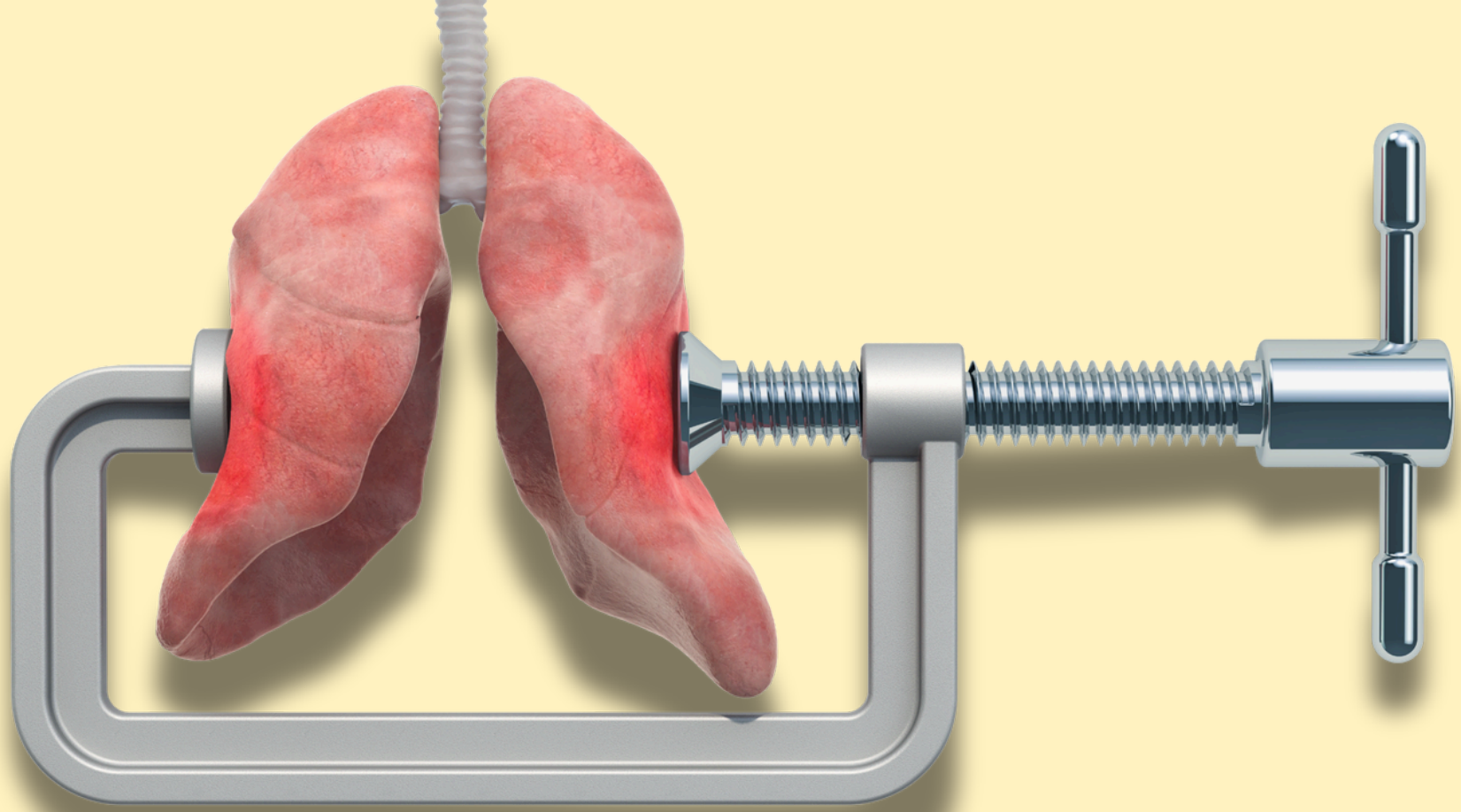




Persistent Pulmonary Hypertension of the Newborn (PPHN): Review and Management

Source: Chojnacka K, Singh Y, Gahlaut S, Blaz W, Jerzak A, Szczapa T. Persistent Pulmonary Hypertension of the Newborn: A Pragmatic Review of Pathophysiology, Diagnosis, and Advances in Management. Biomedicines 2025, 13, 2332.

HIPN/PPHN: Hypertension Persistent Pulmonary Syndrome of the Newborn
RVP/PVR: Resistance Pulmonary Vascular
OI: Oxygenation Index

iNO: Inhaled Nitric Oxide
ECMO: Extracorporeal Membrane Oxygenation
BNP/NT-proBNP: B-type natriuretic peptide

PDE: Phosphodiesterase
PGE1: Prostaglandin E1
CCHD: Critical Congenital Heart Disease

The Collapse of the Fetal-Neonatal Transition

Normal Physiology

Abrupt drop in Pulmonary Vascular Resistance (PVR) at birth.

Lung expansion and oxygenation promote vasodilation.

Functional closure of the foramen ovale and ductus arteriosus.

The pathophysiology of HIPN

Sustained Vasoconstriction: Failure to reduce pulmonary vascular resistance (PVR).

