Feeding the Problem:

Parenteral Nutrition-Associated Cholestasis in Neonates

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May 1, 2026

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Learning Objectives

- Describe the pathophysiology and key risk factors of parenteral nutrition-associated cholestasis (PNAC) in neonates
- Identify clinical and laboratory features used to diagnose PNAC in neonates
- Evaluate evidence-based strategies to prevent and manage PNAC in neonates
- Apply a multidisciplinary approach to optimize outcomes in neonates receiving parenteral nutrition (PN)

Definition

- Form of liver dysfunction resulting from prolonged PN
- Commonly defined in the literature as:
  - Direct (conjugated) bilirubin ≥ 2 mg/dL
  - After ≥ 2 weeks of PN exposure
- Diagnosis requires exclusion of other causes
- Part of a broader liver disease spectrum:
  - PN-associated liver disease (PNALD)
  - Intestinal failure-associated liver disease (IFALD)

Gura KM, et al. *Nutr Clin Pract*. 2020;35(1):108-118.

Clinical Impact

- Incidence ~34-54% among neonates receiving prolonged PN
- Risk increases with longer duration of PN
- Results in significant morbidity and mortality in affected infants

Crill CM, et al. *Food Nutr Sci*. 2020;11(10):899-910. | Willis TC, et al. *J Parenter Enteral Nutr*. 2010;34(1):32-37.

Risk Factors

Patient Related

- Prematurity
- Low birthweight
- Infection/sepsis
- Intestinal disease

PN Related

- Prolonged duration
- Lack of enteral feeding
- Excess PN caloric intake
- Soybean-based lipids

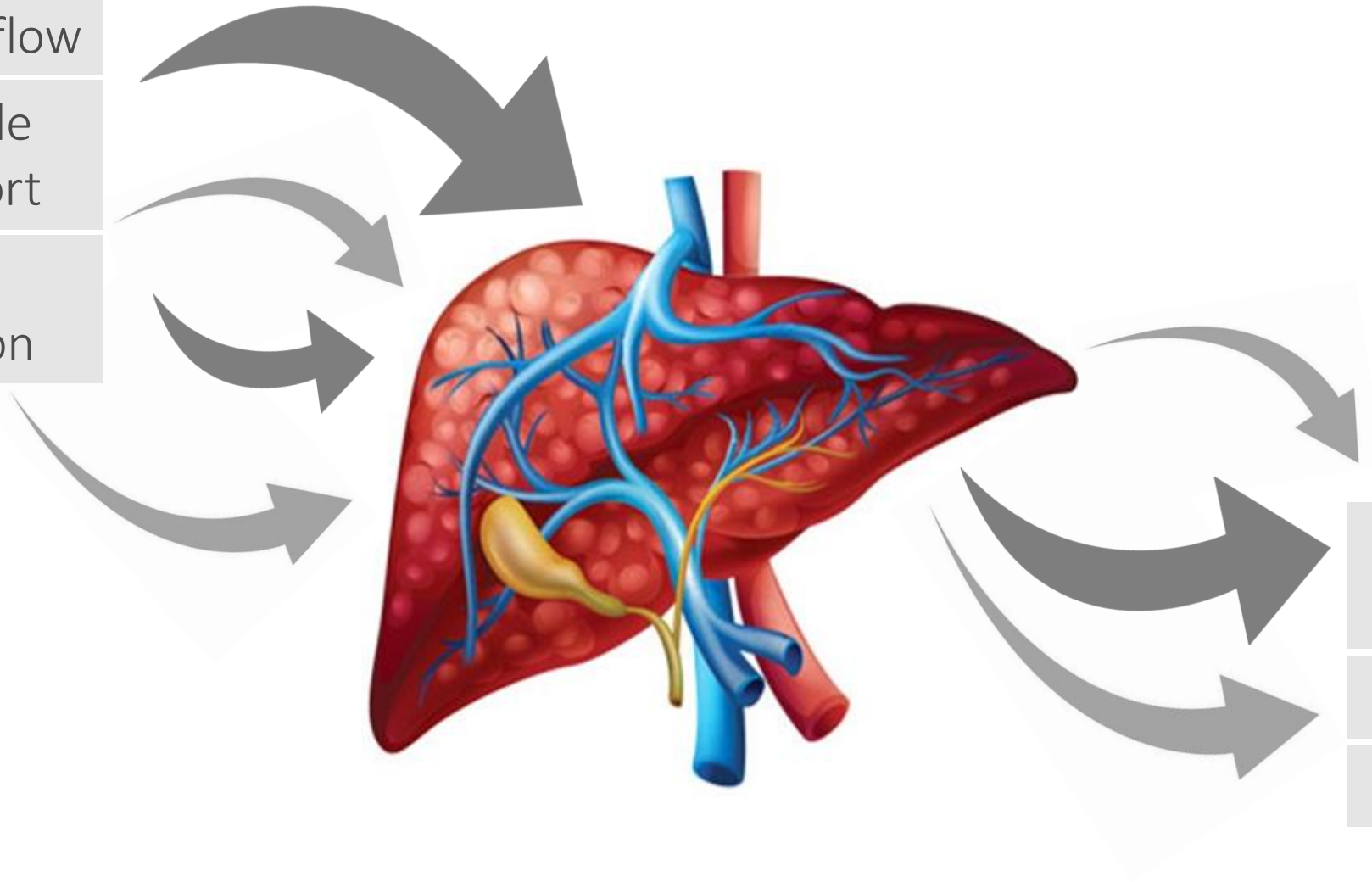
Calkins KL, et al. *Clin Perinatol*. 2014;41(2):331-345. | Gura KM, et al. *Nutr Clin Pract*. 2020;35(1):108-118.

