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Thiamine-Responsive Acute Pulmonary Hypertension of Early Infancy: Unraveling the Metabolic Cascade, Clinical Spectrum, and Therapeutic Paradigms

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Systematic Review

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Abstract

Acute suprasystemic pulmonary arterial hypertension (PAH) in early infancy is a critical, life-threatening emergency classically associated with idiopathic etiologies, congenital cardiac anomalies, or persistent pulmonary hypertension of the newborn (PPHN). However, severe nutritional deficiency—specifically thiamine (vitamin B1) depletion—represents an underrecognized, highly reversible trigger of acute right ventricular strain and pulmonary hypertensive crisis. Because humans cannot synthesize thiamine endogenously and possess minimal storage capacity, rapidly growing infants with maternal dietary deprivations can deplete systemic stores within two weeks. Thiamine deficiency impairs essential carbohydrate metabolism and mitochondrial energy production, triggering systemic metabolic acidosis, dysregulated pulmonary vascular tone, and fulminant right-sided cardiac failure. This comprehensive review synthesizes the cellular, molecular, and metabolic mechanisms underlying thiamine deficiency-mediated pulmonary hypertension, details global epidemiological vulnerabilities, contrasts clinical presentations across international cohorts, and establishes detailed diagnostic decision trees, empirical therapeutic algorithms, and long-term preventive frameworks.

Key message

Thiamine deficiency is a critical, underrecognized, yet entirely reversible cause of acute suprasystemic pulmonary arterial hypertension in young infants. Dietary deprivation leads to severe metabolic acidosis, acute vasoconstriction, and right ventricular failure. Immediate empirical administration of parenteral thiamine, combined with targeted pulmonary vasodilators like sildenafil, aborts fatal cardiovascular collapse and achieves complete structural and hemodynamic normalization.

Introduction

Pulmonary arterial hypertension during early infancy carries substantial morbidity and mortality, often precipitating acute right ventricular failure when pulmonary arterial pressures equal or exceed systemic levels. While clinical evaluations prioritize congenital cardiovascular defects, pulmonary vascular obstructive disease, parenchymal lung disease, or persistent neonatal transition failure, acquired metabolic and nutritional derangements are critical differential diagnoses.

Thiamine is an essential water-soluble micronutrient that acts as an obligate coenzyme across central pathways of cellular energy generation and myocardial contractility. In settings characterized by restrictive maternal postpartum dietary customs, exclusive breastfeeding without maternal micronutrient repletion, or rapid infant somatic growth, severe thiamine deficiency manifests as acute cardiac beriberi, high-output failure, or profound pulmonary hypertensive crises. Because diagnostic biomarkers such as functional erythrocyte transketolase activity (ETKA) are often delayed or clinically unavailable, prompt clinical recognition and empirical thiamine administration are essential life-saving measures. The differential spectrum of acute infantile pulmonary hypertension is summarized in Table 1.

Table 1
Differential Considerations in Acute Infantile Pulmonary Hypertension

Etiological Category	Representative Conditions	Key Distinguishing Features
Nutritional / Metabolic	Thiamine deficiency (Vitamin B1 deficiency / Cardiac Beriberi) [1, 4, 6]	Rapidly reversible with thiamine; linked to maternal white-rice diet or exclusive breastfeeding [1, 4, 6].
Congenital Structural	Large VSD, PDA, AVSD, Total Anomalous Pulmonary Venous Connection (TAPVC)	Intracardiac/extracardiac shunting or anomalous venous drainage visualized on echocardiography.
Neonatal Transitional	Persistent Pulmonary Hypertension of the Newborn (PPHN)	Onset within immediate neonatal period (first hours to days of life); meconium aspiration or birth asphyxia history.
Pulmonary Parenchymal / Vascular	Bronchopulmonary dysplasia, Pulmonary Veno-Occlusive Disease (PVOD)	Prematurity history, structural parenchymal alterations on chest CT, lack of acute nutritional reversibility.

Table 1 Legend: Comparative clinical spectrum of acute pulmonary hypertension presentations in early infancy [1–6].