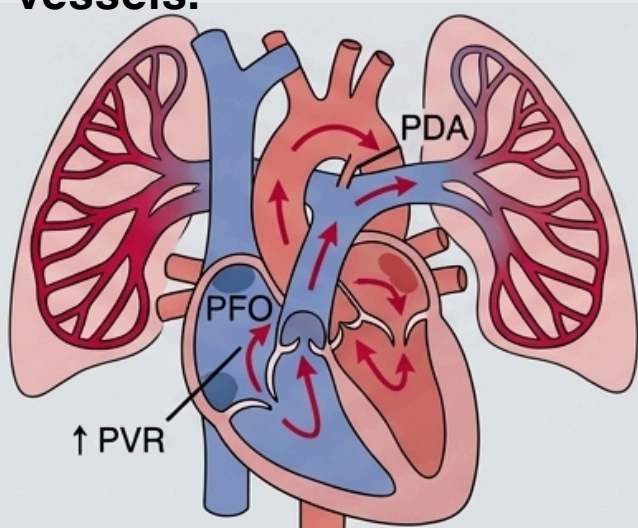
Right-to-Left (R-to-L) Shunt: Blood is diverted away from the lungs through the foramen ovale and ductus arteriosus.

Consequence: Hypoxemia severe and refractory to the use of supplemental oxygen, culminating in acute respiratory failure.

The 3 Clinical Phenotypes: Where is the Resistance?

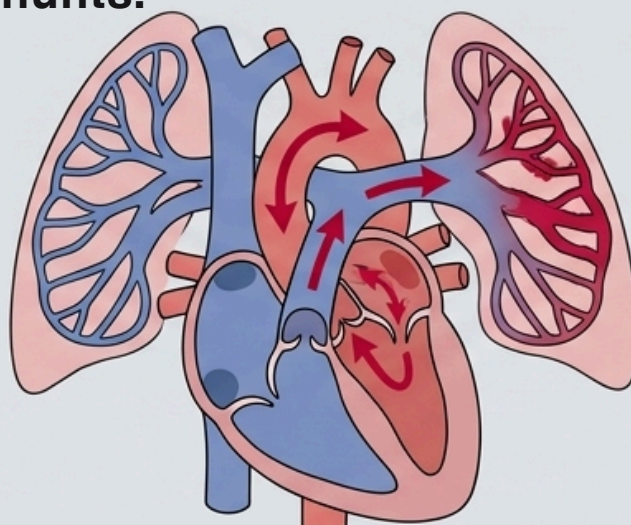
Type 1 (Pre-Capillary)

Most Common Phenotype: Primary Increase in Pulmonary Vascular Resistance (PVR).
Bottleneck: Constricted or thickened pre-capillary vessels.



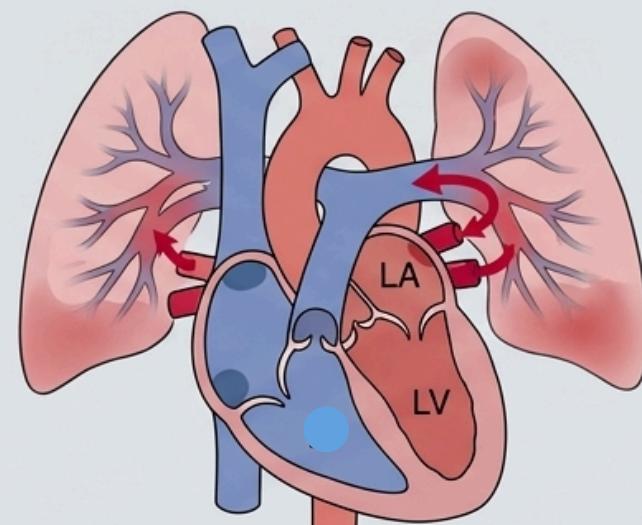
Type 2 (Increased Flow)

Vascular Remodeling
Mechanism: Increased pulmonary blood flow leading to hypertension. **Bottleneck:** Persistent arteriovenous malformations or left-to-right shunts.



Type 3 (Post-Capillary)

Venous Hypertension: Increased venous pressure/Left Ventricular (LV) Dysfunction. **Bottleneck:** Venous obstruction (e.g., TAPVC) or LV failure.





Etiology and Risk Factors



Maternal and Genetic Factors

- **Maternal diabetes and smoking.**
- **Use of medications during pregnancy (NSAIDs, SSRIs).**
- **Genetic predisposition: polymorphisms in the eNOS gene (failure in endothelial nitric oxide production).**

