

Neonatal Refeeding Syndrome— Considerations for Infants at Risk



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Disclosure

I have no commercial relationships to disclose



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Learning Objectives

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

- 1) Review the physiology and clinical signs of refeeding syndrome (RFS)
- 2) Identify infants who are at risk for developing RFS
- 3) Describe strategies/interventions to minimize or prevent RFS in at-risk infants

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Refeeding Syndrome: General Definition and Key Features^{1,2}

Definition and Biochemical Features

Involves metabolic and electrolyte disturbances, chiefly hypophosphatemia, after nutrition reintroduction

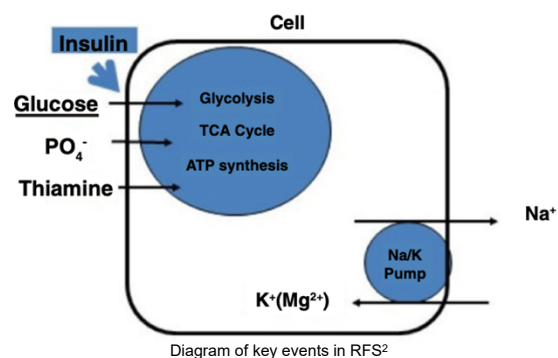
Clinical Risks and Outcomes

If unrecognized, RFS can cause respiratory failure, arrhythmias, neuromuscular weakness, and death

A.S.P.E.N. Consensus Definition¹

A decrease in any 1, 2, or 3 of serum phosphorus (P), potassium (K), and/or magnesium (Mg) and/or organ dysfunction

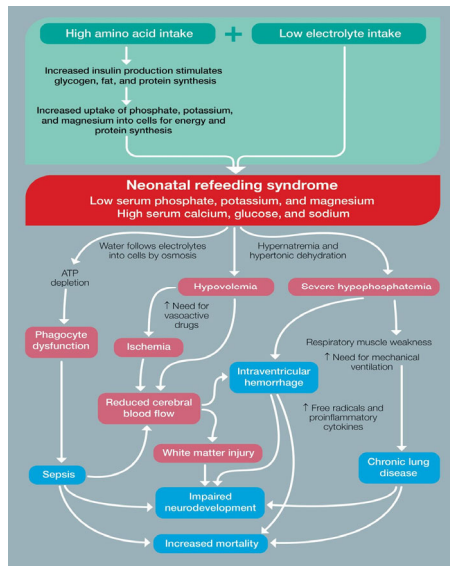
- Mild: 10-20% decrease
- Moderate: 20-30% decrease
- Severe: > 30 % decrease and/or thiamin deficiency



¹Da Silva JS et al. *Nutr Clin Pract.* 2020; ²De Silva A, Nightingale JMD. *Frontline Gastroenterol.* 2020.

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Neonatal Refeeding Syndrome^{3,4}



Condition of metabolic derangements attributable to impaired transplacental nutrient transfer followed by a relative abundance of nutrient availability⁴

Associated with:

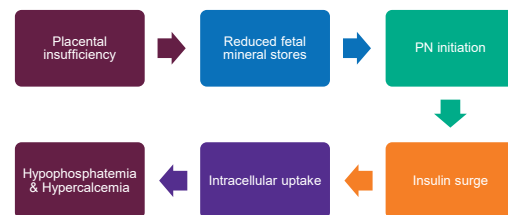
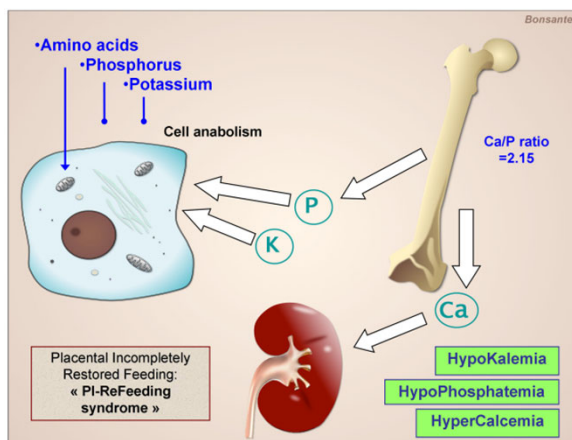
Hypophosphatemia	Metabolic acidosis
Hypokalemia	Hypovolemia
Hypomagnesemia	Respiratory alkalosis
Hypercalcemia	Delayed time to full enteral feeding
Hypernatremia	Sepsis
Hyperglycemia	Chronic Lung disease

