

Intestinal Failure-Associated Liver Disease (IFALD)

Alan L. Buchman, M.D., M.S.P.H.

Professor of Clinical Surgery (Gastroenterology),
Medical Director, Intestinal Rehabilitation and Transplant Center
University of Illinois at Chicago
Medical Director, Gastroenterology, Anthem Health



UI Health |



Disclosures

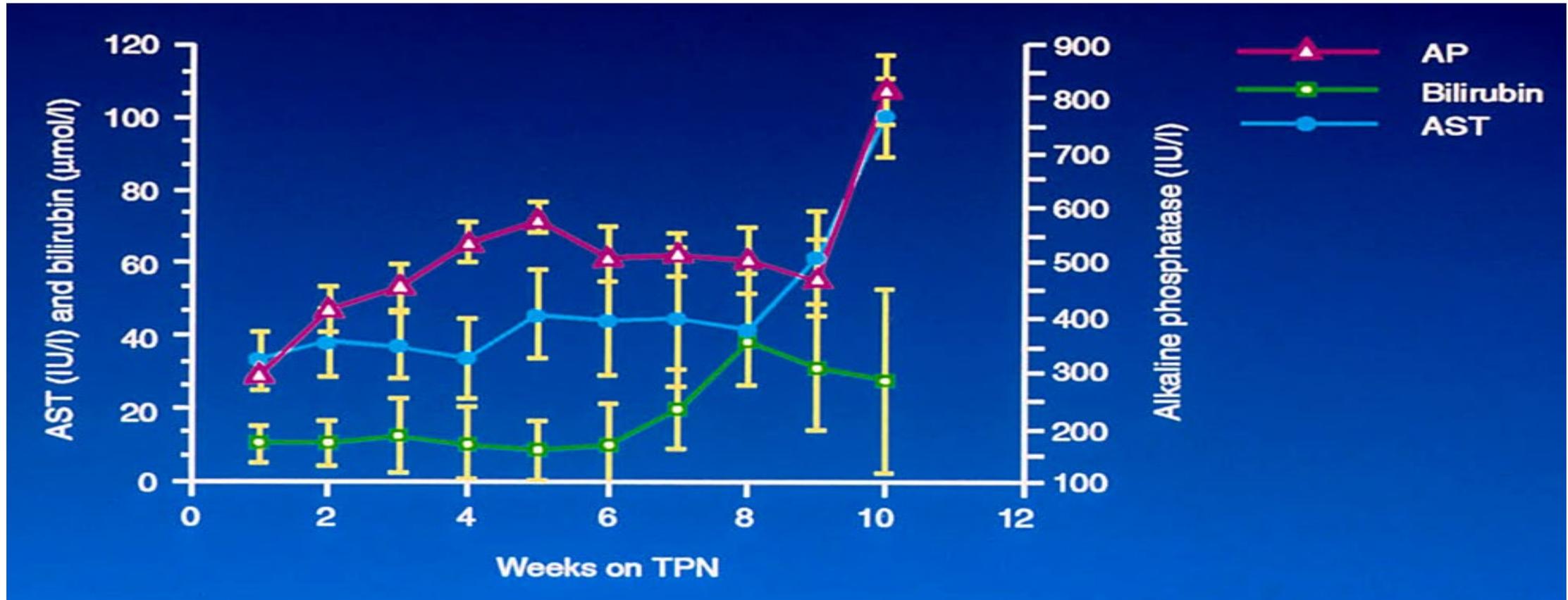
Conflict of Interest:

Protara Therapeutics (minor shareholder)

Liver Test Abnormalities During PN (parenteral nutrition)

- First identified as early as 1971
- May occur in as many as 2/3 of older children and adult patients parenterally fed for 2 wks or more; even prevalence in neonates
- Rise may be transient, peaking at 3-5 wks except AP and remain elevated for 1-4 wks after PN stopped
- Bilirubin not generally elevated except in neonates
- Insensitive and nonspecific indicators of hepatic pathology

Mean Plasma Bilirubin Concentration, AST, and Alkaline Phosphatase Activity in Patients Fed for at Least Four Weeks