Part I: Biochemical and Pathophysiological Mechanisms

Cellular Bioenergetics and Mitochondrial Failure

Thiamine is converted into its biologically active form, thiamine pyrophosphate (TPP), via the action of thiamine diphosphokinase. Intracellular TPP serves as an indispensable prosthetic group for three rate-limiting multi-enzyme complexes:

- Pyruvate Dehydrogenase (PDH): Catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA, linking cytosolic glycolysis to the mitochondrial tricarboxylic acid (TCA) cycle. When PDH is inhibited, pyruvate cannot enter the Krebs cycle and is shunted into lactate via lactate dehydrogenase, generating profound hyperlactatemia.
- α -Ketoglutarate Dehydrogenase: Catalyzes the conversion of α -ketoglutarate to succinyl-CoA within the mitochondrial matrix. Its inhibition completely halts forward ATP generation through oxidative phosphorylation.
- Transketolase: Modulates the non-oxidative branch of the pentose phosphate pathway, crucial for synthesizing ribose-5-phosphate and regenerating cytosolic NADPH. NADPH depletion compromises glutathione reductase activity, precipitating severe oxidative stress and endothelial nitric oxide synthase (eNOS) uncoupling.

Figure 1 Legend: Interruption of central carbohydrate pathways during thiamine deficiency leading to mitochondrial bioenergetic exhaustion, impaired transketolase activity, and systemic lactic acidosis [1–4, 6].

Pathophysiology of Pulmonary Hypertensive Crises

When TPP levels drop below critical thresholds, uncoupling of oxidative phosphorylation shifts cellular metabolism toward anaerobic glycolysis, driving systemic accumulation of lactate and pyruvate [1, 4]. This bioenergetic crisis mediates pulmonary hypertensive collapse through three converging pathways:

- Hypoxic and Acidotic Pulmonary Vasoconstriction: Severe metabolic acidosis and localized microvascular hypoxia act as potent vasoconstrictive stimuli within the pulmonary arterial bed, abruptly elevating pulmonary vascular resistance (PVR) [1, 4].
- Right Ventricular Myocardial Energetic Failure: The high energetic requirements of the neonatal and infantile right ventricle rely heavily on efficient carbohydrate oxidation [4]. TPP depletion directly impairs cardiomyocyte ATP synthesis, diminishing right ventricular contractility precisely as afterload escalates [4].
- High-Output/Low-Resistance Systemic Vasodilation: Concomitant peripheral microvascular vasomotor collapse (classic wet beriberi) can augment venous return to the right heart, aggravating chamber dilation, tricuspid annular stretching, and suprasystemic right ventricular systolic pressures [4, 6].

Part II: Epidemiology, Risk Factors, and Clinical Characteristics

Vulnerable Patient Demographics

Because the human body maintains minimal thiamine storage (approximate half-life of two weeks), symptomatic deficiency can develop rapidly during periods of high metabolic demand. The peak incidence of infantile thiamine deficiency occurs between 1 and 7 months of age, with a particular concentration between 1 and 3 months [6]:

- Exclusive Breastfeeding from Deficient Mothers: Human milk thiamine concentrations directly reflect maternal dietary intake. Infants nursing from mothers consuming polished, washed white rice diets with minimal dietary diversification receive severely deficient milk.
- Maternal Cultural Food Restrictions: Postpartum dietary taboos restricting animal proteins, unpolished grains, and fresh produce accelerate maternal-infant thiamine depletion.
- High Somatic Metabolic Turnover: The disproportionately high caloric and carbohydrate utilization of early infancy precipitates rapid consumption of endocardial and vascular TPP reserves.

The main published case series highlighting clinical features and outcomes in infantile thiamine-responsive PAH are summarized in Table 2 [4–6].