Proposed mechanisms for neonatal RFS and possible effects on clinical outcomes³

³Cormack BE et al. *J Parenter Enteral Nutr*, 2021; ⁴Robinson DT, Taylor SN, Moya F. *J Perinatol*, 2023.

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Pathophysiology of Neonatal RFS⁵



⁵Bonsante F et al. *PLOS One*, 2013.

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Neonatal Populations: Who is at Risk for RFS?⁶⁻⁷

- ✓ Maternal Risk Factors
 - Preeclampsia, Pregnancy-induced HTN, Chronic HTN
 - Placental insufficiency
- ✓ Fetal Risk Factors
 - Increased resistive indices in the umbilical artery
 - Small-for-Gestational-Age (SGA)
 - Fetal Growth Restriction (FGR)
 - Previously, intrauterine growth restriction (IUGR)
- ✓ Neonatal Factors
 - Extremely or Very Low Birth Weight (ELBW/VLBW)
 - Initial high amino acid intake
 - Delayed phosphorus supplementation

HTN: hypertension; ELBW: ≤ 1000 grams; VLBW: ≤ 1500 grams

⁶Ross JR et al. *J Perinatol*. 2013; ⁷Sung SI et al. *PLoS One*. 2019.



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Why is Neonatal RFS Different?

Adult RFS	Neonatal RFS
Prolonged starvation or chronic illness	Placental deprivation; fetal growth restriction
Occurs with eating (by mouth, EN, or PN)	Occurs with initiation of IV amino acids & glucose (early PN) -typically, within 1-2 hours after birth -decreased initial electrolyte supplementation
Insulin forces P, K, Mg into the cell	Kidneys + metabolic systems cannot balance rapid influx of nutrients with low mineral supplies
Low serum P, K, Mg levels	Low P, often K, hypercalcemia, metabolic acidosis

P = Phosphorus; K = Potassium; Mg = Magnesium

¹Cormack BE et al. *J Parenter Enteral Nutr*, 2021.



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Biochemical Manifestations and Incidence

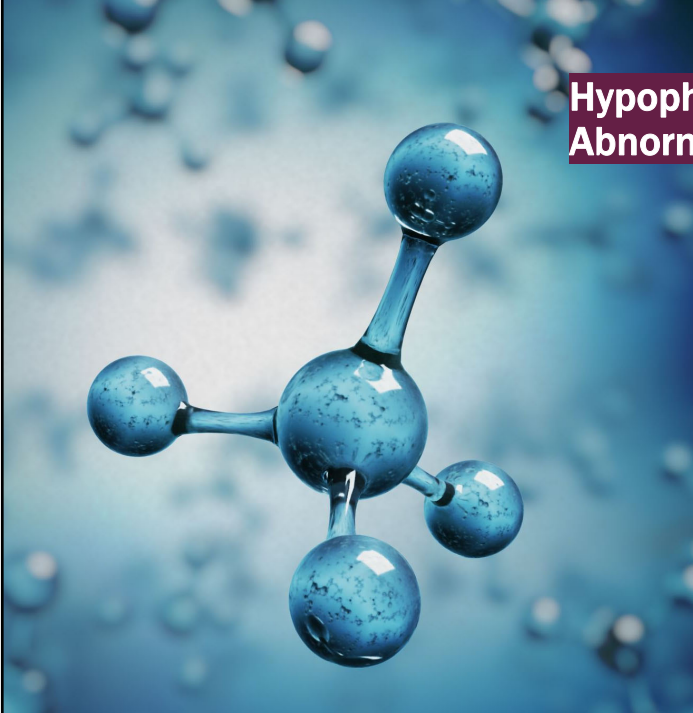
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Common Biochemical Abnormalities in Neonatal RFS ^{6,7}

Most Common	
Hypophosphatemia	Most common neonatal RFS abnormality
Hypercalcemia	Arises from low phosphorus affecting bone mineralization
Hypokalemia	Due to insulin-driven cellular uptake
Additional Findings	
Hypomagnesemia	Worsens hypokalemia by impairing kidney's potassium retention
Hyperglycemia	Excess glucose delivery Relative insulin resistance
Hypernatremia	Fluid imbalance Concentrated PN solution

⁶Ross JR et al. *J Perinatol.* 2013; ⁷Sung SI et al. *PLoS One.* 2019.

