ASPEN 2025 NUTRITION SCIENCE & PRACTICE CONFERENCE

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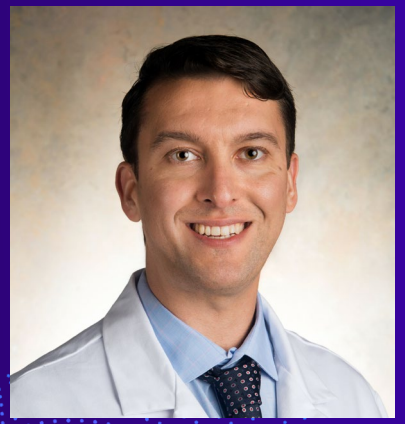
THRIVE-1: A MULTI-CENTER, CROSS-SECTIONAL, OBSERVATIONAL STUDY TO ASSESS THE PREVALENCE OF CHOLINE DEFICIENCY INPATIENTS DEPENDENT ON PARENTERAL SUPPORT



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Disclosures

- Takeda Pharmaceuticals, Consultant
- Ironwood Pharmaceuticals, Consultant
- Takeda Pharmaceuticals, Speaker’s Bureau
- Protara Therapeutics, Consultant

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Learning Objectives

Upon completion of this educational activity, the learner will be able to:

- Understand the demographics, baseline characteristics, and parenteral support history of patients dependent on parenteral support (PS)
- Assess the prevalence of choline deficiency in patients dependent on PS
- Assess the relationship between choline deficiency and liver injury

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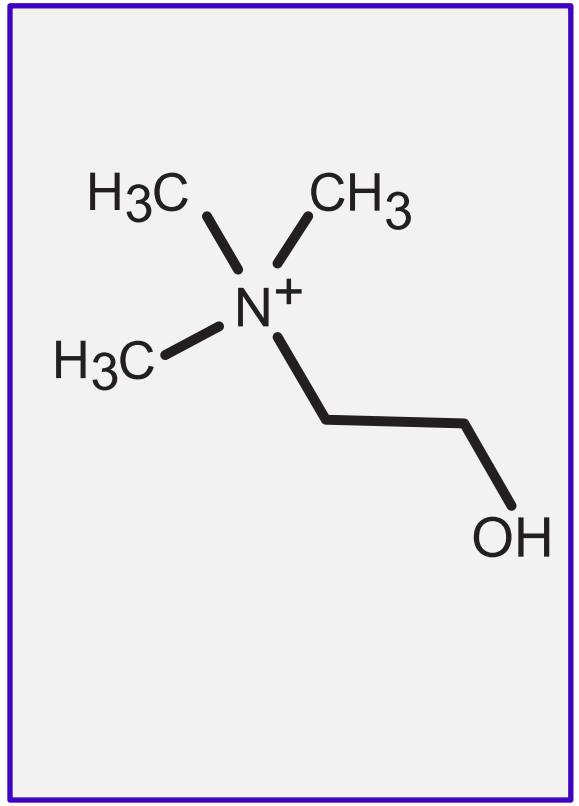
Background: Choline – A Key Essential Nutrient

- Choline is a quaternary amine that is an essential dietary nutrient in humans recognized by the Institute of Medicine in 1998[1,2]
  - Choline plays a critical role in several metabolic processes
  - Methyl donor in many key metabolic reactions, similar to B-vitamins and folate
  - Vital for cell structure membranes (phospholipids), triglyceride transport via very-low-density lipoprotein (VLDL) synthesis, cholesterol transport in bile, intracellular messaging, brain development and function (acetylcholine)

- The American Society for Parenteral and Enteral Nutrition, and the Academy of Nutrition and Dietetics' Dietitians in Nutrition Support both recommend that choline be required in PS products[3]
  - Normal subjects become choline deficient and rapidly show signs of liver injury when dietary intake of choline is restricted[4]
  - Choline is essential for patients with intestinal failure (IF) who are dependent on PS when oral or enteral nutrition is not possible, insufficient, or contraindicated
  - Current PS formulations lack sufficient choline, affecting an estimated 40,000 long-term PS patients who are or may become deficient[5]
  - Currently, there are no approved intravenous choline products for PS patients globally