Table 2
Clinical Characteristics Across Published Cohorts of Infantile Thiamine-Responsive PAH

Author & Year	Cohort Size (n)	Age Profile	Key Findings & Diagnostic Observations
Bhat et al. (2017) [4]	29 infants [4]	Mean: 78.5 days [4]	Acute right heart failure, severe metabolic acidosis, exclusively breastfed cohort from lower/middle socioeconomic backgrounds [4].
Narsimha et al.	55 infants	Mean: 3.9 months	High-output cardiac failure, documented maternal/infant low ETKA, rapid clinical and echocardiographic recovery post-thiamine.
Uppalapati et al. (2023) [5]	10 infants [5]	1–5 months (90% > 2 mos) [5]	Acute presentation of thiamine-responsive pulmonary arterial hypertension in early infancy [5].
Panigrahy et al. (2020) [6]	Clinical Series [6]	1–7 months [6]	Characterized the clinical spectrum of Thiamine-Responsive Acute Pulmonary Hypertension of Early Infancy (TRAPHEI) [6].

Table 2 Legend: Summary of published pediatric clinical series demonstrating infantile pulmonary arterial hypertension secondary to nutritional thiamine deficiency [4–6].

Part III: Diagnostic Framework and Multimodal Evaluation

Clinical Manifestations

Infants with thiamine-responsive PAH commonly present with acute respiratory distress, severe tachypnea, grunting, tachycardia, gallop rhythm, hepatomegaly, and varying degrees of cyanosis without initial evidence of congenital heart defects. The absence of hyperpyrexia or prominent inflammatory signs frequently leads to misdiagnosis as idiopathic PAH or structural cardiomyopathy.

Diagnostic Workup and Biochemical Profiling

- Laboratory Investigations: Baseline evaluation typically demonstrates profound lactic acidosis with an elevated anion gap, uncompensated by respiratory alkalosis [1, 4].
- Functional Biomarkers:
    - Erythrocyte Transketolase Activity (ETKA): Demonstrates baseline reduction in functional transketolase enzyme performance [2, 3].
    - Thiamine Pyrophosphate Effect (TPPE): An in vitro increase in transketolase activity $> 15\% - 25\%$ following exogenous TPP addition confirms functional intracellular thiamine exhaustion [2, 3].
- Electrocardiography (ECG): Demonstrates classic features of right heart strain, including tall P waves (RA enlargement), marked right axis deviation, and tall R waves in right precordial leads (RV hypertrophy).

- Echocardiography: Key imaging modality revealing gross right atrial and right ventricular dilation, pulmonary artery enlargement, flattening or systolic leftward bowing of the interventricular septum, moderate-to-severe tricuspid regurgitation, and suprasystemic estimated RV systolic pressures ($> 100\ :\mathrm{mmHg}$) in the absence of intracardiac shunts.

The multimodal diagnostic triage pathway for suspected nutritional PAH is illustrated in Fig. 3 [1–4, 6].

Part IV: Therapeutic Management and Clinical Outcomes

Acute Interventional Strategy

Given the high risk of rapid circulatory collapse and cardiac arrest in suprasystemic PAH, empirical thiamine therapy should be instituted immediately upon suspicion, without awaiting confirmatory enzyme assays [1, 5]:

- Parenteral Thiamine Administration: Intravenous or intramuscular thiamine hydrochloride (typically 50–100 mg/day) delivers rapid bioavailability to replenish intracellular TPP, reactivate PDH and transketolase, and restore aerobic oxidative phosphorylation [1, 4].
- Pulmonary Vasodilator Therapy: Targeted pulmonary vasodilators, such as oral sildenafil (1–3 mg/kg/day divided every 6 to 8 hours), reduce right ventricular afterload and break the cycle of acute right ventricular ischemic failure during the initial 48–72 hours.
- Correction of Acid-Base Imbalances: Careful hemodynamic and respiratory support to avoid hypoxemia and acidosis-induced pulmonary vascular reactivity [1, 4].
- Maternal Treatment: Concurrent oral thiamine supplementation (100 mg daily) and dietary re-education for the lactating mother to ensure sufficient micronutrient transfer via breast milk.

The chronological recovery milestones and treatment phases are outlined in Table 3 [1, 4, 6].