IFALD – Definition

- Liver injury resulting from intestinal malabsorption and/or PN solutions in the absence of other etiologies including viral/autoimmune hepatitis, alcohol/drugs, and/or biliary obstruction.¹ Requires IF/long-term PN
- “a persistent elevation of liver enzymes, alkaline phosphatase and γ -glutamyl transferase 1.5x the upper limit reference range which persist for more than or equal to 6 months in adults and more than or equal to 6 weeks in children.”² Requires both cholestasis (\uparrow bili or ALP or bx) and steatosis (imaging or bx), although one may be predominant).³ There may also be other signs of liver injury (fibrosis / cirrhosis / End Stage Liver Disease [ESLD])

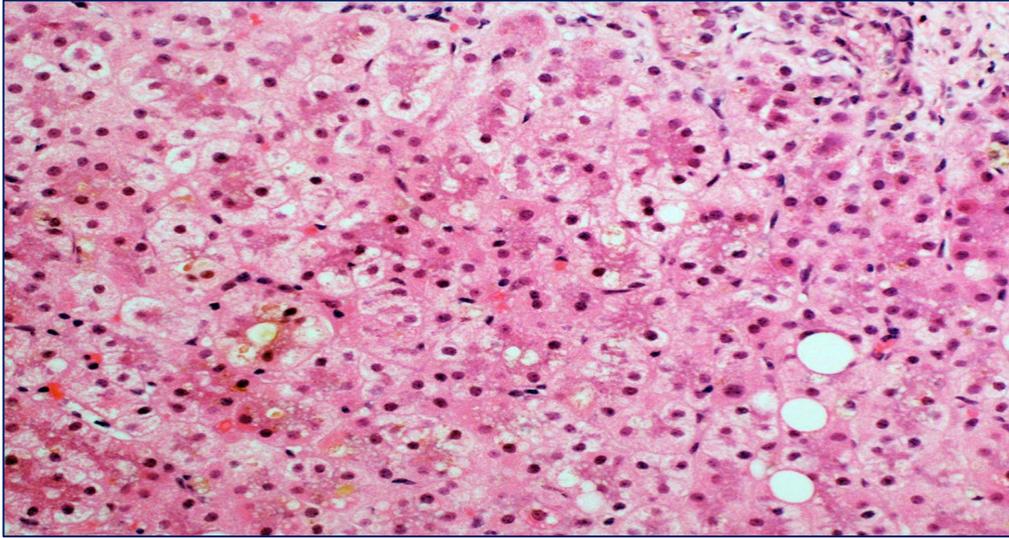
1 Adapted from Lal et al, Clin Nutr; 2018:1794-7

2 [IRTA] Beath et al. Transplantation. 2008; 85:1378-84.

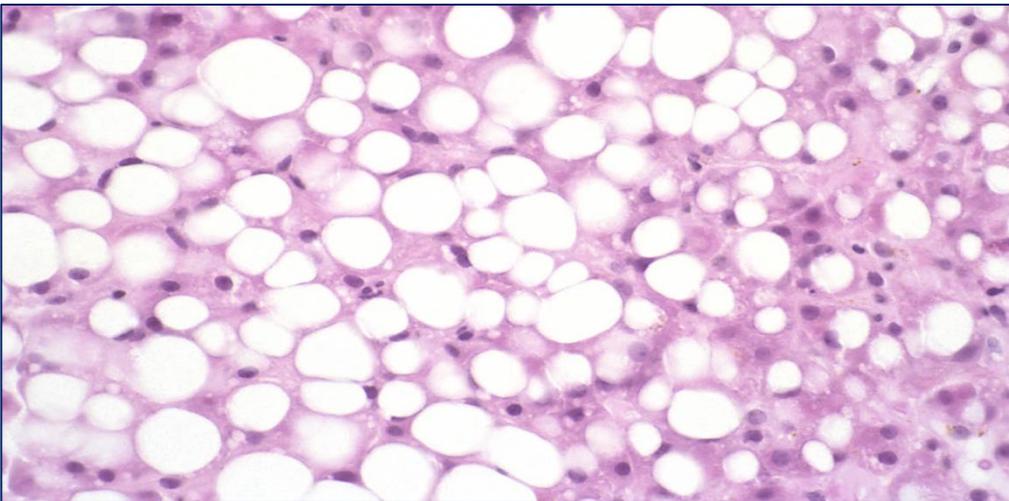
3 Buchman et al. Sem in Liver Dis: 2017; 37:33-44.