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Hypophosphatemia: Hallmark Abnormality⁶⁻⁸

- Decreased ATP Production
- Respiratory Dysfunction (diaphragm weakness)
- Hemolysis, thrombocytopenia, leukocyte dysfunction, decreased O₂ delivery
- Neuromuscular dysfunction
- Ileus/delayed gut motility

⁶Ross JR et al. *J Perinatol.* 2013; ⁷Sung SI et al. *PLoS One.* 2019; ⁸Mihatsch WA et al. *Clin Nutr.* 2018.

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Other Electrolyte Disturbances and Metabolic Effects^{5,8}

Hypercalcemia and Bone Mineralization
Neonatal hypercalcemia arises from low phosphorus availability affecting bone mineralization and increasing calcium levels.

Hypokalemia and Hypomagnesemia Interaction
Hypokalemia and hypomagnesemia often occur together due to insulin shifts, with magnesium deficiency impairing potassium correction.

Hyperglycemia and Hyponatremia Causes
Hyperglycemia results from high glucose infusion or insulin resistance; hyponatremia may stem from concentrated nutrition or fluid restriction.

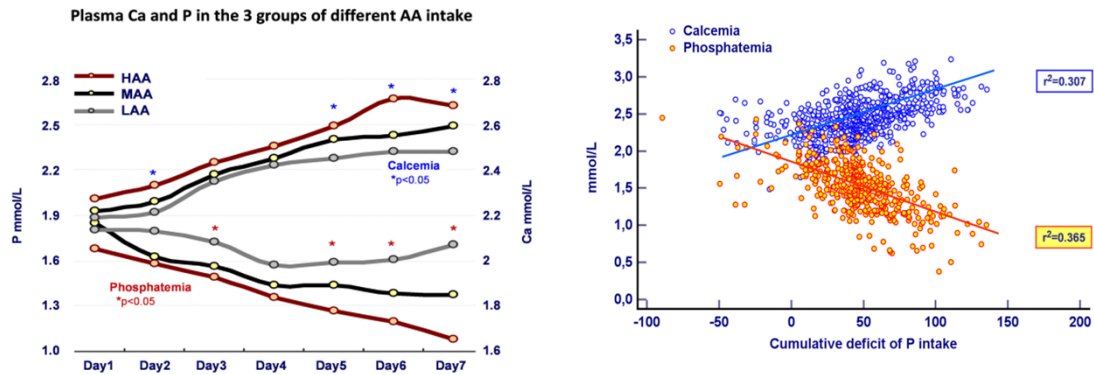
⁵Bonsante F et al. *PLOS One.* 2013; ⁸Mihatsch WA et al. *Clin Nutr.* 2018.

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Hypercalcemia and Hypophosphatemia^{5,8}

- Elevated calcium should raise concern for phosphorus deficiency
- Increased amino acid intake increases severity



⁵Bonsante F et al. *PLOS One*. 2013

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Hypokalemia and Hypomagnesemia^{1,6,8}

- Hypokalemia
 - Arrhythmia risk
 - Neuromuscular dysfunction with weakness and paresthesia
 - Ileus/delayed gut motility
 - Seizures
- Hypomagnesemia
 - Impairs correction of potassium (impairs Na/K ATPase)
 - Weakness, tremors, seizures
 - Delayed gut motility

¹Da Silva JS et al. *Nutr Clin Pract*. 2020 ; ⁶Ross JR et al. *J Perinatol*. 2013; ⁸Mihatsch WA et al. *Clin Nutr*. 2018.