Table 3
Phased Management Strategy and Clinical Milestones in Thiamine-Responsive PAH

Treatment Phase	Primary Objective	Therapeutic Modality	Expected Clinical Response
Hyperacute (Hours 0–24)	Restore cellular ATP synthesis and reduce acute RV afterload [1, 4]	IV/IM Thiamine (50–100 mg) + Pulmonary Vasodilator (e.g., Sildenafil) + Oxygen therapy [1, 4]	Rapid clearance of metabolic acidosis, reduction in tachypnea, hemodynamic stabilization [1, 4].
Subacute (Days 2–7)	Normalize pulmonary pressures and right ventricular chamber dimensions	Continued daily thiamine supplementation + targeted vasodilator titration	Drastic drop in RVSP (e.g., from suprasystemic levels down to ~ 20 mmHg), resolution of tricuspid regurgitation.
Maintenance & Prevention (Months 1–6)	Prevent recurrence, normalize maternal milk stores, promote milestone attainment	Maternal/infantile oral thiamine + dietary diversification + serial echocardiographic follow-up	Complete structural normalization of right heart chambers, normal growth and development.

Table 3 Legend: Chronological intervention framework for the clinical stabilization and resolution of infantile thiamine deficiency-associated pulmonary arterial hypertension [1, 4, 6].

Prognosis and Long-Term Recovery Dynamics

Unlike anatomical or primary idiopathic pulmonary arterial hypertension, thiamine-responsive PAH exhibits exceptional reversibility when managed promptly [1, 4, 6]. Marked improvements in tachypnea, arterial oxygenation, and blood lactate levels typically occur within 24 to 48 hours of thiamine administration [1, 4]. Serial echocardiography confirms rapid reduction in right ventricular systolic pressure (e.g., dropping from suprasystemic levels $> 140\backslash:\mathrm{mmHg}$ down to normal physiological pressures within 7 to 10 days), accompanied by complete long-term remodeling and chamber normalization at medium- and long-term follow-up.

Conclusions

Thiamine deficiency is a critical, completely reversible cause of acute suprasystemic pulmonary arterial hypertension and right heart failure in young infants [1, 4, 6]. Disruptions in mitochondrial carbohydrate metabolism lead to severe lactic acidosis and severe pulmonary vasoconstriction [1, 4]. Because exclusive breastfeeding by mothers with unsupplemented, polished-grain diets places infants at high risk, clinicians must maintain a high index of suspicion [1, 2, 4]. Immediate initiation of empirical parenteral thiamine, augmented by pulmonary vasodilators like sildenafil, rapidly resolves life-threatening pulmonary hypertension, restores normal cardiac architecture, and prevents fatal cardiovascular collapse [1, 4, 6].

Abbreviations

• 4D Flow CMR
Four-Dimensional Flow Cardiovascular Magnetic Resonance
• ATP
Adenosine Triphosphate
• ECG
Electrocardiography
• ETKA
Erythrocyte Transketolase Activity
• IV/IM
Intravenous / Intramuscular
• NO
Nitric Oxide
• PAH
Pulmonary Arterial Hypertension
• PAP
Pulmonary Artery Pressure
• PDH
Pyruvate Dehydrogenase
• PH
Pulmonary Hypertension
• PPHN
Persistent Pulmonary Hypertension of the Newborn
• PVR
Pulmonary Vascular Resistance
• RA
Right Atrium / Right Atrial
• ROS
Reactive Oxygen Species
• RV
Right Ventricle / Right Ventricular
• RVOTO
Right Ventricular Outflow Tract Obstruction
• RVSP
Right Ventricular Systolic Pressure
• TAPSE
Tricuspid Annular Plane Systolic Excursion
• TCA
Tricarboxylic Acid

• TEE
Transesophageal Echocardiography
• TOF
Tetralogy of Fallot
• TPP
Thiamine Pyrophosphate
• TPPE
Thiamine Pyrophosphate Effect
• TR
Tricuspid Regurgitation
• TRAPHEI
Thiamine-Responsive Acute Pulmonary Hypertension of Early Infancy
• TTE
Transthoracic Echocardiography
• VSD
Ventricular Septal Defect
• WSS
Wall Shear Stress

Declarations

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Author contribution:

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References

1. Qureshi UA, Sami A, Altaf U, et al. Thiamine responsive acute life threatening metabolic acidosis in exclusively breast-fed infants. Nutrition. 2016;32(2):213–216.
2. Whitfield KC, Bourassa MW, Adamolekun B, et al. Thiamine deficiency disorders: diagnosis, prevalence, and a roadmap for global control programs. Ann N Y Acad Sci. 2018;1430(1):3–43.
3. Soukaloun D, Lee SJ, Chamberlain K, et al. Erythrocyte transketolase activity, markers of cardiac dysfunction and the diagnosis of infantile beriberi. PLoS Negl Trop Dis. 2011;5(2):e971.
4. Bhat JI, Rather HA, Ahangar AA, et al. Shoshin beriberi-thiamine responsive pulmonary hypertension in exclusively breastfed infants: A study from northern India. Indian Heart J. 2017;69(1):24–27.
5. Uppalapati T, Krishna YS, Eregowda A. Clinical spectrum of infants with thiamine responsive pulmonary arterial hypertension. Int J Contemp Pediatr. 2023;10(3):380–386.
6. Panigrahy N, Chirla DK, Shetty R, et al. Thiamine-Responsive Acute Pulmonary Hypertension of Early Infancy (TRAPHEI)—A Case Series and Clinical Review. Children (Basel). 2020;7(11):199.