The Histology of IFALD

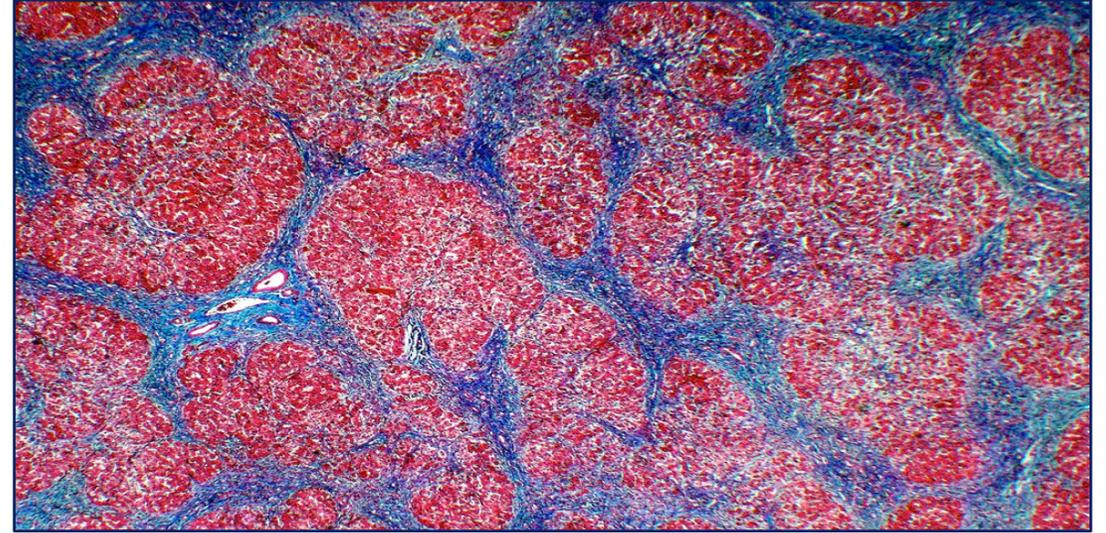
Macrosteatosis with Steatosis (Steatocholestasis)