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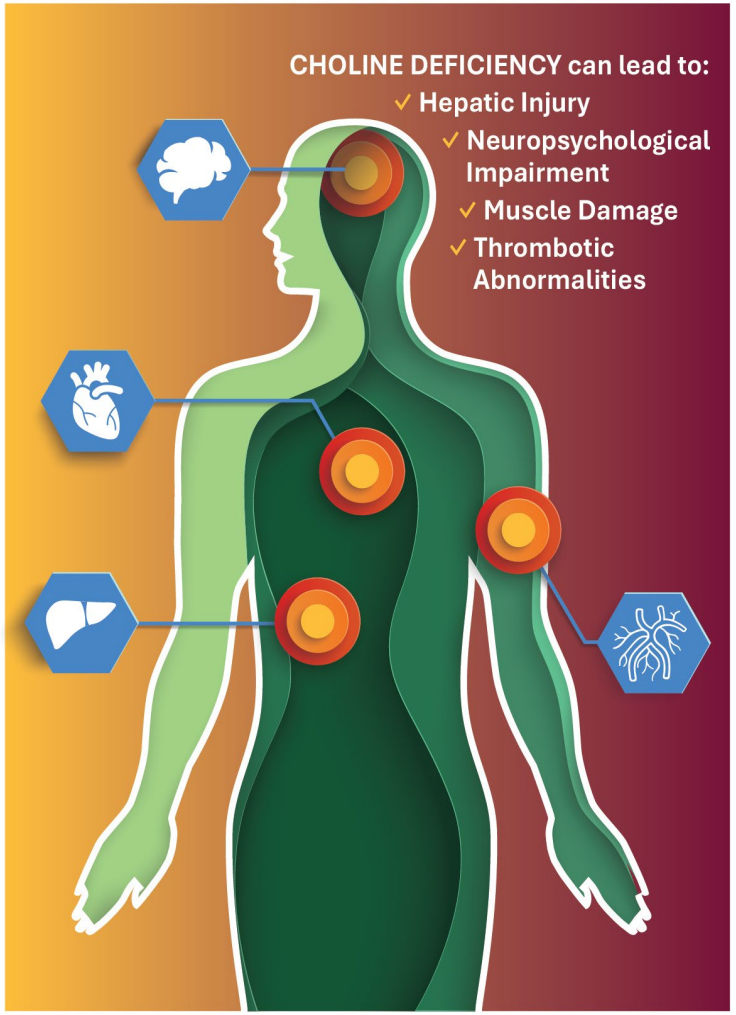
4. Zeisel SH, et al. *FASEB J*. 1991 Apr;5(7):2093-2098.
5. Ireton-Jones C, et al. *Nutr Clin Pract*. 2003 Aug;18(4):310-317.

Background: Choline Deficiency

- Patients with intestinal failure dependent on PS are at high risk of choline deficiency because choline is not routinely added to parenteral nutrition (PN) solutions.
- Dependence on PS leads to choline deficiency, which can subsequently lead to the development of hepatic injury (and rapid progression of liver disease), neuropsychological impairment, muscle damage, and thrombotic abnormalities[4,6,7,8].
- PS dependent patients develop choline deficiency, with a decrease of plasma free choline concentrations of 33%–50% within 2 weeks of beginning PS.
- Choline deficiency causes impaired triglyceride export from the liver due to reduced VLDL synthesis, leading to fatty accumulations[9,10], abnormal bile composition, and progressive hepatocellular injury.



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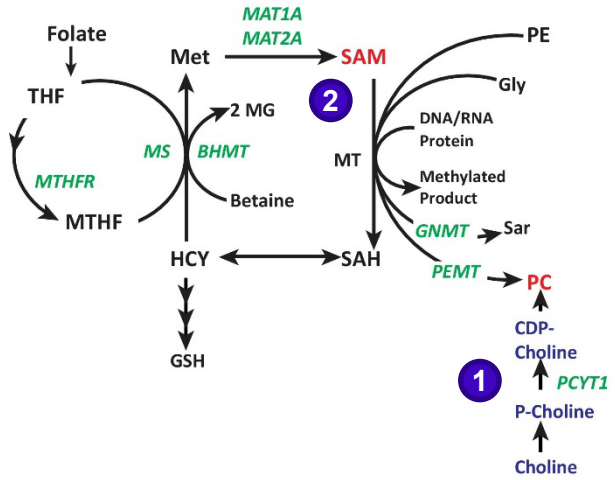
Background: Choline Deficiency Results in Hepatobiliary Pathophysiology