Fetal and Antepartum Factors

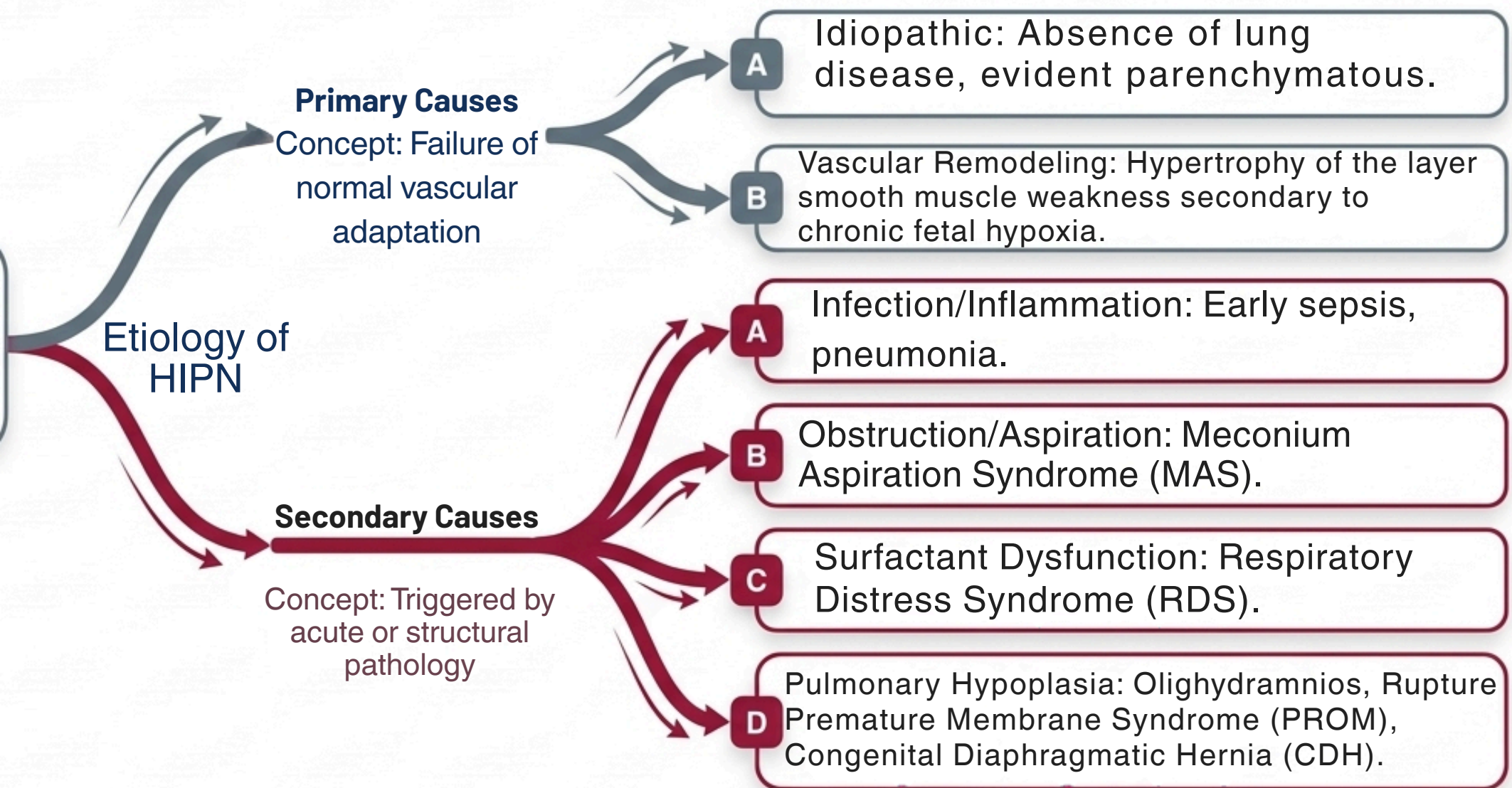
- **Fetal hypoxia and acidosis.**
- **PPROM (Prolonged Premature Rupture of Membranes).**
- **Congenital Diaphragmatic Hernia (CDH) and pulmonary hypoplasia.**

Neonatal Factors (Secondary HIP)

- **SAM: Meconium Aspiration Syndrome (classic trigger).**
- **RDS: Respiratory Distress Syndrome.**
- **Severe perinatal asphyxia.**
- **Neonatal pneumonia.**
- **Neonatal Sepsis.**

Etiology and Risk Factors

The pathogenesis of HIP is multifactorial, encompassing genetic, environmental, and physiological factors.





Clinical Diagnosis

Clinical Presentation (suspected)

Cyanosis and hypoxemia refractory to oxygen. Early respiratory distress. Heart murmur (excessive flow or tricuspid regurgitation).

Critical Differential Diagnosis (Mandatory Exclusion)

Congenital heart disease (CHD) that mimics hypothyroidism should be ruled out.

TAPVC (Total Anomalous Pulmonary Venous Drainage).

TGA (Transposition of the Great Arteries).

Pulmonary Atresia (with/without VSD).

Severe Tetralogy of Fallot / Tricuspid Atresia.

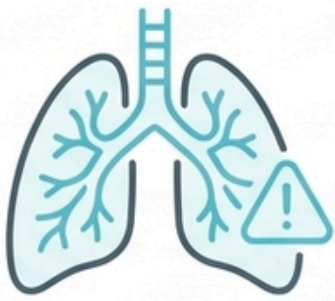
Obstructive diseases of the left heart (Coarctation of the Aorta, HLHS).

Confirmation (Echocardiography)

Isolated primary or secondary HIPN.



Clinical Diagnosis



Refractory Hypoxemia

Low levels of arterial oxygenation that do not respond adequately to conventional oxygen supplementation.



Cyanosis and Respiratory Distress

Early signs of respiratory failure that appear soon after birth, requiring immediate intervention.



Oxygenation Differential (Pre/Post-ductal)

Difference in oxygen saturation (SpO₂) > 5-10% between the right hand (pre-ductal) and the lower limbs (post-ductal), confirming shunt via PDA.