Figures

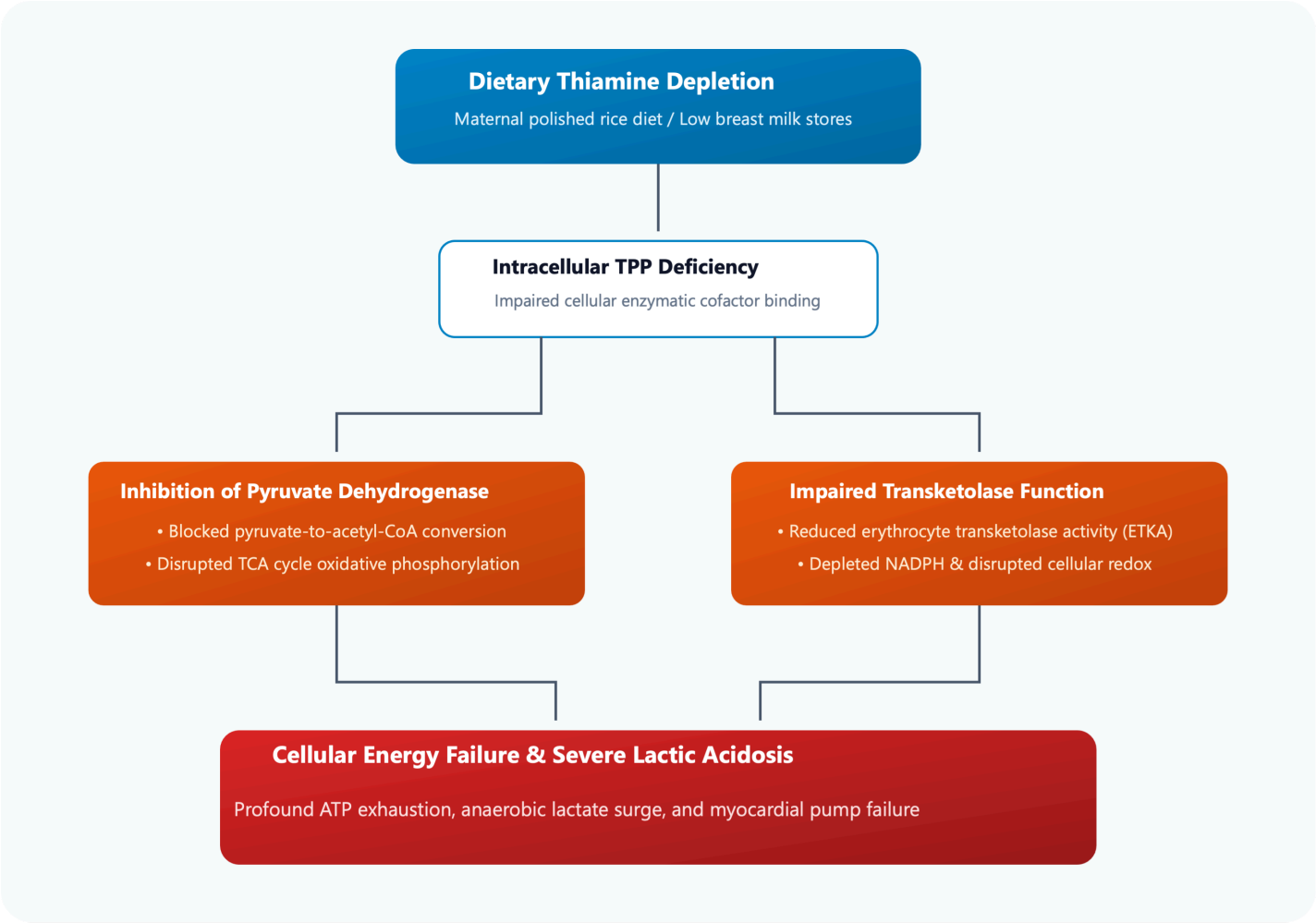


Figure 1

Cellular Bioenergetics and Metabolic Cascade in Thiamine Depletion

Legend: Interruption of central carbohydrate pathways during thiamine deficiency leading to mitochondrial bioenergetic exhaustion, impaired transketolase activity, and systemic lactic acidosis [1–4, 6].