Macro- and Micro-steatosis

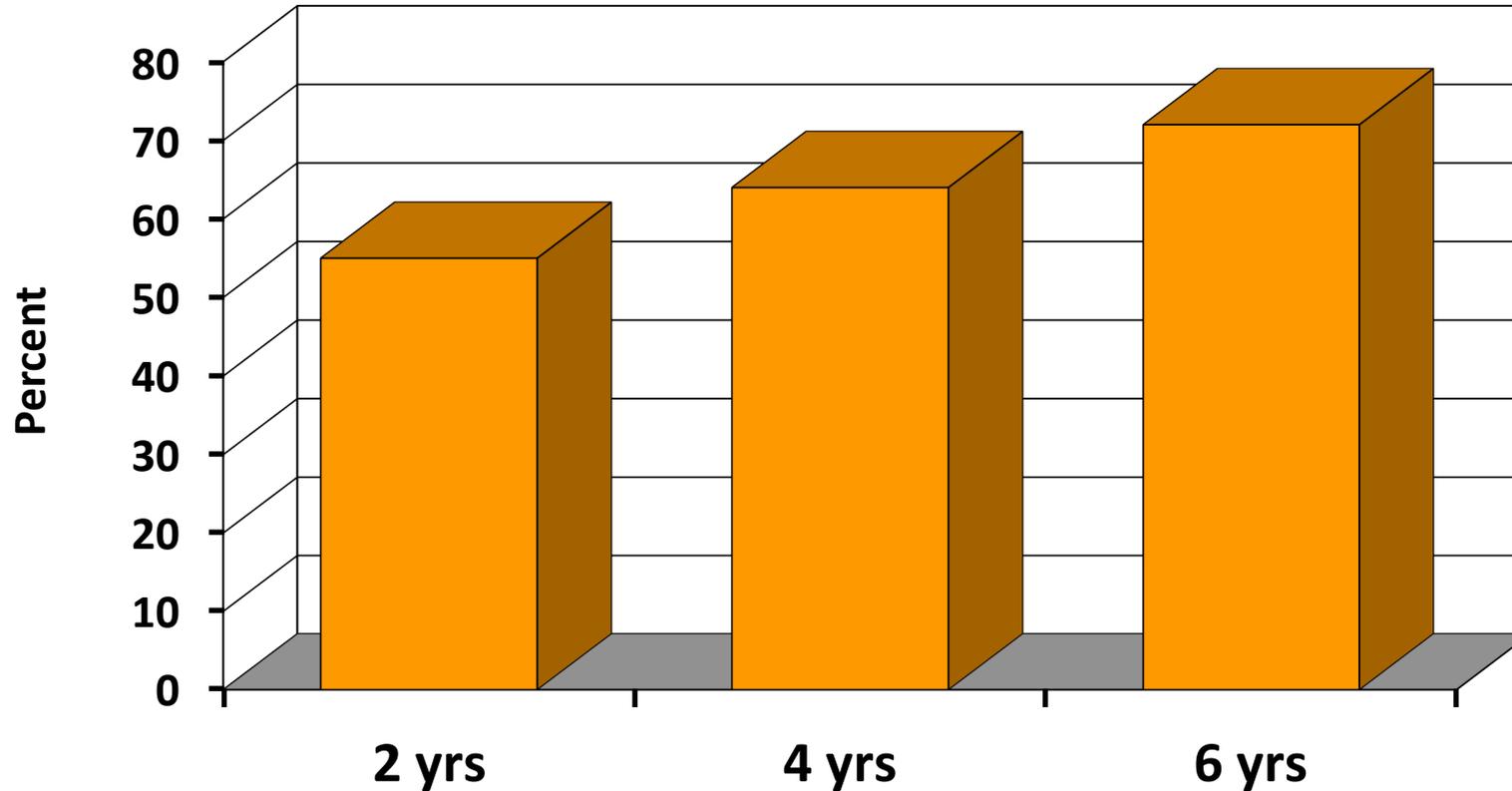


Cirrhosis

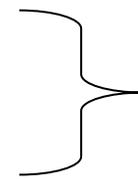


Fibrosis begins with portal expansion and may progress to cirrhosis, often in a characteristic “jig-saw” pattern. Masson Trichrome stain demonstrating collagen (blue) surrounding hepatocytes (red) which have a cirrhotic pattern