Heart Murmurs

Audible flow murmurs due to shunt via PDA, tricuspid regurgitation, or associated underlying congenital defects.

Immediate recognition is vital to prevent long-term tissue damage.

Differential Diagnosis

Exclusion of Critical Congenital Heart Disease (CCHD)

Common Presentation:
Severe cyanosis +
Refractory hypoxemia

Elimination
Filter

HIPN (Physiological)

Reversible vascular dysfunction.
Treatment: Vasodilators (iNO).

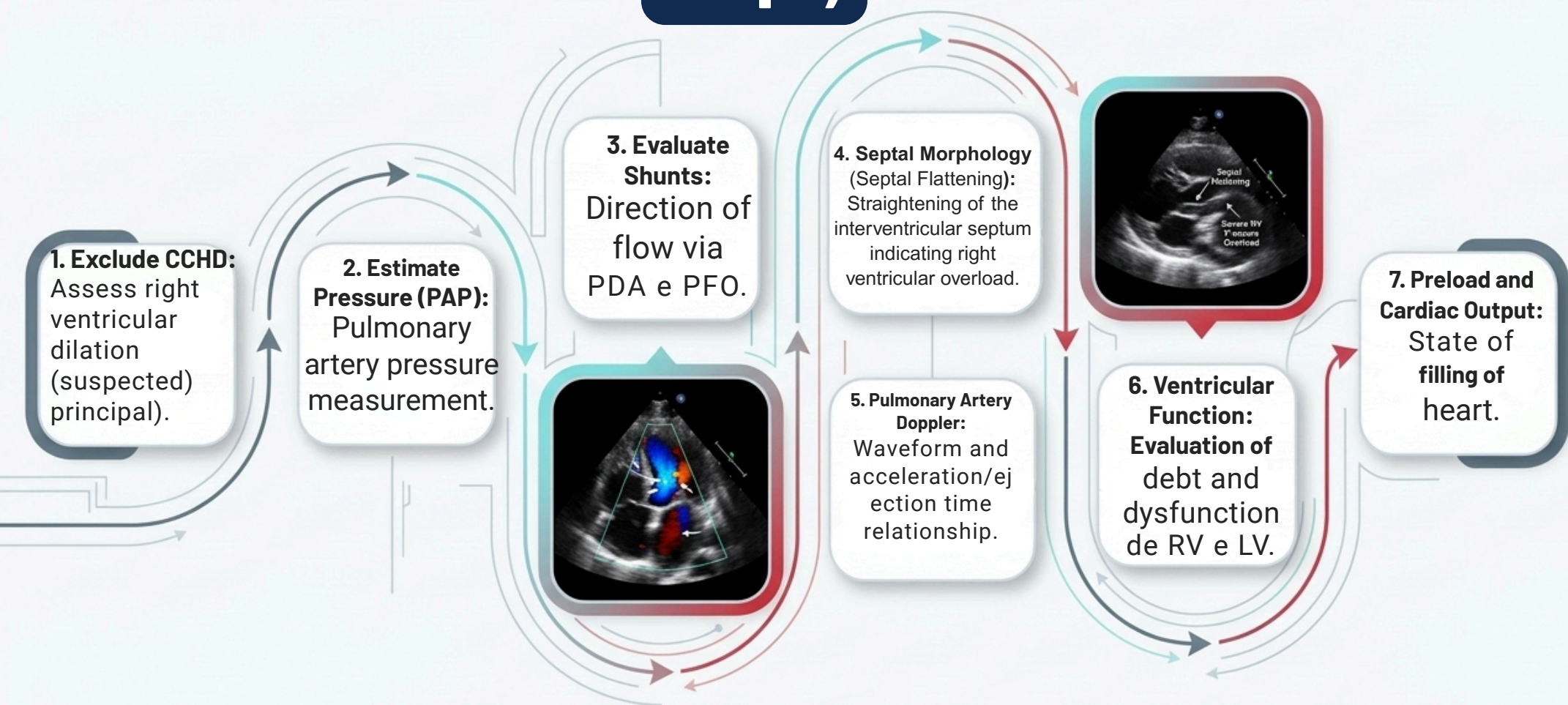
CCHD (Structural)

Masked Anomalies: Venous Return

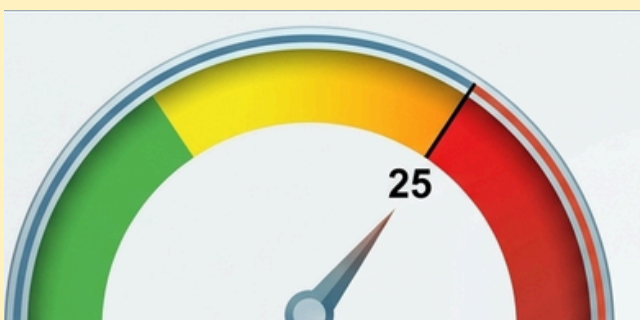
Total Anomalous Pulmonary Artery (TAPVC), Transposition of the Great Arteries (TGA), Pulmonary Atresia, Severe Tetralogy of Fallot, Left Obstructive Lesions.

The indiscriminate use of vasodilators without prior echocardiography may be detrimental in specific structural anomalies.