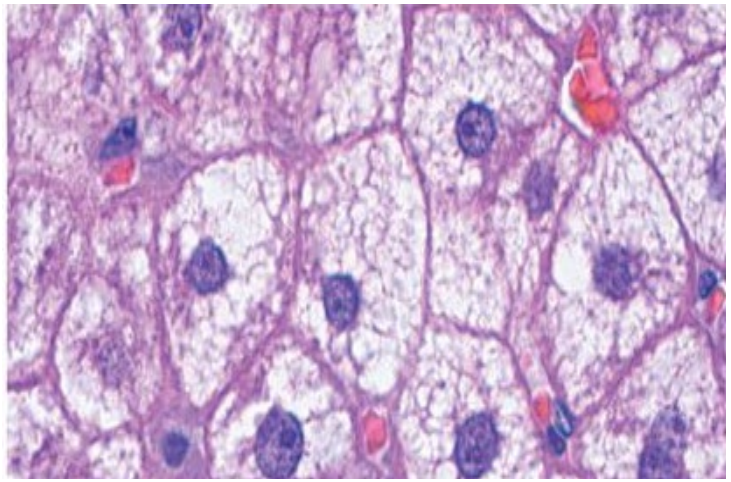
Diminished Choline = Insufficient phosphatidylcholine (PC), resulting in hepatobiliary injury

Affected pathways



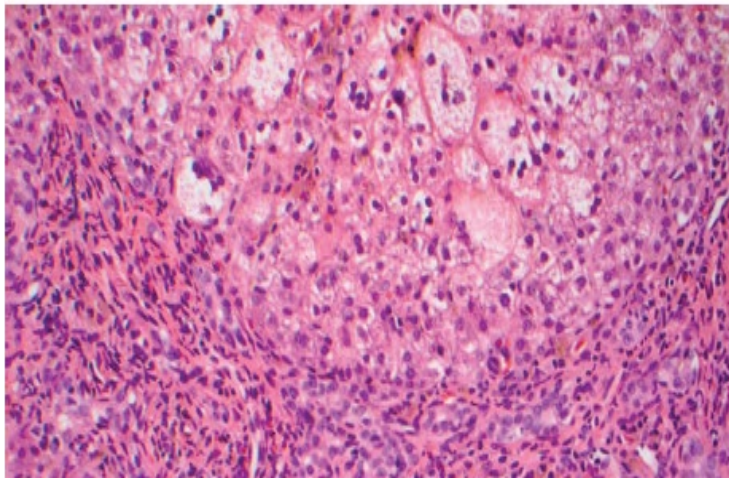
- PC is the most ubiquitous phospholipid in the body
  1. Throughout the body, PC is synthesized almost exclusively through exogenous choline consumption (Kennedy pathway)
  2. Intra-hepatically, the phosphatidylethanolamine N-methyltransferase pathway (PEMT) pathway can provide 30% of the liver's needs[11]

Steatosis



- PC is the primary lipid of the VLDL particle surface mono-layer. Low PC levels inhibit VLDL packaging and secretion. Without sufficient VLDL fats rapidly accumulate in hepatocytes[12]

Cholestasis



- PC comprises ~ 40% of bile's organic matter[13]. Insufficient PC in bile increases free bile salts, restricting bile flow and damaging biliary epithelium[14, 15]