Pathophysiology

Reduced bile flow

Impaired bile acid transport

Increased inflammation



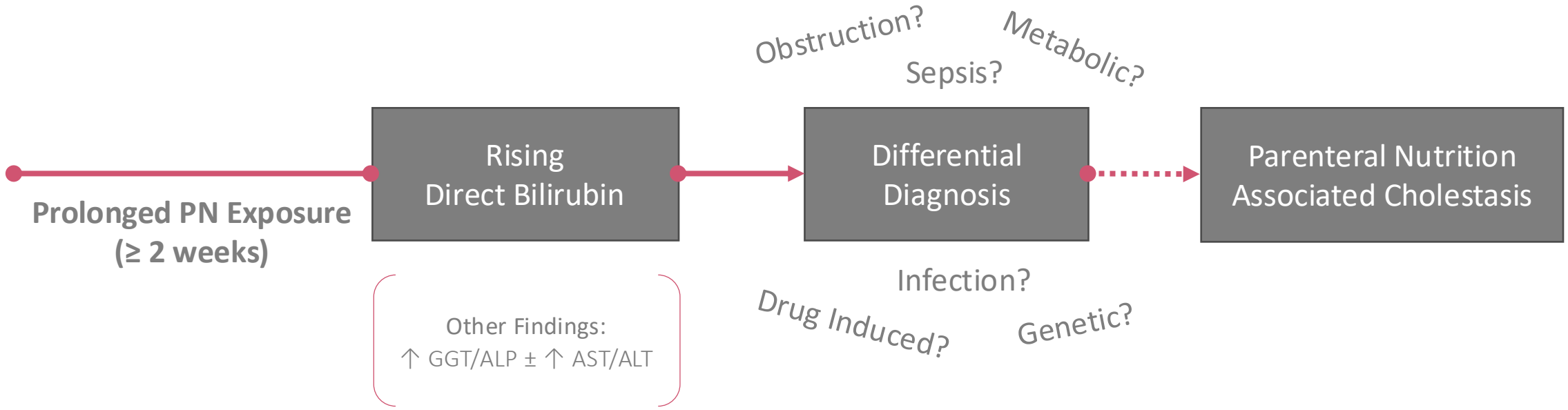
Bile acid accumulation

Hepatocyte injury

Fibrosis/cirrhosis

Calkins KL, et al. *Clin Perinatol*. 2014;41(2):331-345. | Gura KM, et al. *Nutr Clin Pract*. 2020;35(1):108-118.

Diagnosis



GGT = γ -glutamyl transferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase

Management

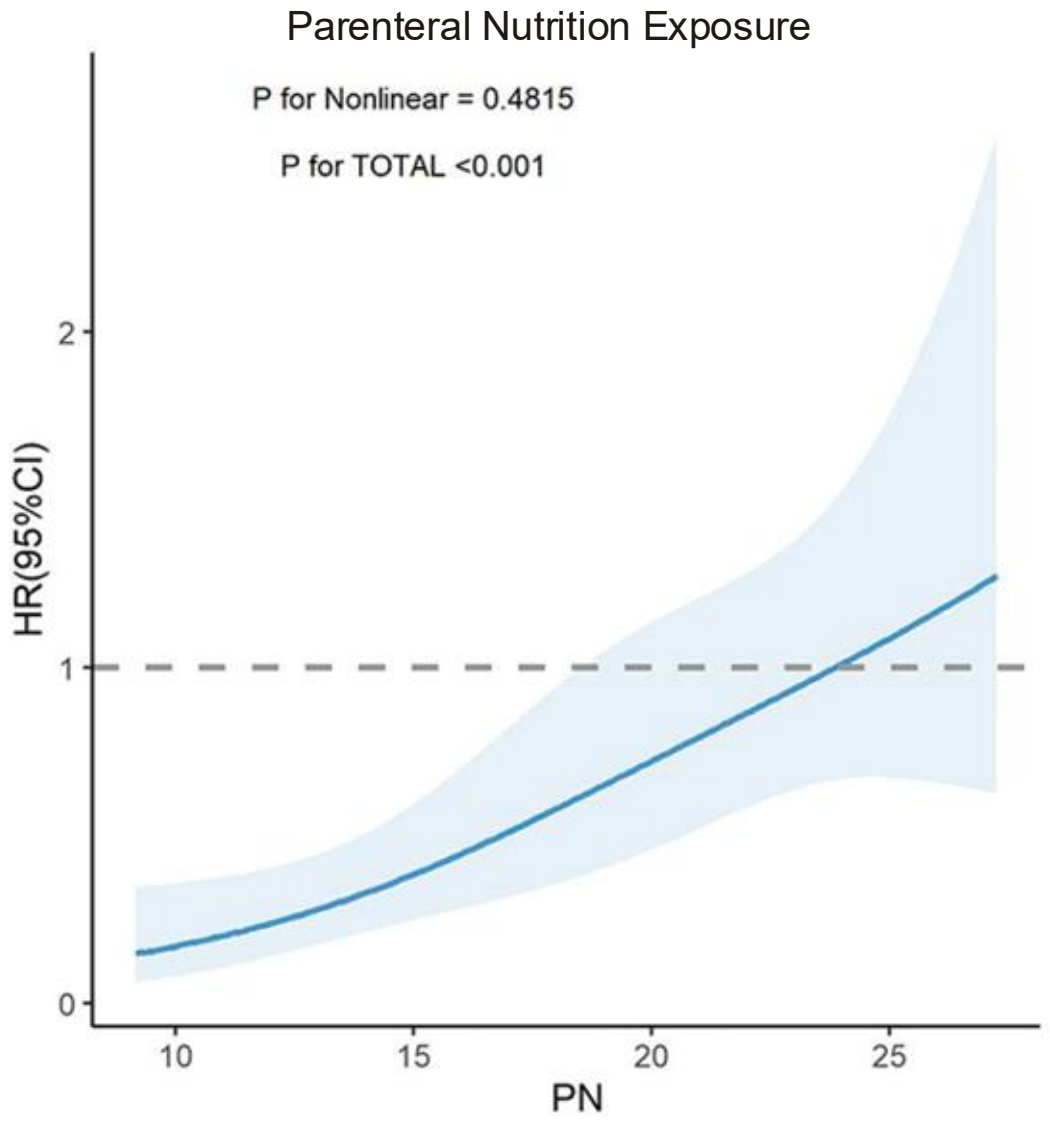
Enteral Feeding

Even minimal (trophic) enteral feeds stimulate bile flow and may reduce PNAC risk

Hartman C, et al. *Clin Nutr*. 2018;37(6 Pt B):2418-2429.