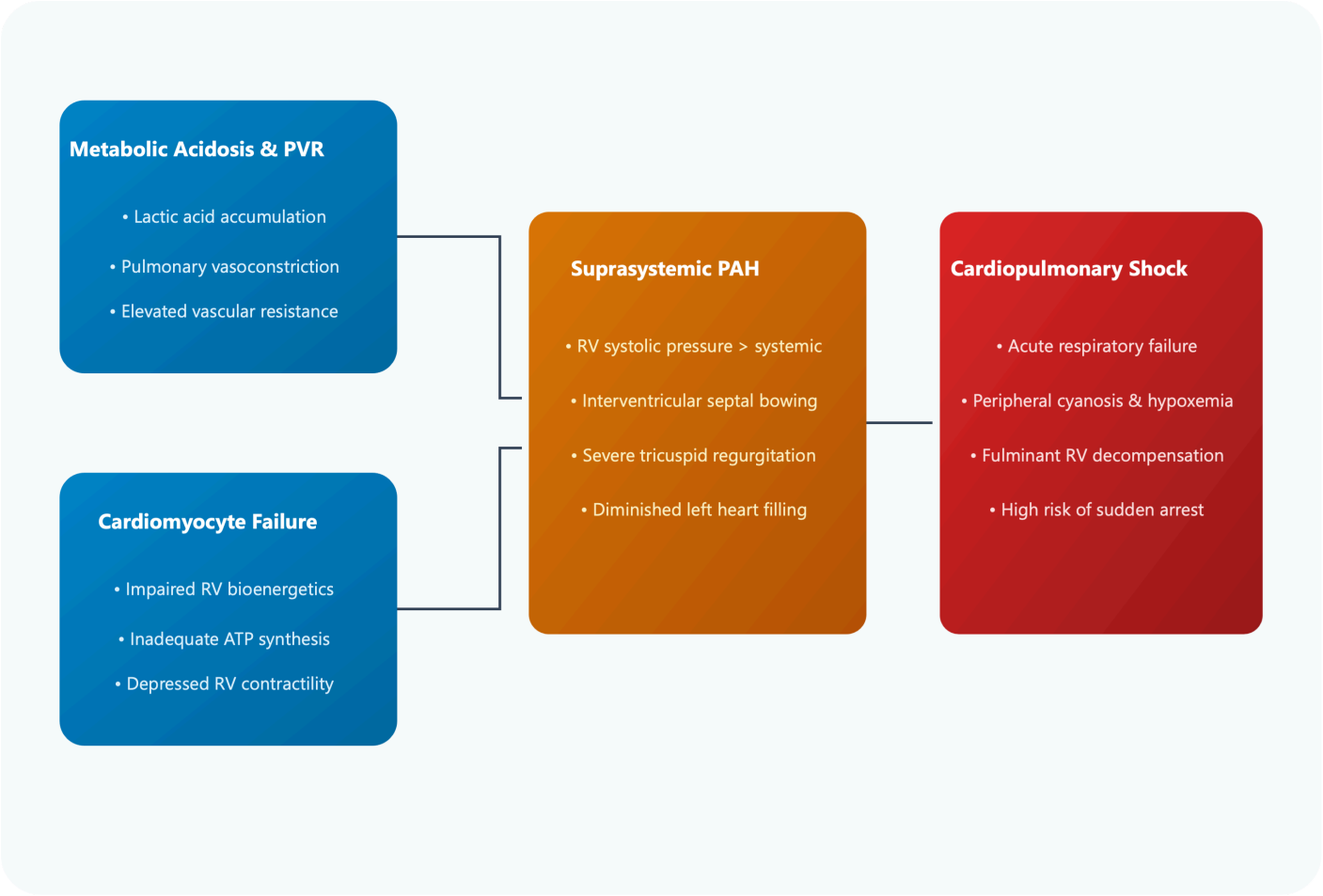


Figure 2

Hemodynamic Progression to Acute Cardiopulmonary Shock

Legend: Pathophysiological progression from localized metabolic and bioenergetic derangements to acute suprasystemic pulmonary hypertension and right ventricular collapse [1, 4, 6].