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Hypernatremia and Hyperglycemia^{1,7,9}

- Hypernatremia
 - Concentrated PN
 - Fluid restriction, hypovolemic
- Hyperglycemia
 - Insulin implications
 - Early PN/excessive glucose administration
 - Possible dehydration (increased urine output)

¹Da Silva JS et al. *Nutr Clin Pract.* 2020; ⁷Sung SI et al. *PLoS One.* 2019; ⁹Jochum F et al. *Clin Nutr.* 2018.



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Biochemical Values⁴

Biochemical Value	Abnormal serum level	Incidence in Neonatal RFS
Hypophosphatemia*	< 4 mg/dL; severe < 2.5 mg/dL	20-90%
Hypokalemia	< 3.5 mEq/L	< 10% to 67%
Hypomagnesemia	< 1.5 mg/dL	
Hypercalcemia	Ionized: > 1.5 mmol/L Total: > 2.8 mmol/L	
Hypernatremia	> 145 mEq/L	
Hyperglycemia	Varies: > 150 or 180 mg/dL	

*Values vary—no consensus on severe hypophosphatemia definition

⁴Robinson DT, Taylor SN, Moya F. *J Perinatol.* 2023.



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Incidence of Neonatal RFS—How Common is it?^{3,6,10}

Study	Population	Finding
Ross 2013	IUGR VLBW	41.2% hypophosphatemia
Ross 2013	IUGR VLBW	11.4% severe hypophosphatemia
Cormack 2020	ELBW infants	~20% refeeding syndrome
Bradford Review 2021	High-risk infants	20–90% depending on definition

Incidence varies considerably – no universally accepted neonatal definition

Key Evidence^{3,6,7}

Ross Study (2013) on IUGR and Hypophosphatemia

Ross et al. revealed higher hypophosphatemia rates in infants with intrauterine growth restriction compared to peers.

Cormack Study (2021) on Clinical Outcomes

Cormack linked neonatal refeeding syndrome to increased morbidity and mortality in extremely low birth weight infants.

Sung Study (2019) on Nutrition Practices

Sung demonstrated that high amino acid intake in small-for-gestational-age infants raises severe hypophosphatemia risk.

Implications for Neonatal Care

These studies support early risk identification and careful nutrition adjustments to improve neonatal outcomes.

Short- and Long-Term Morbidities^{3,6}



**Respiratory
Complications**

**Cardiac and
Hematologic
Effects**

**Infection
Susceptibility**

**Clinical
Significance
and Outcomes**

³Cormack BE et al. *JPEN*. 2021; ⁶Ross JR et al. *J Perinatol*. 2013.

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Prevention, Monitoring, and Management

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Screening and Biochemical Monitoring Strategies⁴

Risk Identification and Baseline Screening

High-risk neonates require baseline biochemical screening within 24 hours to assess phosphorus, potassium, magnesium, and calcium levels.

Daily Monitoring After Nutrition Start

Daily biochemical monitoring during first 3-5 days detects electrolyte abnormalities emerging post nutritional initiation.

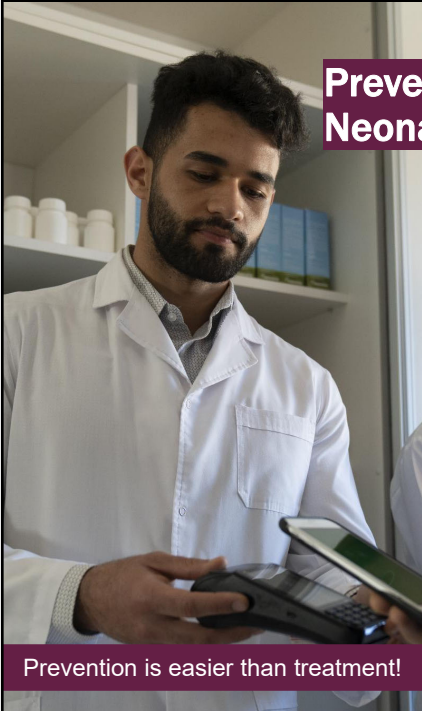
Standardized NICU Protocols

Standardized monitoring protocols ensure consistency and early identification of downward biochemical trends in neonates.