Enteral Feeding

- ↑ PN exposure → ↑ PNAC risk
- ↑ EN exposure → ↓ PNAC risk
- ↑ PN/EN ratio → ↑ PNAC risk



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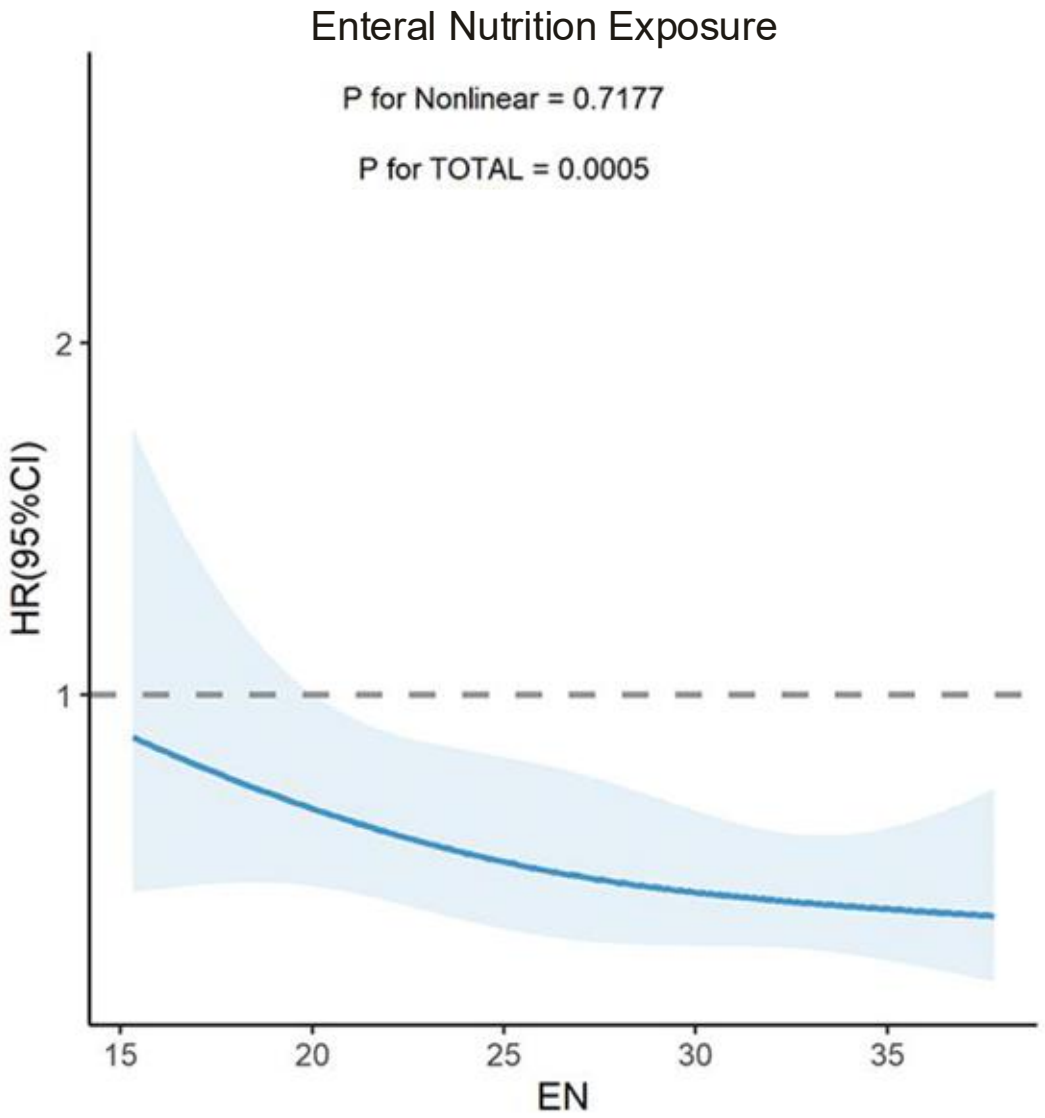
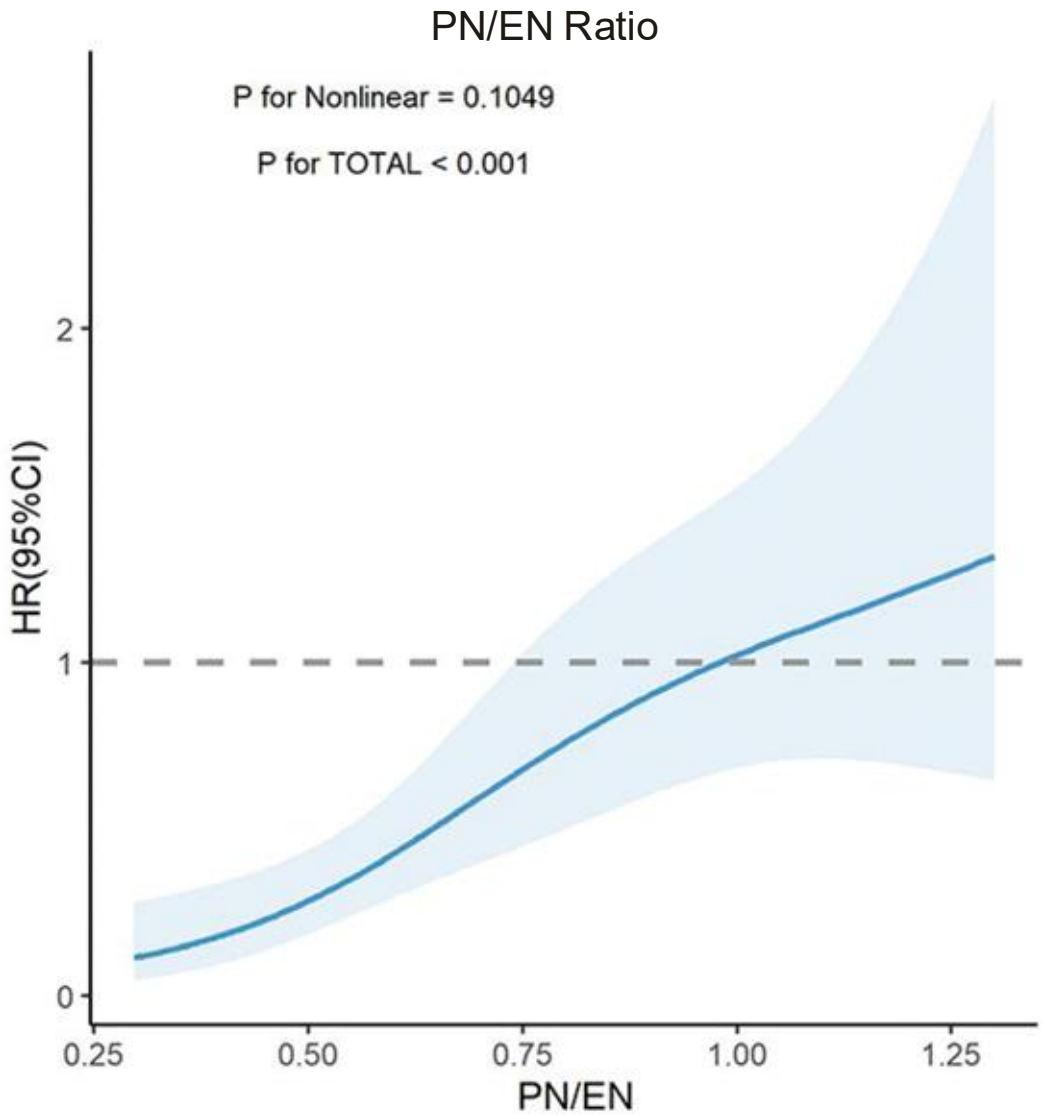


Ma X, et al. *Front Pediatr*. 2025;13:1651046.

