR after administration of vitamin K
  - Evaluation for hypoglycemia

- Elevation of ferritin and AFP support some degree of liver damage

- Treat affected infants with synthetic liver dysfunction: IVIG/DVET

Take-home points

- Neonatal ALF is a rare disease with overall high morbidity and mortality
- ALF in neonates has distinct features from older infants and children
- Young infants have good outcomes after OLT but few neonates with ALF receive OLT
- GALD-NH is a leading cause of neonatal ALF diagnosed by a constellation of clinical, biochemical, and pathologic findings
- Prevention of GALD-NH relies on diagnosis of the index case
- Unmet need to improve prognostic stratification to improve outcomes

Questions?