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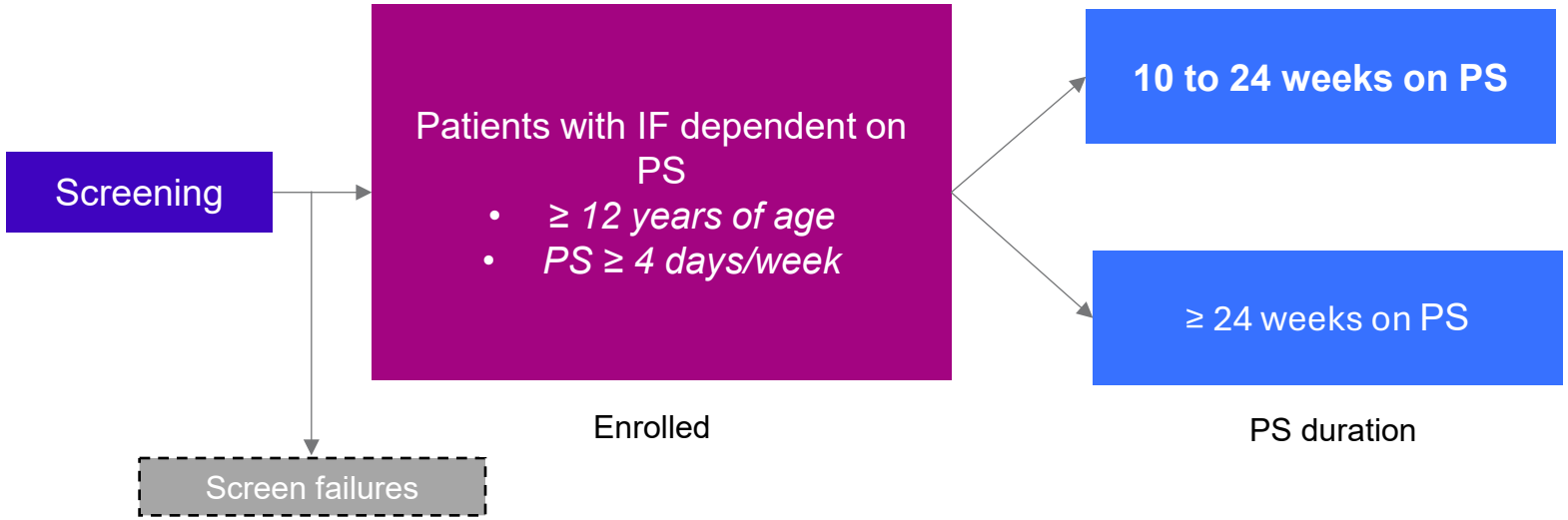
Methods: THRIVE-1 , A Multi-center, Cross-sectional, Observational Study

- THRIVE-1 was a multi-center, cross-sectional, observational study to assess the prevalence of **choline deficiency** and **liver injury** in patients dependent on PS



Key Assessments

- Choline deficiency was defined as plasma free choline concentrations of **< 9.5 nmol/ml***.
- Liver injury was defined as **any elevated liver tests** (>1.5 x ULN; ALP, AST, ALT, GGT, direct bilirubin, total bilirubin) or **steatosis** (MRI-PDFF ≥ 8%).

Note: This study included patients dependent on PS (≥ 4 days a week) for 10 weeks or longer. The number of patients enrolled who have been on PS for a duration of 10 to 24 weeks were capped at 25%.
Note: Data collection occurred during a single clinic visit.

*ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; MRI-PDFF, magnetic resonance imaging derived proton density fat fraction; ULN, upper limit of normal.

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Results: Demographics and Baseline Characteristics

- 78 patients enrolled; 75 completed; 3 withdrew from the study
- Mean age was 51.9 years (SD: 16.6)
- Demographics:
  - 55.1% male; 44.9% female
  - 92.3% White; 3.8% Black or African American; 2.6% Asian
  - 96.2% not Hispanic or Latino; 3.8% Hispanic
- Mean BMI was 23.0 kg/m² (SD: 3.8)

Characteristics	Enrolled Set (N = 78)
Age (years)	
Mean (SD)	51.9 (16.6)
Age group, n (%)	
12-<18	2 (2.6)
18-65	61 (78.2)
>65	15 (19.2)
Sex, n (%)	
Male	43 (55.1)
Female	35 (44.9)
Race, n (%)	
Asian	2 (2.6)
Black or African American	3 (3.8)
White	72 (92.3)
Other	1 (1.3)
Ethnicity, n (%)	
Hispanic	3 (3.8)
Non-Hispanic	75 (96.2)
Height (cm)	
Mean (SD)	167.6 (10.2)
Weight (kg)	
Mean (SD)	64.7 (13.5)
BMI (kg/m^2)	
Mean (SD)	23.0 (3.8)

*BMI, body mass index; SD, standard deviation

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Results: Parenteral Support History

Total infusion volume of PS/day or night, N = 78
Mean: 2614.9 mL (SD: 1151.8)
Median: 2350.0 mL (Min: 721, Max: 6433)