Gold Standard: Bedside Echocardiography (7 steps)



Gravity Stratification: OI and Biomarkers



Metric 1: Oxygenation Index (OI)
Calculation of dependence on ventilatory support for oxygenation. **OI > 25**: Indicates severe hypoxemia. Defines a very high risk of pulmonary dysfunction and is a critical indicator for ECMO evaluation.



Metric 2: Right Ventricular Strain (BNP/ NT-proBNP)

Released by the myocardium in response to pressure/volume overload.

NT-proBNP: More stable (half-life of 60-120 min), preferred for reproducible tests. Predictive Threshold: BNP > 850 pg/mL demonstrated high density for predicting the need for iNO. Clinical Use: Essential for serial monitoring (trends) and prediction of rebound HIP during weaning.

Severity Classification: Oxygenation Index (OI)

The primary marker to guide the escalation of respiratory support and ECMO.

The screenshot shows the 'neofast' app interface for calculating the Oxygenation Index (OI). The title bar is blue with a back arrow and the 'neofast' logo. Below it is a purple header with the text 'Oxygenation Index - OI'. The main content area is white and contains a purple box with the formula
$$OI = (MAP \times FiO_2 \times 100) \div PaO_2$$
. Below the formula are three input fields: 'MAP (cmH2O)', 'FiO2', and 'PaO2 (mmHg)'. Below these fields is a note: 'Values between 0.21 and 1.00, where 1.00 equals 100% and 0.40 equals 40%, for example.' At the bottom is a purple box labeled 'Reference'.

$$OI = (FiO_2 \times MAP \times 100) / PaO_2$$

(Fraction of Inspired Oxygen x Mean Airway Pressure x 100) / Partial Pressure of Oxygen

Mark S. Mammen (editor), Anton F. L. G. van Roon (editor), Steven M. Donn (editor) - Manual of neonatal respiratory care. (2022), p. 628 — ECMO criterion.

Get IO with classification and intervention suggestions using NeoFast.

←

neofast

Oxygenation Index - OI

Σ FORMULA

$$OI = (MAP \times FiO_2 \times 100) \div PaO_2$$

MAP (cmH2O)

10

FiO₂

1

Values between 0.21 and 1.00, where 1.00 equals 100% and 0.40 equals 40%, for example.

PaO₂ (mmHg)

35

28.57

Oxygenation index



Green Zone (OI < 10):
HIPN Leve

Continuous monitoring, ventilatory support, and baseline oxygenation.

Yellow Zone (OI 10-25):
Moderate to Severe HIPN

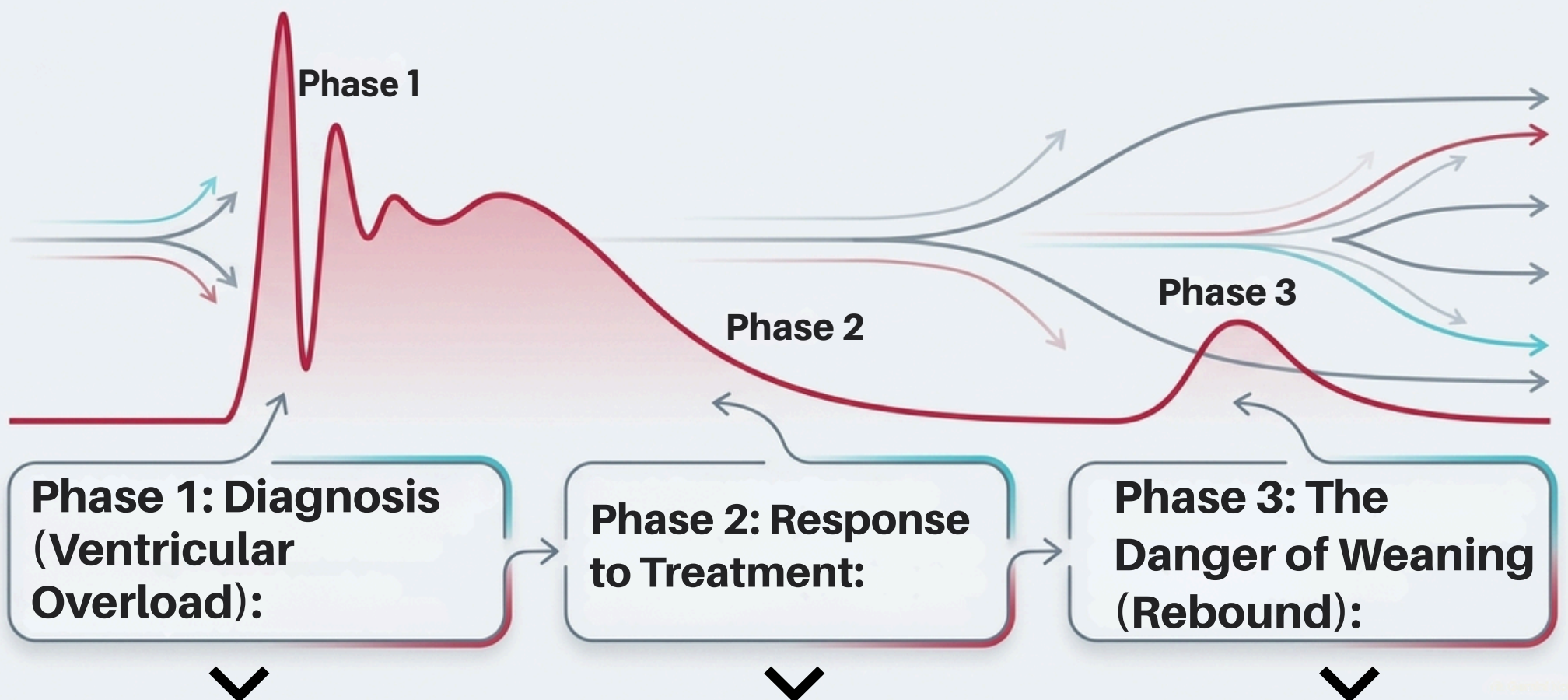
Threshold for pharmacological intervention. Initiation of targeted vasodilators (iNO).