Enteral Feeding

- ↑ PN exposure → ↑ PNAC risk
- ↑ EN exposure → ↓ PNAC risk
- **↑ PN/EN ratio → ↑ PNAC risk**



Management Strategies

- Early initiation of enteral feeds
- Advancement of enteral feeds
- Cycling parenteral nutrition
- Lipid modification
- Pharmacologic therapy

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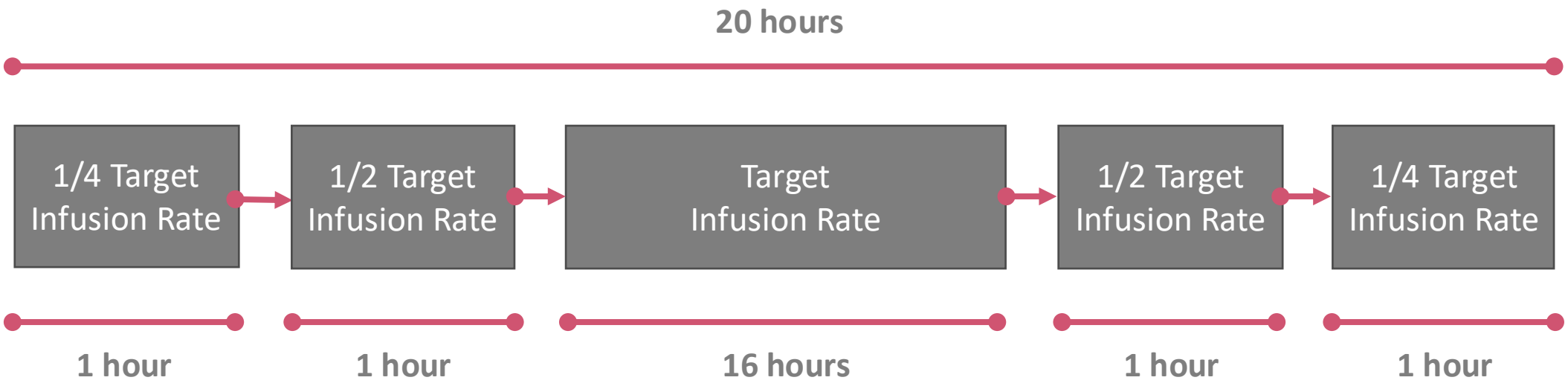
Cycling Parenteral Nutrition



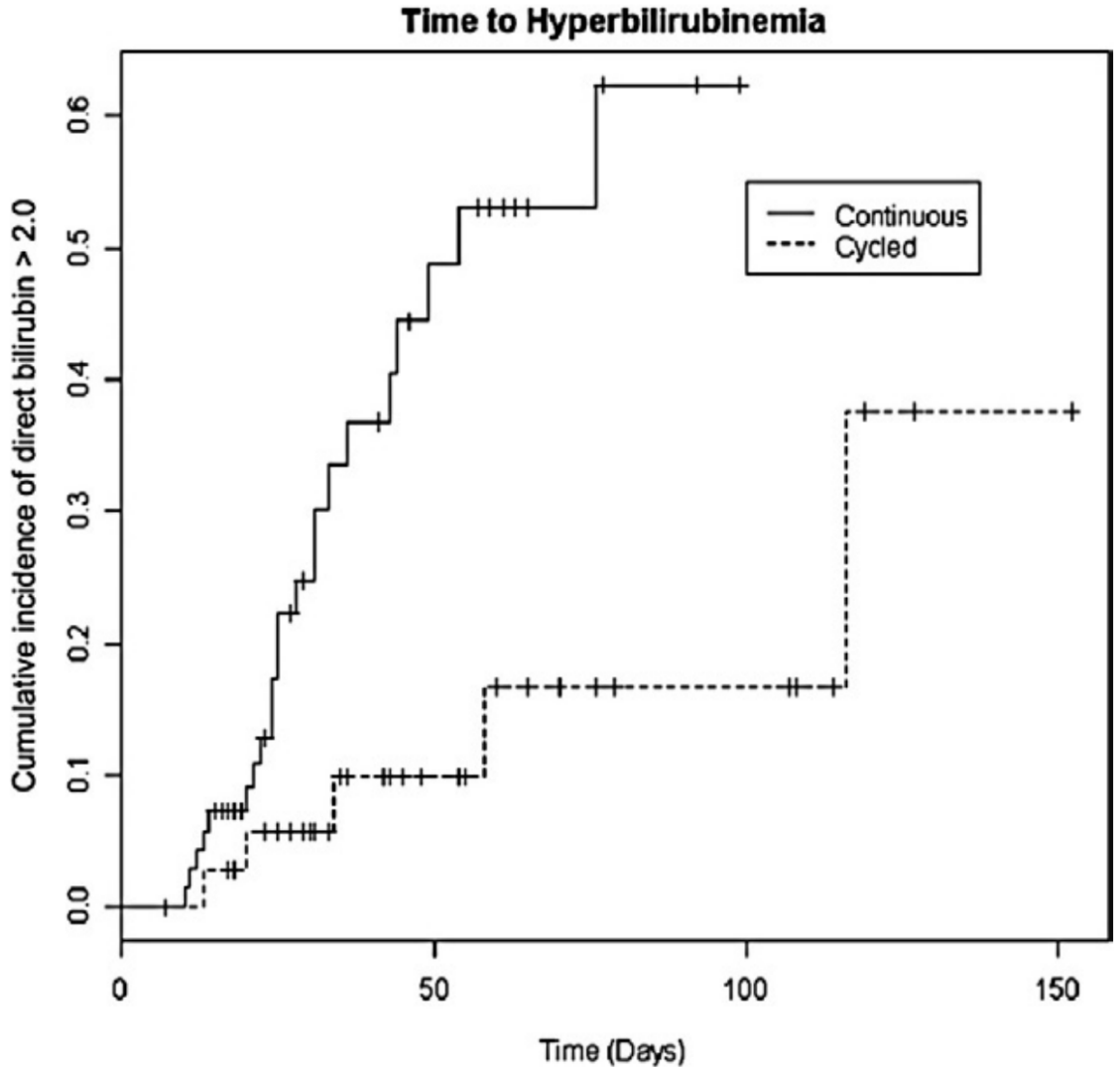
Introduces rest period to reduce hepatic injury