Infusion duration, N = 78
Mean: 708.5 minutes (SD: 124.1)
Median: 720.0 (Min: 360, Max: 1200)

Number of weeks on PS, N = 78
Mean: 482.3 weeks or ~9 years (SD: 484.3)
Median: 334.0 (Min: 10, Max: 2319)

PS frequency (days per week), N = 78
Mean: 6.6 (SD: 0.9)
Median: 7.0 (Min: 4.0, Max: 7.0)

Lipid frequency (days per week), N = 78
Mean: 3.0 (SD: 2.4)
Median: 2.0 (Min: 0.0, Max: 7.0)

PS components, mean (SD)	Enrolled set (N = 78)
Amino Acids (grams per day per week)	60.7 (33.5)
Amino Acids (grams per kg day per week)	1.0 (0.5)
Dextrose (kcal per day per week)	997.5 (595.3)
Dextrose (kcal per kg day per week)	16.4 (11.4)
Lipids (grams per day per week)	18.7 (18.2)
Lipids (grams per kg day per week)	0.3 (0.3)

- Most patients received mixed or plant-based lipids
  - No lipids: 10.3% (8/78)
  - Fish oil-based: 1.3% (1/78)
  - Plant-based: 48.7% (38/78)
  - Mixed oil-based: 39.7% (31/78)
- All patients received B12 and folic acid each night

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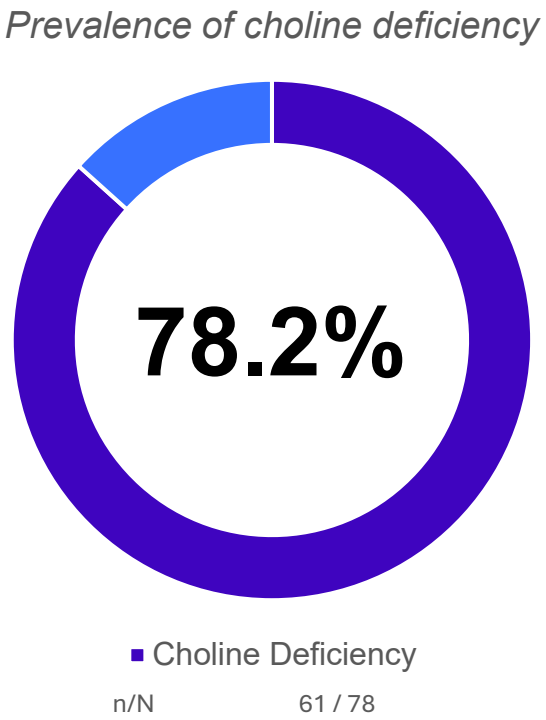
Results: Approximately 78% of patients were choline deficient



- Mean plasma free choline concentration: 7.5 nmol/mL (SD: 3.9)
- Choline deficiency was present in 78.2% (61/78) of patients
- These findings are consistent with the published literature on prevalence of choline deficiency

Choline concentration (nmol/mL)	
Mean (SD)	7.5 (3.9)
Median	6.6
Min, Max	2.6, 27.1
Number of patients with choline deficiency, n (%)	
All	61/78 (78.2)

Note: Percentages are based on the number of patients in the Enrolled Set with observed data for the given endpoint.
Note: Choline deficiency is defined as < 9.5 nmol/ml. Various studies in PS-dependent patients report choline deficiency as baseline concentrations of plasma free choline ranging from approximately 5.2 ± 2.1 nmol/mL to 7.2 ± 2.5 nmol/mL.
Note: Liver injury was defined as any elevated liver tests (1.5 x ULN; ALP, AST, ALT, GGT, Direct Bilirubin, Total Bilirubin) or Steatosis (MRI-PDFF ≥ 8%).