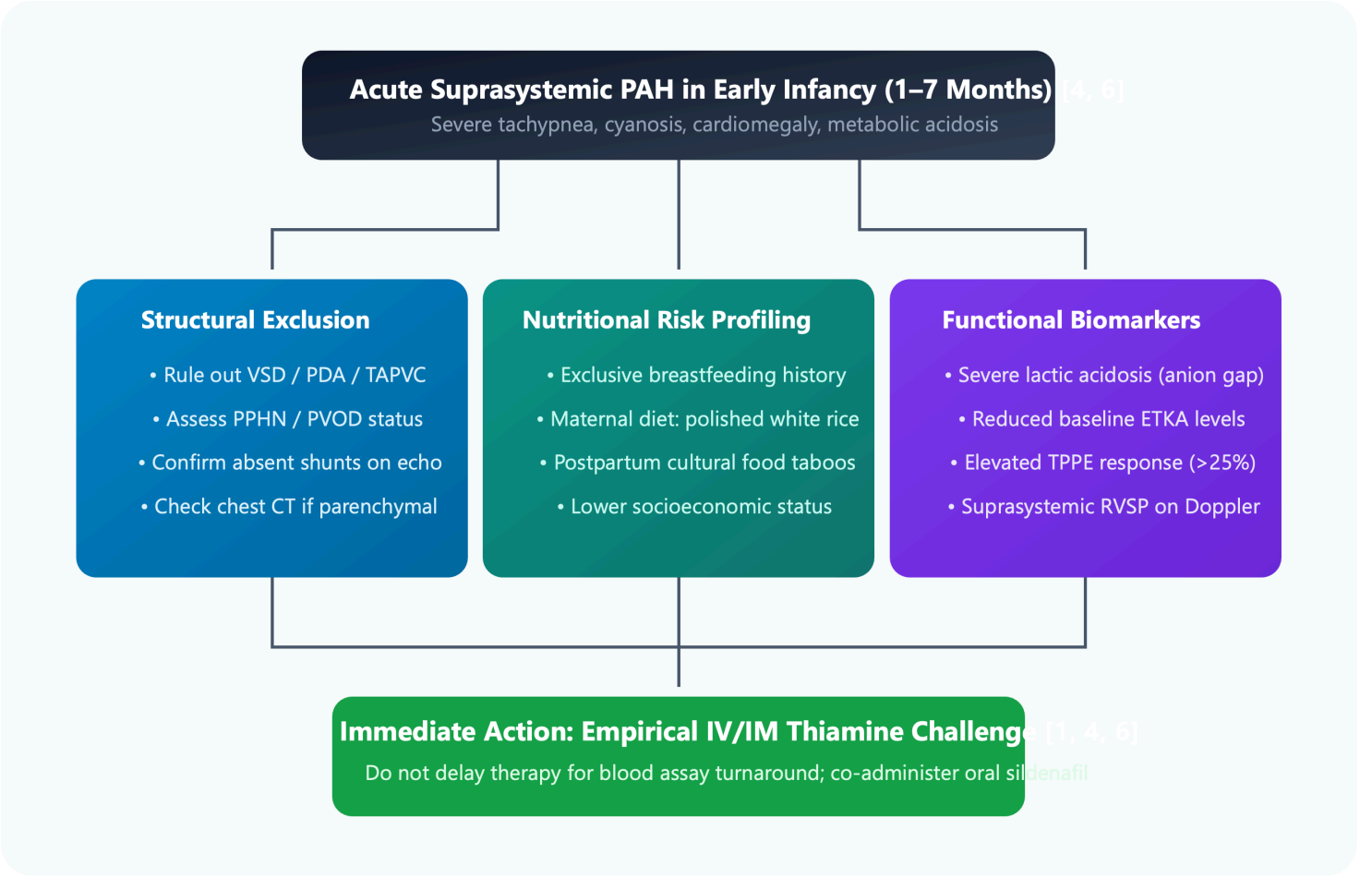


Figure 3

Diagnostic Decision Pathway for Infantile Pulmonary Hypertensive Crisis

Legend: Multimodal diagnostic algorithm integrating anatomical exclusion of congenital cardiac defects, dietary risk factor identification, and immediate empirical therapeutic trial [1–4, 6].

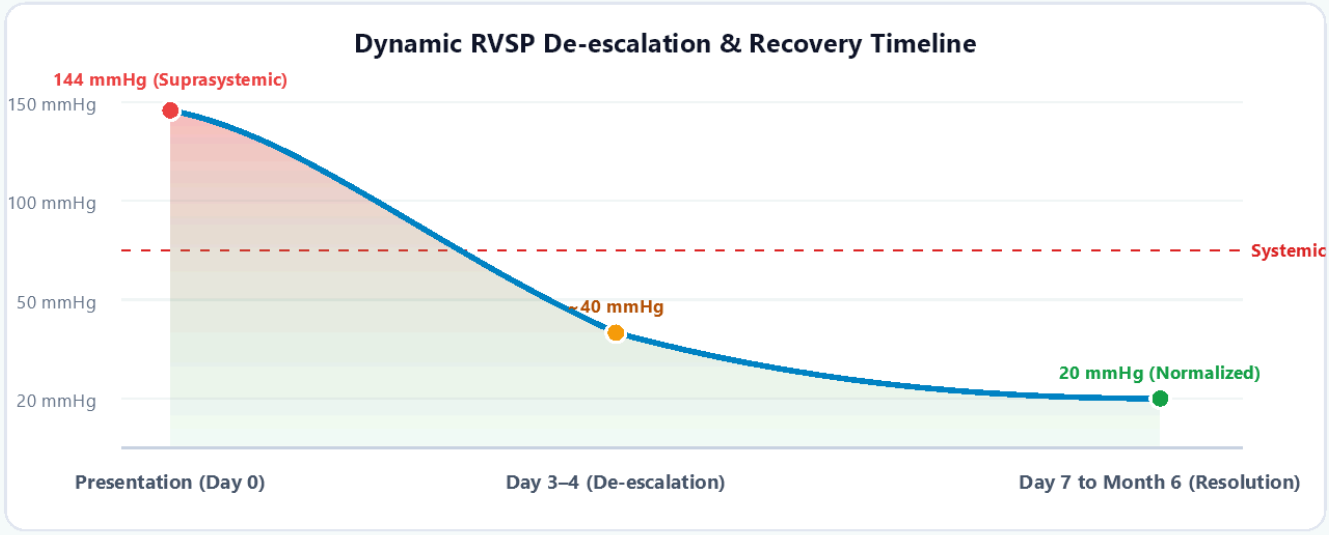


Figure 4

Dynamic Hemodynamic De-escalation Following Thiamine Replacement

Legend: Illustrative timeline of right ventricular systolic pressure (RVSP) regression following immediate parenteral thiamine administration and targeted pulmonary vasodilator therapy [1, 4, 6].

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- groupimage1.jpeg