Chronic Cholestasis* During PN



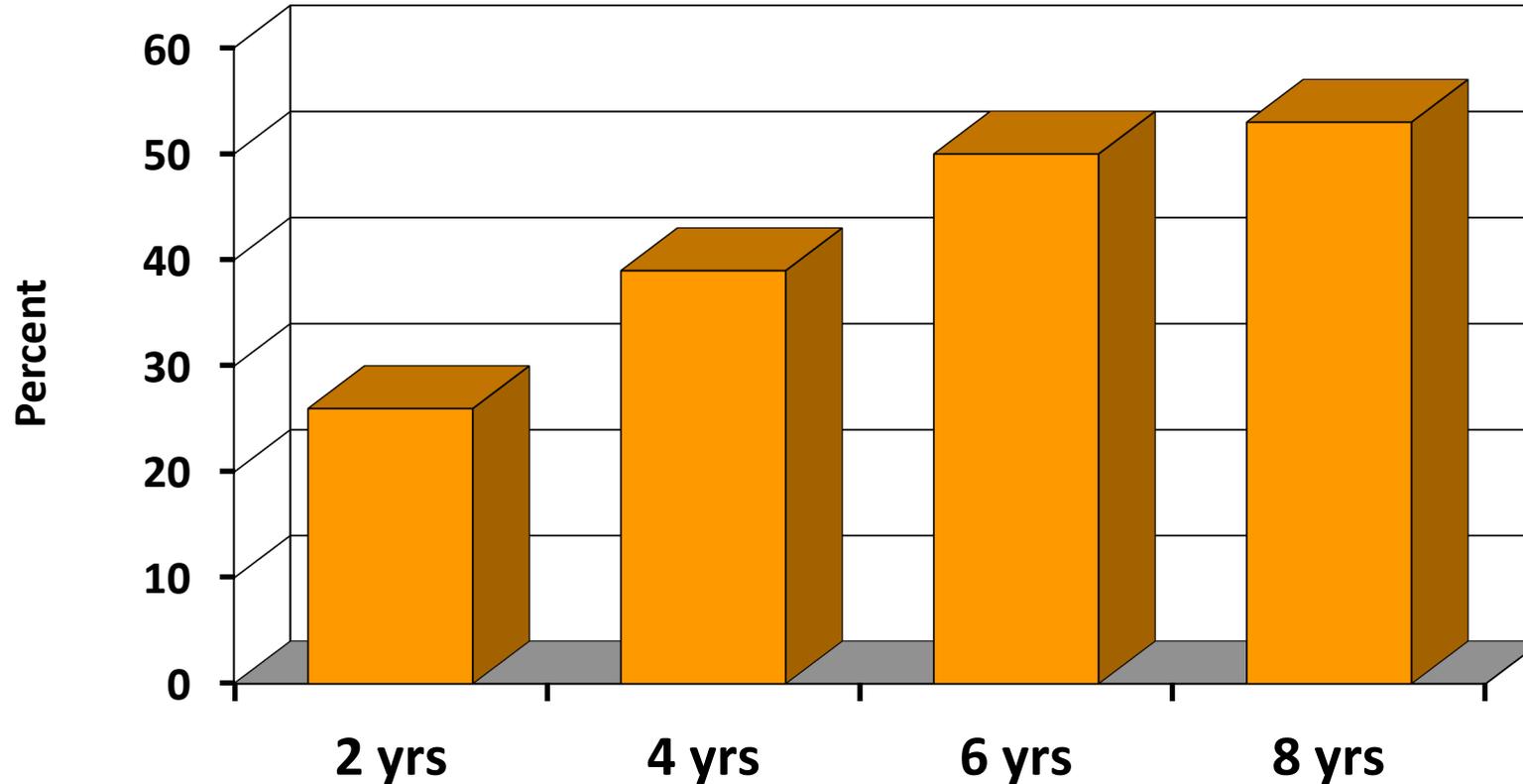
*2 or more: ALT
AST
Alk Phos



>1.5 x ULN > 6 mos.