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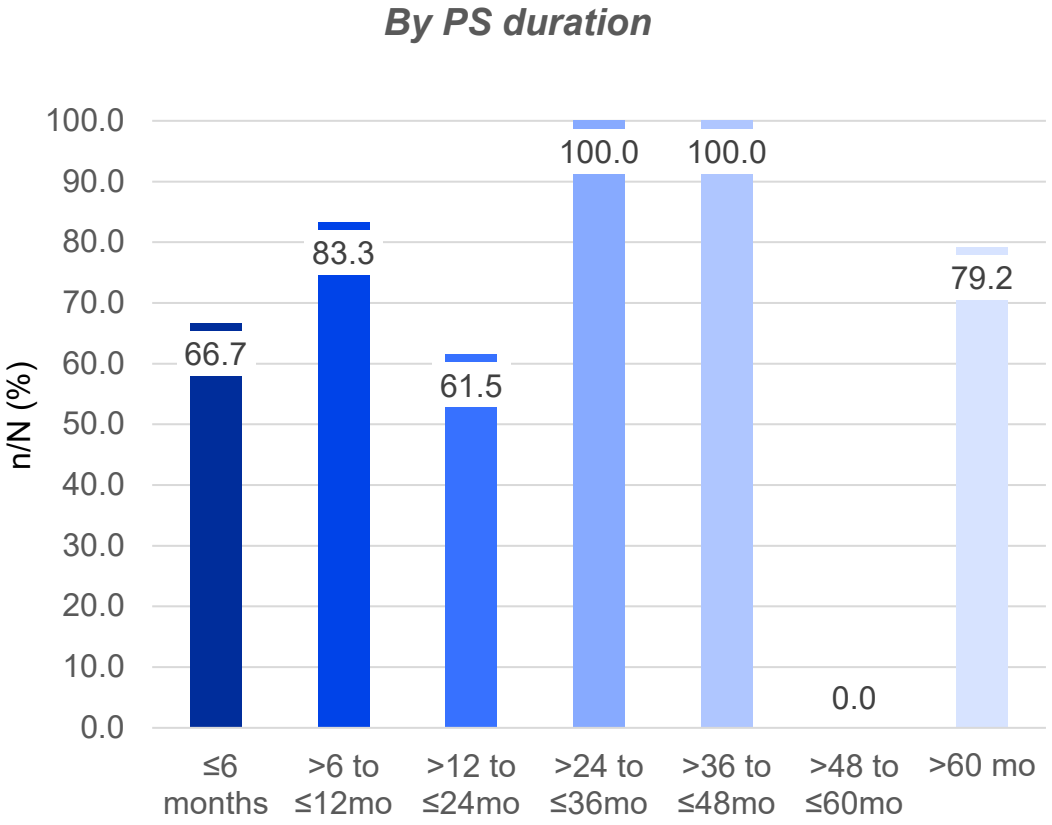
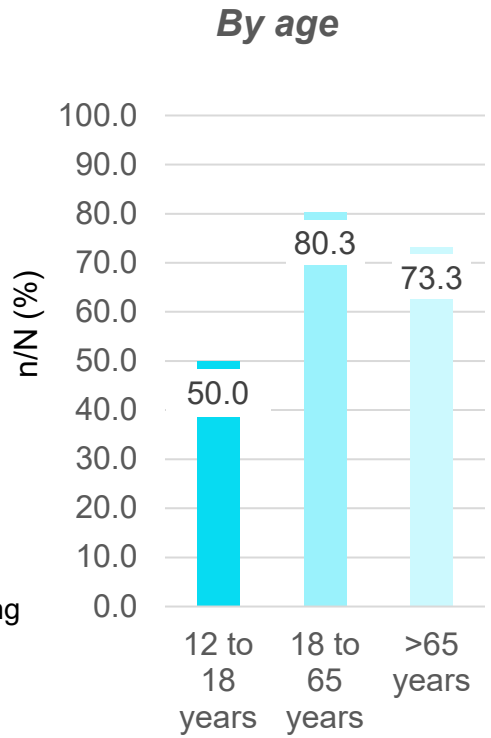
Results: High prevalence of choline deficiency across subgroups including by PS duration and age



By PS duration	n/N (%)
≤6 months	2/3 (66.7)
>6 months to ≤12 months	5/6 (83.3)
>12 months to ≤24 months	8/13 (61.5)
>24 months to ≤36 months	4/4 (100.0)
>36 months to ≤48 months	4/4 (100.0)
>48 months to ≤60 months	0/0
>60 months	38/48 (79.2)



By age	n/N (%)
12 years to 18 years	1/2 (50.0)
18 years to 65 years	49/61 (80.3)
>65 years	11/15 (73.3)

Note: Enrolled set (N = 78); Percentages are based on the number of patients in the Enrolled Set with observed data for the given endpoint.
Note: Choline deficiency is defined as < 9.5 nmol/ml. Various studies in PS-dependent patients report choline deficiency as baseline concentrations of plasma free choline ranging from approximately 5.2 ± 2.1 nmol/mL to 7.15 ± 2.5 nmol/mL.