Red Zone (OI > 25):
Critical Respiratory Failure

Imminent risk of severe pulmonary dysfunction. Indication for aggressive rescue therapies and immediate evaluation for ECMO.

The Strategic Role of Biomarkers

BNP and NT-proBNP: More than just diagnosis, tools for longitudinal monitoring.



Consistently elevated levels in HIPN compared to other causes of respiratory failure. Insight: BNP > 850 pg/mL predicts high sensitivity to the need for iNO.

The half-life of BNP (~20 min) and the stability of NT-proBNP (~60-120 min) allow for real-time assessment of right ventricular strain relief.

Serial monitoring is crucial for predicting rebound pulmonary hypertension during vasodilator withdrawal.

Fundamentals of Management

Gentle Ventilation (Optimized)

Lung protection strategy to minimize barotrauma

Pre-ductal oxygen saturation targets between 93-97% (PaO₂ 55-80 mmHg) - hyperoxia increases the formation of free radicals and lung injury.

Hemodynamic Support and Sedation

Maintaining systemic pressure to minimize right-to-left shunting. Appropriate sedation to manage pain and stress, avoiding spikes in vascular resistance.

Surfactant Therapy and Metabolic Correction

Surfactant administration in cases associated with deficiencies (e.g., RDS, MAS). Strict correction of electrolyte imbalances and acidosis.

The basis of treatment focuses on preventing further lung damage before escalating to vasodilators.

Specific targeted therapies (iNO, Sildenafil) require prior hemodynamic stability.

First-Line Therapy: Inhaled Nitric Oxide (iNO)

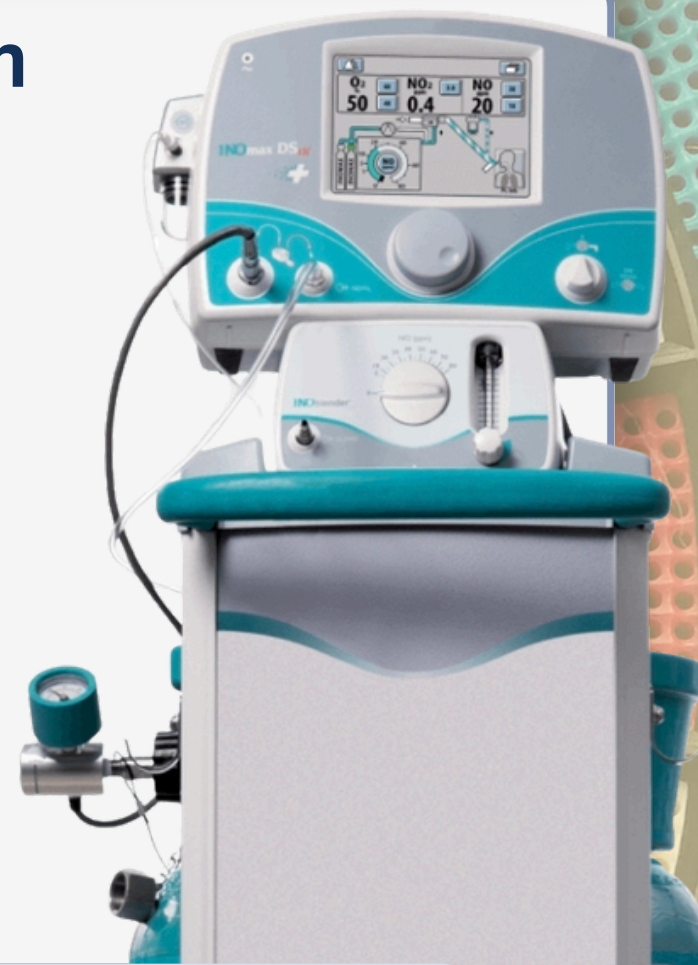
Mechanism of Action: Selective pulmonary vasodilation (direct relaxation of smooth muscle without affecting systemic pressure). Ultra-short half-life (2 to 6 seconds). Expected clinical response within 30 minutes.

Standard Initial Dose: **20** ppm
(Term or near term).

Specific Considerations:

Preterms: **5 a 10** ppm.

Refractory cases: 40–80 ppm
if there is no initial response.



Targets: Reduction $>10\%$ in Oxygenation Index, increase $>10\%$ in PaO₂, and reduction $>10\%$ in Pulmonary Artery Pressure (PASP).

Targeted Vasodilators I: Sildenafil - loading dose

Prescription Card Sildenafil

Phosphodiesterase type 5 (PDE5) inhibitor.