Cycling PN: Supporting Evidence

- Bae HJ et al (2019): *Cyclic vs Continuous PN*
  - Significant ↓ direct bilirubin and ↓ PNAC incidence
  - No significant ↑ in hypoglycemia
- Nghiem-Rao et al (2013): *Early vs Delayed Cycling*
  - Significant ↓ peak direct bilirubin with early cycling
  - No significant difference in PNAC incidence
- Sujka J et al (2018): *Early vs Delayed Cycling*
  - No significant difference in PNAC incidence, time to development, or resolution
  - Numerical trends favored early cycling
  - Hypoglycemia occurred (n=3)

Bae HJ, et al. *Asia Pac J Clin Nutr*. 2019;28(1):42-48. | Nghiem-Rao TH, et al. *Nutr Clin Pract*. 2013;28(6):745-752 | Sujka JA, et al. *Pediatr Surg Int*. 2018;34:1177-1181

Cycling PN: Supporting Evidence



Jensen AR, et al. *J Pediatr Surg*. 2009;44:183-189.

Cycling PN: Clinical Impact

- Associated with reductions in direct bilirubin
- Associated with delayed onset of cholestasis
- May help limit progression of PNALD
- Data are largely observational, with limited neonatal-specific and heterogeneous evidence

Cycling PN: Considerations

- Requires gradual ramp up/down to avoid hyper/hypoglycemia
- Risk of hypoglycemia during infusion-free period
- May be poorly tolerated in very premature or unstable neonates
- Not ideal early in illness with unstable metabolic demands
- Requires careful patient selection and close glucose monitoring

Management Strategies

- Early initiation of enteral feeds
- Advancement of enteral feeds
- Cycling parenteral nutrition
- **Lipid modification**
- Pharmacologic therapy

Lipid Emulsions

		Intralipid®/Nutrilipid® 20%	Clinolipid® 20%	SMOFlipid® 20%	Omegaven® 10%
Approval in the U.S.		1975 / 1993	2019	2016	2018
Approval Indication		All ages	All ages	All ages	Infants and children with PNAC
Oil Composition	Soybean	100%	80%	30%	---
	MCT	---	---	30%	---
	Olive	---	20%	25%	---
	Fish	---	---	15%	100%
Fatty Acids Composition		↑ ω-6 (↓ ω-3)	↑ ω-9 (↓ ω-6)	Mixed ω-3 / ω-6 / ω-9	↑ ω-3 (↓ ω-6)
Vitamin E (tocopherols)		↑ γ-tocopherol	↑ α-tocopherol	↑ α-tocopherol	↑ α-tocopherol
Phytosterol Content		High	Moderate	Reduced	Minimal/none
Dose		Up to 3 g/kg/day	Up to 3 g/kg/day	Up to 3 g/kg/day	1 g/kg/day
Hepatic Effect		Pro-inflammatory; PNAC risk	Less inflammatory; limited data	Less inflammatory; ↓ PNAC risk	Anti-inflammatory; may reverse PNAC

Lipid composition influences inflammation, bile flow, and risk of PNAC

MCT = medium chain triglycerides

Gura KM, et al. *Nutr Clin Pract*. 2020;35(1):108-118. | Wolff J, et al. *Nutr Clin Pract*. 2025;40(2):350-367.

Lipid Emulsion Management

- Formulation
  - Minimize exposure to soybean-only lipid emulsions
  - Prefer mixed-oil lipid emulsions when ongoing PN is needed
  - Transition to fish oil-based emulsions in established PNAC
- Dose
  - Individualize lipid dosing based on clinical status
  - Consider lipid dose reduction in PNAC

Lapillonne A, et al. *Clin Nutr*. 2018;37(6 Pt B):2324-2336. | Wales PW, et al. *J Parenter Enteral Nutr*. 2014;38(5):538-557.

Lipid Reduction and EFAD Risk

- Complete lipid omission → ↑ EFAD risk
- Risk of EFAD depends on linoleic acid (ω-6) content of the lipid formulation
- Lipid emulsions cannot be dose reduced equivalently
  - Minimum linoleic acid to prevent EFAD
    - Preterm: 0.25 g/kg/day
    - Term: 0.1 g/kg/day

EFAD = essential fatty acid deficiency

Lapillonne A, et al. *Clin Nutr*. 2018;37(6 Pt B):2324-2336. | Wolff J, et al. *Nutr Clin Pract*. 2025;40(2):350-367.

Lipid Formulation: Supporting Evidence

- Gura KM et al (2008): *Fish Oil vs Soybean Oil (historical cohorts)*
  - Significant ↓ direct bilirubin and faster reversal of cholestasis
  - Associated with improved survival compared to historical soybean cohorts
- Lapillonne A et al (2018): *Mixed Oil vs Soybean Oil*
  - ↓ liver enzymes; inconsistent effect on PNAC incidence
  - Supports consideration of mixed-oil emulsions for PNAC prevention
- Wales PW et al (2014): *Mechanistic/Guideline Data*
  - Phytosterols + ω-6 fatty acids → inflammation + cholestasis
  - Supports observed increased PNAC risk with soybean emulsions

Gura KM, et al. *Pediatrics*. 2008;121(3):e678-686. | Lapillonne A, et al. *Clin Nutr*. 2018;37(6 Pt B):2324-2336. | Wales PW, et al. *J Parenter Enteral Nutr*. 2014;38(5):538-557.

Lipid Formulation: Clinical Impact

Soybean oil lipids

- Consider minimizing use in prolonged PN when alternatives available
- Strongest association with PNAC development

Mixed oil lipids

- Reasonable option to reduce PNAC risk when ongoing PN needed
- May improve liver enzymes

Fish oil lipids

- Consider use for established PNAC
- Associated with PNAC reversal in observational studies

Checkpoint

A 26-week gestational age neonate has been NPO and receiving PN with a soybean oil-based lipid for 18 days. Labs show a direct bilirubin level of 2.4 mg/dL. Other causes of cholestasis have been ruled out. Enteral feeding is not currently feasible.