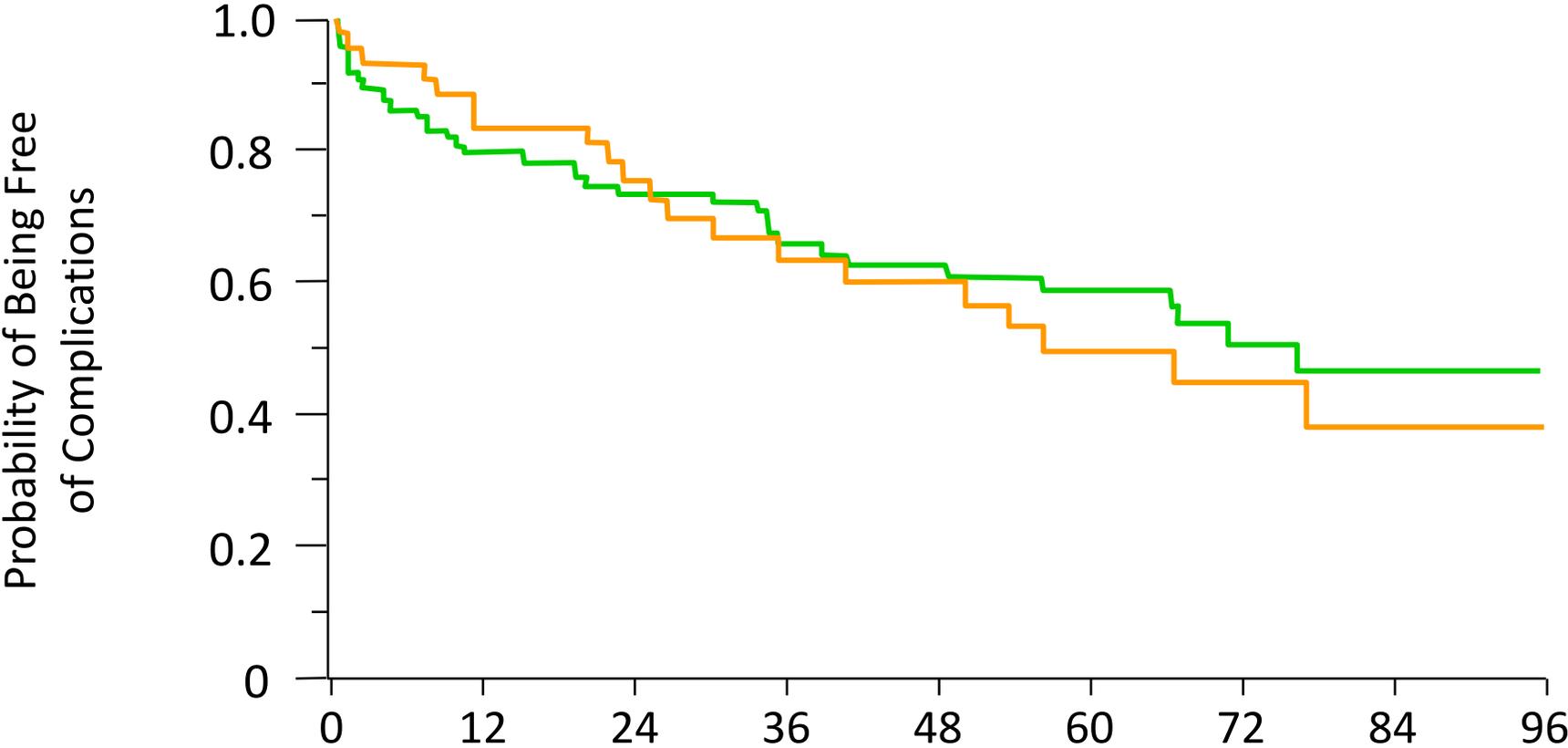
IFALD

Complicated Liver Disease*



*Definition: extensive portal fibrosis or cirrhosis, bili ≥ 3.5 mg/dl for ≥ 1 m, ascites, portal HTN, hepatic encephalopathy or factor V $< 50\%$