Intravenous route

Loading Dose: 0,4 mg/kg over 3 hours

Maintenance: 0,067 mg/kg/hour.

Via oral

Initial Dose: 0,5mg/kg

(or 1 mg/kg every 6 hours for 48-72 hours).

Maintenance: 1 a 2 mg/kg every 6 hours.

neofast

Continuous medication

Sildenafil

IV continuous

0.8mg/mL Solution

10mg/12.5mL Solution

Continuous

Loading

Weight (kg)

2

Desired dose (mg/kg)

0.4

Suggested Loading dose: 0.4 mg/kg/day

Sildenafil	
IV continuous - 0.8mg/mL Solution	
Dose	0.8mg
Dose	1mL
Dilute with NS	1mL
Final concentration	0.4mg/mL
Total volume to be administered	2mL
Drip	0.67mL/h
Infusion rate	3h

Targeted Vasodilators I: Continuous Sildenafil

Prescription Card Sildenafil

Phosphodiesterase type 5 (PDE5) inhibitor.

Intravenous route

Loading Dose: *0,4* mg/kg over 3 hours

Maintenance: *0,067* mg/kg/hour.

Via oral

Initial Dose: *0,5* mg/kg

(or 1 mg/kg every 6 hours for 48-72 hours).

Maintenance: *1 a 2* mg/kg every 6 hours.

neofast

Continuous medication

Sildenafil

IV continuous

0.8mg/mL Solution

10mg/12.5mL Solution

Continuous

Loading

Weight (kg)

2

Desired dose (mg/kg/h)

0.067

Continuous dose: 0.067 mg/kg/h

Intended drip (mL/h)

0.5

Sildenafil

IV continuous - 0.8mg/mL Solution

Dose	4.02mL
Dilute with NS	7.98mL
Final concentration	0.27mg/mL
Total in 24 hours	12mL

Targeted Vasodilators I: Continuous Milrinone

neofast

Continuous medication

Milrinone

IV continuous

1mg/mL0.2mg/mL

LoadingMaintenance

Weight (kg)
2

Desired dose (mcg/kg/min)
0.25

Suggested maintenance dose: 0.3 to 0.75 mcg/kg/min

Intended drip (mL/h)
0.2

Milrinone

IV continuous - 1mg/mL

Dose	0.72mL
Dilute with NS , D5W	4.08mL
Final concentration	150mcg/mL
Total in 24 hours	4.8mL
Interval	Continuous by 35h

Prescription Card Milrinone

PDE3 inhibitor. Excellent for left ventricular/right ventricular dysfunction.

Continuous intravenous administration

Dose: *0,2 a 1* mcg/kg/min

Ideal target range: 0.25 to 0.75 mcg/kg/min

It is especially indicated if left or right ventricular dysfunction is confirmed by echocardiography.

Targeted Vasodilators II: Bosentan and Prostanoids

Prescription Card

Bosentan

Endothelin Receptor Antagonist.
Frequent use as adjunctive therapy
or if iNO fails/is unavailable.

Via Oral (VO):

1 a 2 mg/kg
1 to 2 mg/kg every 12 hours.

Prescription Card

**Prostanoids -
Powerful vasodilators.**

Iloprost Inhaler:

1 to 2.5 mcg/kg every 2 to 4 hours.

Intravenous (IV) Epoprostenol:

1 to 2 ng/kg/min. 50 to 80 ng/kg/min

**Note: Treprostinil may also be
considered in this functional class.**

Inotropic Support, Vasopressor and Ductal Patency

Critical Highlight: Prostaglandin E1 (PGE1)

Indication: HIPN Phenotype 3 or Right Ventricular Failure (ductal closure with RV dysfunction). Keeps the ductus arteriosus open as a 'safety valve'.

Dose IV: 5 to 10 ng/kg/min.

Table of Vasopressors and Inotropes (If MAP < 45-50 mmHg post-volume):

Drug	Dose	Specific Indication
Adrenaline	0,05 0,4 mcg/kg/min	If LV function decreases or pulse pressure decreases
Norepinephrine	0,05 0,4 mcg/kg/min	If sepsis, SVR, or elevated pulse pressure.
Dobutamine	5 - 20 mcg/kg/min	Alternative if milrinone is inadequate or without echo.
Vasopressin	0.01 -0.05 U/kg/h	In cases of resistant hypotension.
Hydrocortisone	2-2.5 mg/kg every 6 hours	Adjunct in blood pressure support.

PGE1

≡

neofast

Continuous medication

+

Alprostadil (Prostin® and Prostavasin®)

▼

IV continuous

500mcg/mL Solution

10mcg/mL Powder

20mcg/mL Powder

No Fluid Restriction

Fluid restriction

+

Weight (kg)

+

Desired dose (mcg/kg/min)

+

Intended drip (mL/h)

Additional information

Bibliographical references

>

Please note: the information presented in this application is taken from bibliographical references

≡

neofast

Continuous medication

+

Alprostadil (Prostin® and Prostavasin®)

▼

IV continuous

500mcg/mL Solution

10mcg/mL Powder

20mcg/mL Powder

No Fluid Restriction

Fluid restriction

+

Weight (kg)

2

+

Desired dose (mcg/kg/min)

0.01

Suggested dose: 0.01 to 0.4 mcg/kg/min

+

Intended drip (mL/h)

0.2

Alprostadil (Prostin® and Prostavasi...