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Results: High prevalence of choline deficiency across subgroups of underlying conditions by intestinal failure subtype

- Patients had at least one of the following underlying conditions based on European Society for Clinical Nutrition and Metabolism (ESPEN) Pathophysiological IF Classification:
  - Short bowel syndrome: 59.0% (46/78)
  - Mucosal diseases: 46.2% (36/78)
  - Chronic intestinal dysmotility disorders: 33.3% (26/78)
  - Mechanical obstruction: 7.7% (6/78)
  - Intestinal fistulae: 6.4% (5/78)

Patients with choline deficiency by underlying condition (IF classification)	Enrolled set (N = 78)
Short bowel syndrome	38/46 (82.6)
Mucosal diseases	28/36 (77.8)
Chronic intestinal dysmotility disorders	20/26 (76.9)
Mechanical obstruction	2/6 (33.3)
Intestinal fistulae	4/5 (80.0)

Note: Percentages are based on the number of patients in the enrolled set with observed data for the given endpoint.
Note: Choline deficiency is defined as < 9.5 nmol/ml. Various studies in PS-dependent patients report choline deficiency as baseline concentrations of plasma free choline ranging from approximately 5.2 ± 2.1 nmol/mL to 7.15 ± 2.5 nmol/mL.

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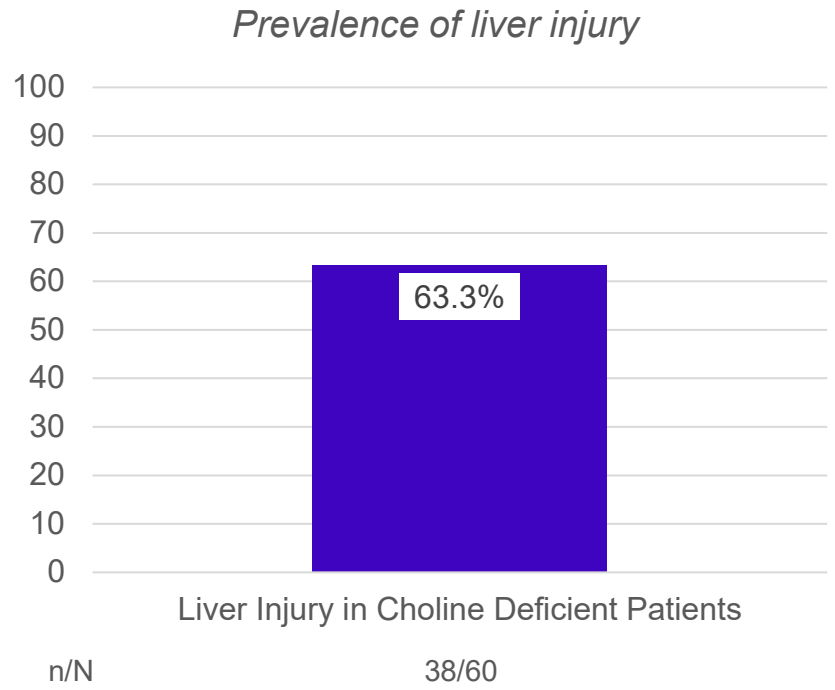
Results: Liver injury was present in approximately 63% of choline deficient patients



- Liver injury was defined as any elevated liver tests (> 1.5 x ULN; ALP, AST, ALT, GGT, direct bilirubin, total bilirubin) or steatosis (MRI-PDFF ≥ 8%)

Note: Percentages are based on the number of patients in the enrolled set with observed data for the given endpoint.

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Summary/Highlights

- Choline deficiency is a significant problem in the IF population and has been associated with liver injury.
- Significant heterogeneity of liver injury was observed and warrants further investigation.
- IV Choline Chloride, an investigational phospholipid substrate replacement therapy, is being developed as a source of choline for PS patients
- A Phase 2b/3 study with IV Choline Chloride in PS-dependent patients is underway.

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