Free of Liver Complications

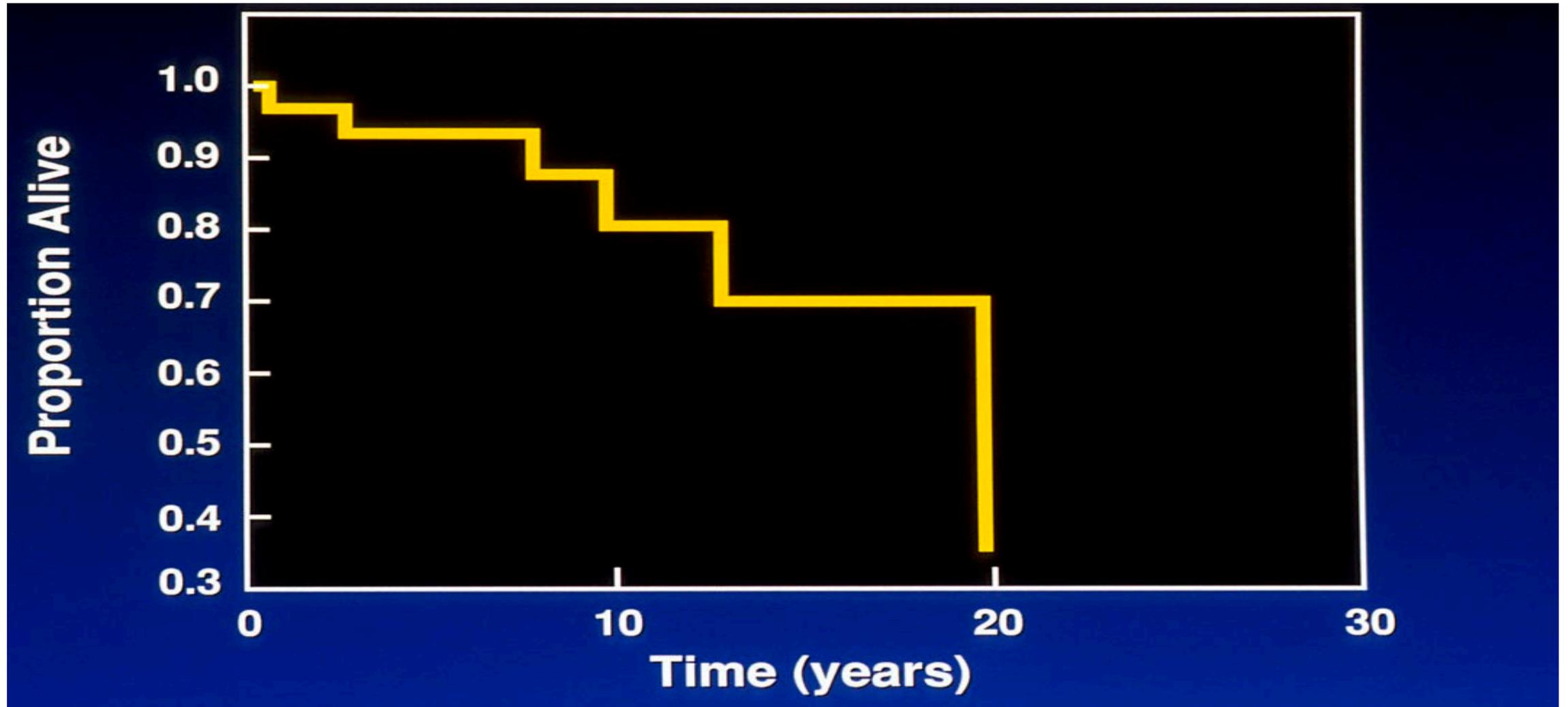


Complications, n	0	12	24	36	48	60	72	84	96
Clinical and Biological	90	57	60	45	34	29	16	12	7
Histologic	57	50	43	36	25	18	12	9	5

Cavicchi et al, Ann Int Med 132:529, 2000

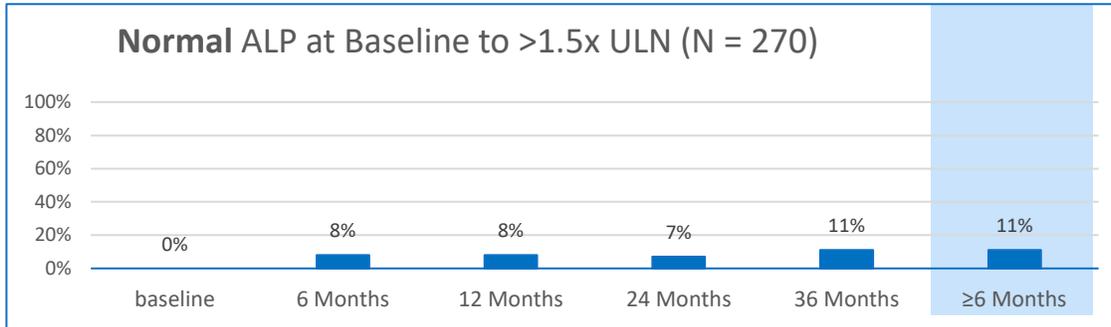
Death From TPN-Associated Liver Disease

The Boston Brigham Hospital Experience

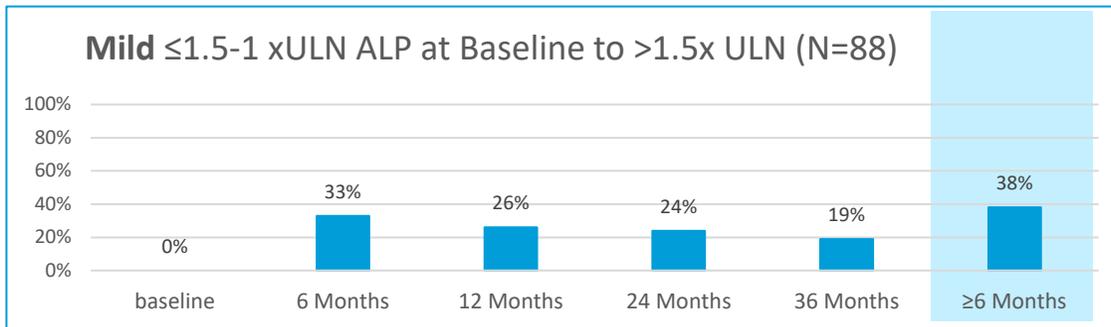


ALP findings by baseline levels (N=464 pts)

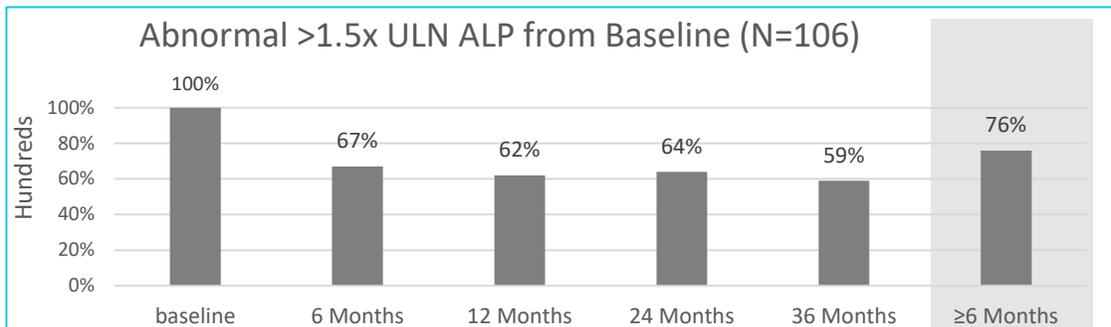
ALP concentration can decrease through medical management but 30% of patients have persistent ALP elevations at 36m