⁴Robinson DT, Taylor SN, Moya F. *J Perinatol.* 2023.

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Prevention and Management of Established Neonatal RFS^{8,12}

Prevention Strategies

Align nutrient delivery to infant metabolic needs; early phosphorus provision is crucial in parenteral nutrition.

Risk Identification and Tailored Nutrition

Identify high-risk infants early to customize amino acid advancement and electrolyte supplementation.

Management of Established RFS

Replace phosphorus promptly, correct magnesium and potassium, reassess nutrition plans.

Interdisciplinary Collaboration

Neonatologist, dietitian, pharmacist, and nurse collaboration ensures effective prevention and management.

Prevention is easier than treatment!

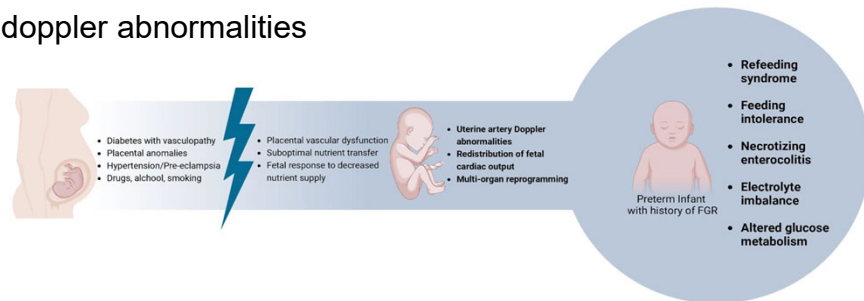
⁸Mihatsch WA et al. *Clin Nutr.* 2018; ¹²Wright TB et al. *JPEN.* 2025.

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Review: Infants at High-Risk for RFS^{4,11}

- ✓ Placental insufficiency
- ✓ Maternal preeclampsia, pregnancy-induced HTN, chronic HTN
- ✓ Umbilical artery doppler abnormalities
- ✓ SGA
- ✓ FGR



Early PN with high amino acids sets the stage for ALL ELBW and VLBW infants to show metabolic disturbances consistent with RFS

⁴Robinson DT, Taylor SN, Moya F. *J Perinatol.* 2023; ¹¹De Rose DU et al. *Front Nutr.* 2024.



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Management and Prevention of RFS – Establishing Guidelines for Clinical Practice

- ✓ Early identification of high-risk neonates
- ✓ Identify severity using established criteria
- ✓ Early phosphorus provision
 - ✓ Include in initial/early PN
 - ✓ Appropriate Ca:P molar ratio in PN during the first postnatal week
- ✓ Careful advancement of nutrition support (PN)
- ✓ Frequent electrolyte monitoring
 - ✓ Correct phosphorus, potassium and magnesium promptly as needed

For consideration: Early thiamin supplementation



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Reducing the Incidence of Neonatal RFS¹²

Quality Improvement Initiative in ELBW infants

- Increased early phosphorus provision
- Standardized biochemical monitoring
- Evaluated incidence of neonatal RFS before and after intervention

Outcome	Before Intervention	After Intervention
Refeeding Syndrome	11.9%	2.9%
Hypophosphatemia	53.5%	21.2%
Severe Hypophosphatemia	11.3%	1.2%

Early phosphorus provision combined with routine monitoring significantly reduced RFS and severe hypophosphatemia

¹²Wright TB et al. *JPEN*. 2025.



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Thiamin supplementation?^{13,14}

- Routinely provided with pediatric and adult RFS
- Not well-studied in neonatal population (QI studies, case reports)

Study		
Pilot Study (QI) Oyewole 2019	Early IUGR PN with added P and thiamin; 1:1 Ca:P ratio	No incidence of severe hypophosphatemia (< 2.5 mg/dL) with supplementation
Case Report Bradley 2023	SGA full-term neonate with hypoxic ischemic encephalopathy	Electrolyte derangements + lactic acidosis with PN; thiamin added (2 mg/kg); thiamin bolus (25 mg IV) given

¹³Oyewole V, Cerdona J, Bonck M. *Crit Care Med*. 2019.; ¹⁴Bradley C, Hansen A, Levy P, Hashim E. *J Parenter Enteral Nutr*. 2023.