IV continuous - 500mcg/mL Solution

Dose	0.06mL
Dilute with NS	4.74mL
Final concentration	6mcg/mL
Total in 24 hours	4.8mL

Fill in ➡ and obtain the ➡ Results

In seconds!

Adrenaline and Noradrenaline

neofast

Continuous medication

Adrenaline (Epinephrine)

IV continuous

1mg/mL

Weight (kg)

2

Desired dose (mcg/kg/min)

0.05

Suggested dose: 0.05 to 1 mcg/kg/min

Intended drip (mL/h)

0.1

Adrenaline (Epinephrine)

IV continuous - 1mg/mL

Dose	0.14mL
Dilute with NS, D5W or D10W	2.26mL
Final concentration	0.06mg/mL
Total in 24 hours	2.4mL

neofast

Continuous medication

Norepinephrine (Noradrenaline)

IV continuous

1mg/mL

Weight (kg)

2

Desired dose (mcg/kg/min)

0.2

0.2 to 2 mcg/kg/min

Intended drip (mL/h)

0.3

Norepinephrine (Noradrenaline)

IV continuous - 1mg/mL

Dose	0.58mL
Dilute with D5NS, D5W, LR, NS	6.62mL
Final concentration	80mcg/mL
Total in 24 hours	7.2mL

In seconds !

Dobutamine and Vasopressin

neofast

Continuous medication

Dobutamine

IV - central access

IV - peripheral access

12.5mg/mL

Weight (kg)

2

Desired dose (mcg/kg/min)

10

Suggested dose: 2 to 25 mcg/kg/min

Intended drip (mL/h)

0.6

Dobutamine

IV - central access - 12.5mg/mL

Dose	2.3mL
Dilute with NS, D5W, D10W, LR	12.1mL
Final concentration	2mg/mL
Total in 24 hours	14.4mL

Note: the recommended final concentration after dilution is up to 2 mg/mL. If central access is unavailable, perform the

neofast

Continuous medication

Vasopressin

IV continuous

0.2UI/mL

0.4UI/mL

0.6UI/mL

1UI/mL

20UI/mL

UI/kg/min

UI/kg/h

Weight (kg)

2

Desired dose (UI/kg/h)

0.01

0.001 to 0.003 UI/kg/h

Vasopressin

IV continuous - 0.6UI/mL

Dose	0.8mL
Final concentration	0.6UI/mL
Total in 24 hours	0.8mL
Drip	0.033mL/h

Volumes for equipment

IV continuous - 0.6UI/mL

Additional information

Bibliographical references

In seconds!

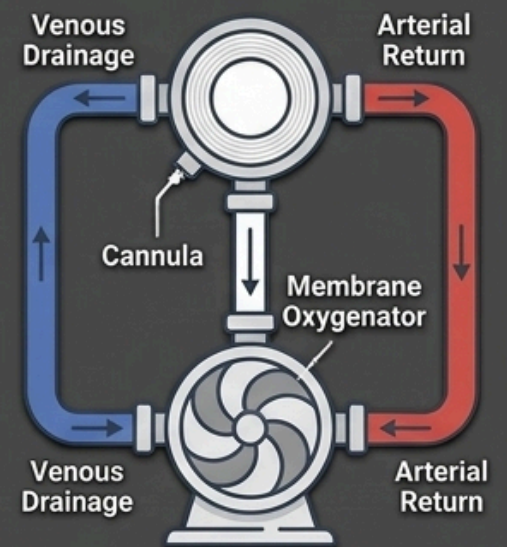
Rescue Therapy: ECMO

What it is: Extracorporeal Membrane Oxygenation. Provides cardiopulmonary bypass support when the neonatal lung fails completely to oxygenate or the heart fails to pump.

Critical Indications for Activating the ECMO Team:

- Oxygenation Index (OI) remains > 25 despite maximized vasodilator and ventilatory therapy.
- Failure to achieve safe respiratory targets ($\text{PaO}_2 > 60 \text{ mmHg}$).
- Persistent or progressive worsening of ventricular function (RV/LV) documented on echocardiography.

Action: Discussion for early referral and counseling with the ECMO center saves lives. Don't wait for irreversible collapse.



Decision Matrix: Resources

Resource Center (iNO/ECMO Available)

1. Overall optimization (Ventilation, fluids, $\text{MAP} > 45 \text{ mmHg}$).

2. Ecological/Clinical Diagnosis → Start iNO 20 ppm.

3. If refractory: Add sildenafil infusion or inhaled prostacyclin.

4. Cardiac support: Milrinone / **Epinephrine / PGE1 (according to Eco)**.

5. No response ($\text{OI} > 25$) → Refer to ECMO.

Limited Resources (No iNO / No ECMO)

1. Strict global optimization. Discard CCHD as quickly as possible.

2. Initiate First Line: Sildenafil IV or PO (1mg/kg every 6 hours for 48 hours → 2mg/kg every 6 hours).

3. If there is no response: Add Bosentan PO (1-2 mg/kg every 12 hours).

4. Aggressive Cardiac Support: Milrinone (or Dobutamine if without Echo), Epinephrine, Hydrocortisone. Vasopressin for refractory hypotension.