- More than half of patients came onto home health with normal ALP levels – by 36 months 11% were >1.5x ULN



- 33% of patients with Mild elevations moved to >1.5x ULN ALP levels by 6 months
- By month 36, 19% of patients were still >1.5x ULN
- At any given time during the 30 months of observation, 38% of these patients found themselves above 1.5x ULN



- 24% of patients came onto home health at abnormal (>1.5x ULN) ALP levels
- By month 36, 59% of these patients were still >1.5x ULN
- At any given time during observation of 6-36 months, 76% found themselves above >1.5x ULN

Comparison of Histological Characteristics of IFALD and NAFLD (NASH)

IFALD	NAFLD (NASH)
Cholestasis	No Cholestasis
Micro-steatosis as well as Macro-	Predominately Macrosteatosis
Steatosis in Zone 1	Steatosis in Zone 3
Features of Biliary Obstruction (portal inflammation, edema; ductular proliferation); ductopenia	No Features of Biliary Obstruction or ductopenia
Steatohepatitis Rare	Steatohepatitis Common
“Jigsaw” Pattern of Fibrosis	Sinusoidal Fibrosis; Ballooned Hepatocytes with Mallory-Denk Bodies

IFALD = Intestinal Failure Associated Liver Disease; NAFLD = Nonalcoholic Fatty Liver Disease; NASH = Nonalcoholic Steatohepatitis

Source: (Buchman et al., Semin Liver Dis, 2017)

Comparison of Typical Presentations of IFALD, NAFLD, and NASH

Disease	Steatosis	Cholestasis/ steatohepatitis	Plasma free choline concentration	Hepatic Enzymes and Progression	Associated Risk Factors
IFALD	Yes or no- Macrovesicular and often microvesicular	Cholestasis with rare steatohepatitis	Low	<ul style="list-style-type: none"> •Mild to moderate transaminase and alkaline phosphatase elevations •Rapid and high rates of liver disease progression and transplantation 	<ul style="list-style-type: none"> •PN and choline deficiency
NAFLD	Yes-predominately macrovesicular	Neither	Normal	<ul style="list-style-type: none"> •Low rates of progression to NASH, fibrosis, cirrhosis, and transplant 	<ul style="list-style-type: none"> •High BMI, diabetes •Hyperlipidemia •Metabolic syndrome •Specific associated medications •Elevated choline
NASH	Yes—Predominately macrovesicular (ie, rarely microvesicular, except with toxin exposure)	Steatohepatitis without cholestasis	Mild elevations	<ul style="list-style-type: none"> •Low to moderate rates of fibrosis, cirrhosis, and transplant 	<ul style="list-style-type: none"> •High BMI, diabetes •Hyperlipidemia •Metabolic syndrome •Specific associated medications •Elevated choline

BMI = Body Mass Index; IFALD = Intestinal Failure Associated Liver Disease; NAFLD = Nonalcoholic Fatty Liver; Disease;

NASH = Nonalcoholic Steatohepatitis; PN = parenteral nutrition

Source: (Buchman et al., Sem Liver Dis, 2017)

Prevalence of IFALD in Infants

Direct hyperbilirubinemia (>2mg/dl) is the most specific predictor of outcome

Group	Prevalence
All Infants	7.4 – 8.4%
PN > 2 weeks	33%
PN > 3 months	67%

Conclusion

1. IFALD is a distinct disease with substantial morbidity and mortality and is the most significant indication for small bowel and multivisceral transplant, yet it currently has no diagnostic code; it desperately needs one for scientific investigators as well as for industry
2. IFALD is not NAFLD/NASH and should not be considered as a cause of NAFLD/NASH. It is a distinct disease with different etiology, pathophysiology and outcome