Which of the following is the most appropriate initial intervention to address this condition?

A. Initiate ursodiol therapy
B. Transition to a fish-oil based lipid emulsion
C. Discontinue lipid emulsion entirely
D. It is too early to diagnose PNAC

Checkpoint

The patient remains NPO with a persistently elevated direct bilirubin of 2.6 mg/dL. The team is considering initiation of cyclic PN.

Which of the following best reflects key considerations when initiating cyclic PN?

A. Increased risk of hypoglycemia during PN interruption
B. Requires enteral feeding tolerance
C. Requires gradual tapering to prevent rebound hypoglycemia
D. Cycling is only beneficial for addressing PN compatibility issues
E. A and C

Checkpoint

The patient is now clinically improving and tolerating minimal enteral feeds. PN is still required to meet total fluid goals and nutritional needs. Direct bilirubin remains elevated.

Which of the following is the most appropriate next step?

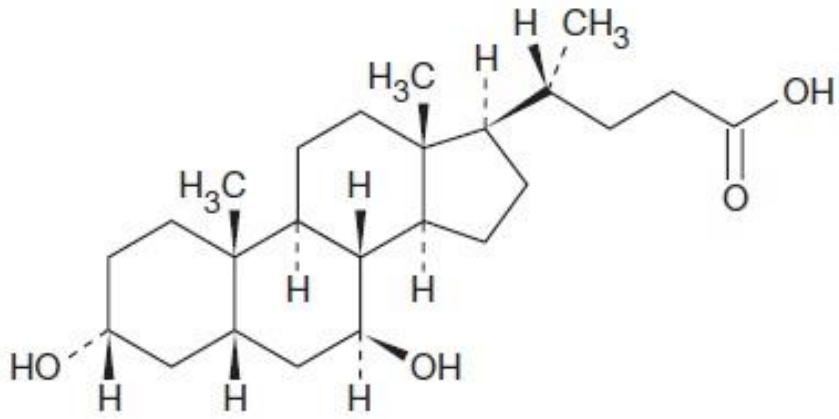
A. Advance enteral feeds as tolerated
B. Initiate erythromycin therapy
C. Discontinue lipid emulsion entirely
D. Continue current regimen without feeding volume advancement

Management Strategies

- Early initiation of enteral feeds
- Advancement of enteral feeds
- Cycling parenteral nutrition
- Lipid modification
- Pharmacologic therapy

Ursodiol (Actigall®)

- Only available in oral tablets and capsules
- Oral suspension must be compounded
- Dose: 10-30 mg/kg/day div every 8-12 hours
- Adverse effects: nausea, vomiting, diarrhea, abdominal pain
- Monitoring:
  - Direct bilirubin levels
  - Hepatic transaminases
- Aluminum-based antacids and bile acid sequestrants decrease ursodiol absorption



Johnson C, et al. *Am J Health Syst Pharm*. 2002;59(4):361-363. | Rust C, et al. *Eur J Clin Invest.* 2000;30(2):135-139.

Ursodiol (Actigall®)

Ursodeoxycholic acid prevention on cholestasis associated with total parenteral nutrition in preterm infants: a randomized trial

Objective	Investigate safety and efficacy of ursodiol in preventing PNAC in preterm neonates
Methods	Prospective, randomized, open-label, proof-of-concept trial Ursodiol 20-25 mg/kg/day initiated on day of life 7 (n=42) vs no prophylaxis (n=60)
Inclusion Criteria	• Gestational age < 34 weeks • Birthweight < 1800 g • Admission to the hospital within 24 hours of birth • PN from first day of life and continued for > 2 weeks
Primary Outcomes	Peak direct and total bilirubin, liver enzymes (ALT, GGT, ALP), total cholesterol and bile acids

GGT = γ-glutamyl transferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase

Liu S, et al. *World J Pediatr*. 2022;18:100-108.

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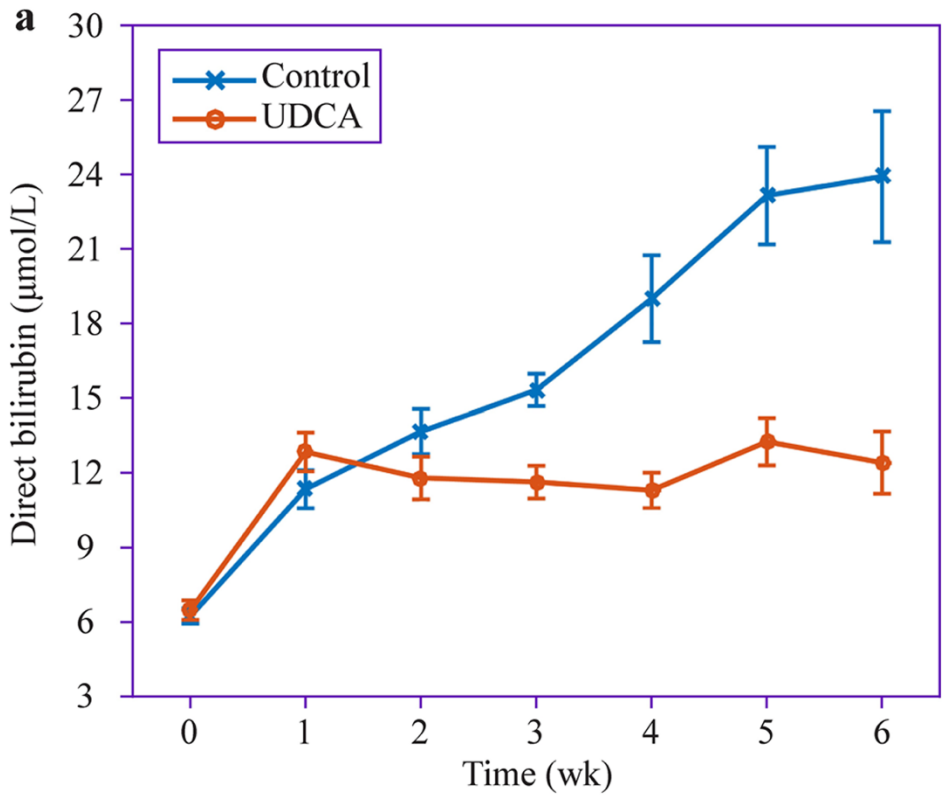