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Suggested Biochemical Monitoring Schedule and Repletion Guidelines^{15,16}

Day	Labs
Birth	P, K, Mg, Ca (at 24 hours of life)
Postnatal Day 1-3	Daily electrolytes with Mg, P
Postnatal Day 4-7	Daily or every other day

Electrolyte	Indication	Replacement Dosing (Neonatal)
Hypophosphatemia	< 3 mg/dL	NaPhos 0.3 mmol/kg/dose IV
Hypokalemia	< 3 mmol/L	KCl 1 mEq/kg/dose IV
Hypomagnesemia	< 1 mg/dL	Mg Sulfate 50 mg/kg/dose IV

¹⁵Adapted from Texas Children's Hospital Pediatric Nutrition Reference Guide (13th ed), 2022.; ¹⁶Dabney, M. Refeeding Syndrome (RFS) Nutrition & Lab Considerations.



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PN Adjustment and Management^{5,10,15}

- Early PN: Consider a customized starter IUGR bag containing phosphorus, lower amino acids (≤ 3 g/kg/d), possibly thiamin
 - A suggested 0.33 mmol of phosphate is needed for every 1 g amino acid
- Calcium:Phosphorus molar ratio 0.8 to 1:1 during the first postnatal week
- Replete electrolytes outside of PN bag as needed
- PN adjustments as needed
 - Increase phosphorus by 0.3-0.5 mmol/kg/day
 - Maintain lower Ca:P ratio during first postnatal week
 - Increase potassium by 1 mEq/kg/d (0.5 mEq/kg with renal concerns)
 - Increase magnesium by 0.1 mEq/kg/d

⁵Bonsante F et al. *PLOS One*. 2013.; ¹⁰Bradford CV, Cober MP, Miller JL. *J Pediatr Pharmacol Ther*. 2021.; ¹⁵Adapted from Texas Children's Hospital Pediatric Nutrition Reference Guide (13th ed), 2022.



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Key Takeaways

Recognition of Neonatal Refeeding Syndrome

Neonatal RFS is a critical yet underrecognized condition in high-risk infants during nutritional rehabilitation.

Key Biochemical Indicator

Hypophosphatemia is the hallmark biochemical abnormality, essential for diagnosing RFS in neonates.

Risk Factors

Infants who are SGA, FGR, or ELBW with placental insufficiency or maternal preeclampsia have the highest risk.

Prevention and Management

Early phosphorus supplementation and structured monitoring significantly reduce the incidence of RFS.



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Learning Assessment—Question #1

Infants at risk for neonatal RFS include all the following, except:

- a. A 36-week infant with significant fetal growth restriction secondary to placental insufficiency
- b. A 24-week SGA infant born to a mother with severe preeclampsia
- c. A 30-week AGA infant delivered secondary to maternal spontaneous rupture of membranes
- d. A 27-week VLBW infant born to a mother with chronic HTN receiving starter PN with dextrose, 3.5 g/kg amino acids, and no electrolytes



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Question #2

Neonatal RFS is activated by the following factor(s):

- a. High amino acid and low electrolyte intakes
- b. High dextrose and fat intakes
- c. Delayed initiation of PN
- d. All the above

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Question #3

What are the most common biochemical findings associated with neonatal RFS?

- a. Hypophosphatemia, Hyperkalemia, Hypomagnesemia
- b. Hypophosphatemia, Hypocalcemia
- c. Hypophosphatemia, Hypokalemia, Hypercalcemia
- d. Hyperglycemia, Hyperkalemia

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Question #4

Which of the following management strategies are effective to minimize or prevent neonatal RFS?

- a. Formulate a customized starter PN solution with lower amino acids (≤ 3 g/kg) with phosphorus
- b. Provide a calcium-to-phosphorus molar ratio of 0.8-1:1 during the first postnatal week
- c. Monitor and electrolytes frequently and replete as needed
- d. All the above

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Questions?



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