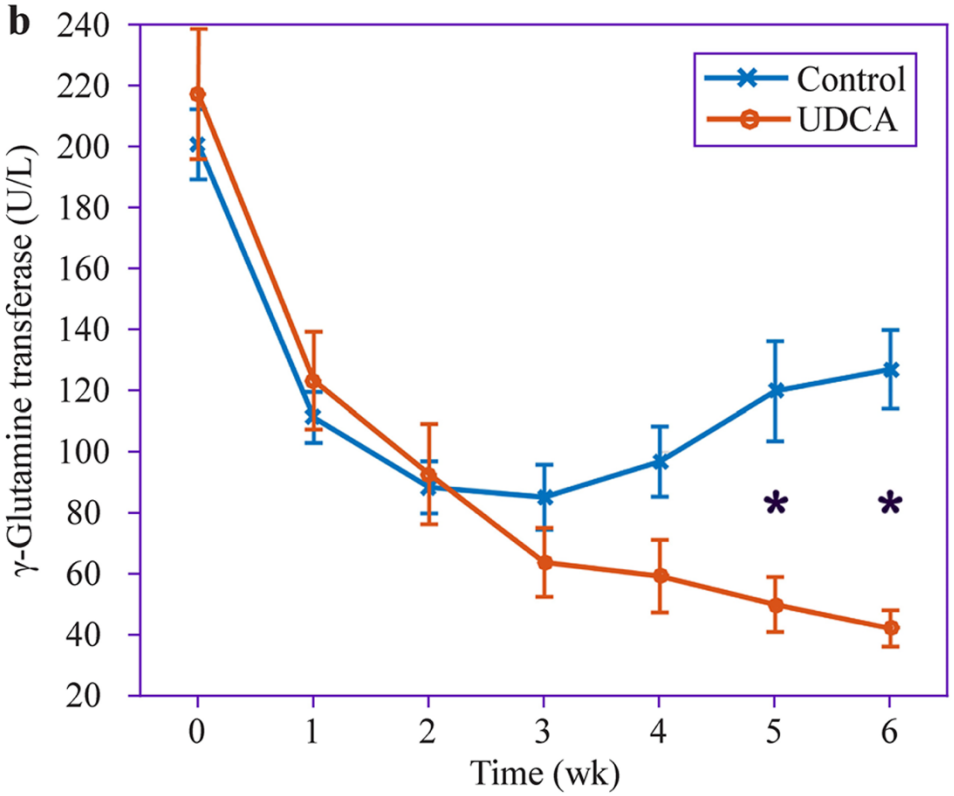

Direct Bilirubin 34 μmol/L ≈ 2 mg/dL

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Results	• ↓ direct bilirubin: 13 (12-16) vs 15.2 (12.5-19.6) µmol/L ($P < 0.05$) • ↓ total bilirubin: 101.1 ± 34 vs 116.5 ± 28.7 µmol/L ($P < 0.05$) • ↓ GGT: 42.1 ± 19.1 vs 127 ± 60.9 U/L ($P < 0.05$) • ↓ cholestasis incidence: 0% vs 11.7% ($P < 0.05$) • No difference: ALT, ALP, total bile acids
Limitations	• Single center, small sample size • Open label design and non-placebo controlled • Multiple surrogate primary endpoints • Imbalance in group sizes (42 vs 60) • Limited generalizability • Potential confounding from enteral feeding practices • Short follow-up
Conclusion	Ursodiol prophylaxis was associated with improved biochemical markers and lower incidence of cholestasis; however, clinical benefit remains uncertain

GGT = γ -glutamyl transferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase

Liu S, et al. *World J Pediatr*. 2022;18:100-108.

Ursodiol (Actigall®)

Ursodeoxycholic acid for preventing parenteral nutrition-associated cholestasis in neonates: A systematic review and meta-analysis

Objective	Determine the role of ursodiol in preventing PNAC in neonates
Methods	Systematic review and meta-analysis comparing ursodiol vs placebo/no intervention for prevention of PNAC
Inclusion	Five studies included (3 randomized controlled trials, 2 non-randomized studies) • Neonates requiring prolonged PN • Ursodiol vs placebo/no prophylaxis
Outcomes	• Clinical: cirrhosis/liver failure, need for transplantation, death • Other: cholestasis incidence, direct bilirubin, time to cholestasis

Anne R, et al. *Fundam Clin Pharm*. 2024;38:685-694.

Ursodiol (Actigall®)

Ursodeoxycholic acid for preventing parenteral nutrition-associated cholestasis in neonates: A systematic review and meta-analysis

Results	Randomized controlled trials: • ↓ feeding intolerance and time to full enteral feeds • ↓ peak direct bilirubin • No effect on PNAC, mortality, sepsis, NEC, PN duration or hospital stay Non-randomized studies: • No consistent benefit across outcomes Certainty of evidence: • Low certainty: feeding intolerance, bilirubin, time to full feeds • Very low certainty: mortality, NEC, cholestasis, sepsis, hospital stay, PN duration
Limitations	• Limited number of studies and small sample size • Inclusion of non-randomized studies • Heterogeneity in patient characteristics and nutritional practices • Variable ursodiol dosing (5-30 mg/kg/day)
Conclusion	• Available evidence is insufficient to determine benefits of prophylactic ursodiol

Anne R, et al. *Fundam Clin Pharm*. 2024;38:685-694.

Ursodiol (Actigall®)

Ursodeoxycholic acid therapy in very-low-birth-weight infants with parenteral nutrition-associated cholestasis

Objective	Determine effects of ursodiol in very-low-birth-weight non-surgical neonates with PNAC
Methods	Retrospective, non-randomized, observational study of ursodiol (n=12) vs no intervention (n=18)
Inclusion	• Birthweight < 1500 g • Received PN > 2 weeks • Negative diagnostic work up for other causes
Outcomes	• Direct bilirubin levels, duration of cholestasis, liver enzymes
Results	• ↓ period of cholestasis: 62.8 ± 10.7 vs 92.4 ± 8.8 (P = 0.006) • ↓ peak direct bilirubin levels: 5.3 ± 0.6 vs 8.7 ± 1.1 (P = 0.023) • No significant difference in peak GGT, AST, ALT, ALP
Limitations	• Study design, small sample size, variable ursodiol dose (10-30 mg/kg/day), treatment group developed cholestasis later than control group, excluded abdominal surgery patients
Conclusion	• Associated with ↓ direct bilirubin and shorter duration of cholestasis

GGT = γ -glutamyl transferase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase

Chen CY, et al. *J Pediatr*. 2004;145(3):317-21.

Ursodiol (Actigall®)

Efficacy and safety of ursodeoxycholic acid in children with cholestasis: A systematic review and meta-analysis

Objective	Evaluate the efficacy and safety of ursodiol in children with cholestasis
Methods	Systematic review and meta-analysis of studies evaluating ursodiol in cholestasis
Inclusion	Randomized clinical trials comparing ursodiol vs placebo/blank control with defined clinical and biochemical outcomes
Results	Of the 32 eligible trials, 8 evaluated for PNAC in subgroup analysis • ↑ biochemical response vs placebo/blank control [RR 1.34, 95% CI (1.16-1.54)] • ↓ direct bilirubin [MD = -20.66 µmol/L, 95% CI (-27.62, -13.17)] • Adverse drug reactions were similar between groups and did not differ across ursodiol doses
Limitations	Limited neonatal data (age not reported in most PNAC studies); primary outcomes varied across studies and were primarily lab-based; small sample size; variable ursodiol dose (5-30 mg/kg/day)
Conclusion	Ursodiol is associated with improved biochemical outcomes in pediatric PNAC (subgroup analysis); however, clinical benefit remains uncertain

Direct Bilirubin 20.66 µmol/L ≈ 1.21 mg/dL

Huang L, et al. *PLoS One*. 2023;18(1):e0280691.

Phenobarbital

- Rationale for use:
  - Hepatic enzyme induction → ↑ bile flow
  - Historically used for:
    - Cholestatic conditions
    - Hepatobiliary iminodiacetic acid (HIDA) scan preparation
- Considerations:
  - Dose: 3-5 mg/kg/day div every 12 hours
  - Available IV and orally
  - Oral solution contains alcohol (~10-15%)
  - Potential neurodevelopmental risk with prolonged use (animal data)

Gleghorn EE, et al. *J Parenter Enteral Nutr*. 1986;10(3):282-283 | Lewis T, et al. *BMC Pediatr.* 2018;18:197.

Phenobarbital

Not supported for PNAC management

- Gleghorn et al (1986):
  - Associated with higher PNAC incidence in phenobarbital group
- Lewis et al (2018):
  - No significant improvement vs ursodiol in neonatal cholestasis
- No high-quality randomized trials in PNAC

Gleghorn EE, et al. *J Parenter Enteral Nutr*. 1986;10(3):282-283 | Lewis T, et al. *BMC Pediatr.* 2018;18:197.

Erythromycin

- Rationale for use:
  - Motilin receptor agonist → ↑ gastrointestinal motility
  - Theoretical benefit:
    - ↓ feeding intolerance → ↓ PN duration → potential ↓ PNAC risk
- Considerations:
  - Prokinetic dosing (studies used intermediate-high doses)
  - Tachyphylaxis limits sustained prokinetic effect
  - QT prolongation
  - Risk of infantile hypertrophic pyloric stenosis (IHPS)
  - Antibiotic exposure could disrupt microbiome and cause resistance

Ng PC, et al. *Gastroenterology*. 2007;132:1726-1739. | Ng YY, et al. *Pediatr Neonatol.* 2012;53:34-40. | Gokmen T, et al. *Perinatol*. 2012;32:123-128.

Erythromycin

Inconsistent evidence for PNAC prevention

- Ng PC et al (2007) & Ng YY et al (2012):
  - Intermediate-high dose erythromycin associated with lower PNAC incidence in preterm VLBW infants
- Gokmen T et al (2012):
  - Improved feeding tolerance, but no significant difference in PNAC incidence vs ursodiol or placebo

Key Takeaway:

May improve feeding tolerance, but does not consistently reduce PNAC incidence

Ng PC, et al. *Gastroenterology*. 2007;132:1726-1739. | Ng YY, et al. *Pediatr Neonatol.* 2012;53:34-40. | Gokmen T, et al. *Perinatol*. 2012;32:123-128.

Pharmacotherapy: Clinical Impact

Medication	Evidence	Role in PNAC	Considerations
Ursodiol	↓ direct bilirubin	Consider in select patients with established PNAC	Requires enteral route
Phenobarbital	No benefit; potential harm	Not recommended	Neurodevelopmental risk
Erythromycin	Improves feeding tolerance; inconsistent PNAC impact	No direct role; indirect effect via improved enteral feeding tolerance	IHPS, QT prolongation, tachyphylaxis, antimicrobial resistance

Checkpoint

A 30-week gestational age neonate developed PNAC following 4 weeks of PN in the setting of necrotizing enterocolitis. Despite optimization of PN, including lipid modification and cycling, PNAC persists with a direct bilirubin level of 3.1 mg/dL. This has continued for an additional 2 weeks despite PN discontinuation and full enteral feeding.

Which of the following is the most appropriate next step?

A. Initiate ursodiol therapy
B. Initiate phenobarbital therapy
C. Initiate erythromycin therapy
D. Continue current regimen and monitor

Checkpoint

The patient is started on ursodiol 30 mg/kg/day divided twice daily.

Which of the following best explains the expected clinical benefit of this therapy?

A. Direct replacement of essential fatty acids
B. Reduction in direct bilirubin levels via enhanced bile flow
C. Improved gastric motility to enhance feeding tolerance
D. Inhibits bilirubin production

Checkpoint

Which of the following best describes the role of pharmacologic therapies in the management of PNAC?

A. Ursodiol is an effective monotherapy that eliminates the need for further nutritional optimization
B. Phenobarbital improves bile flow and is routinely recommended for PNAC management
C. Pharmacologic therapy should be initiated early to prevent progression of cholestasis prior to enteral feeding
D. Erythromycin may support enteral feeding advancement but does not directly treat PNAC

Take-Home Points

- PNAC is a common complication of prolonged PN in neonates
- Diagnosis is primarily lab-based, with rising direct bilirubin often preceding clinical signs
- Prevention and management are driven by:
  - Initiation and advancement of enteral feeds
  - Optimizing PN (e.g., cycling, lipid adjustment)
  - Selective use of pharmacologic therapy (e.g., ursodiol)
- Early, multidisciplinary and individualized care is essential to prevent progression to liver disease

Feeding the Problem:

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