



Bronchopulmonary Dysplasia in Extremely Preterm Infants

Diagnosis, The 2023 **Japanese**
Classification, and Targeted
Treatment Strategies

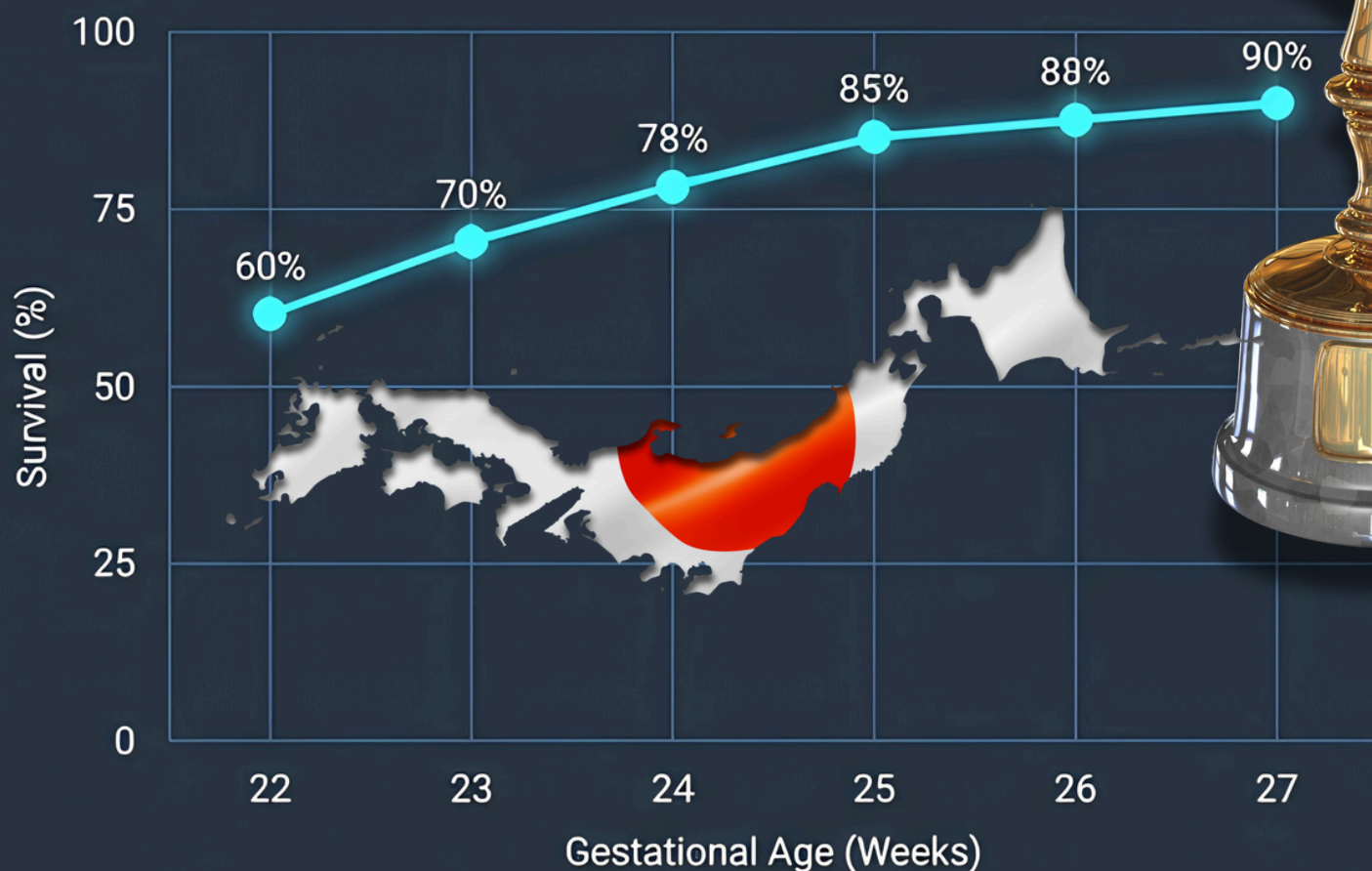
Synthesized from: Neonatal Intensive Care for
Extremely Preterm Infants: **Japanese** NICU
Practices to Prevent Mortality and Morbidities
(Elsevier, 2024).



The Japanese survival advantage demands global attention

60%

Survival rate for periviable infants born at the absolute limit of viability (22 weeks gestation).



The Paradigm Shift

While premature outcomes have improved worldwide, practices vary drastically. Japan's model combines vast accumulated clinical experience with strict standardization, pushing the boundaries of viability and redefining respiratory care.

Defining Chronic Lung Disease (CLD) in the NICU

Clinical Definition Card

A pathological condition characterized by the need for supplemental oxygen (>21%) at more than 28 days of age.

Clinical Presentation Map:

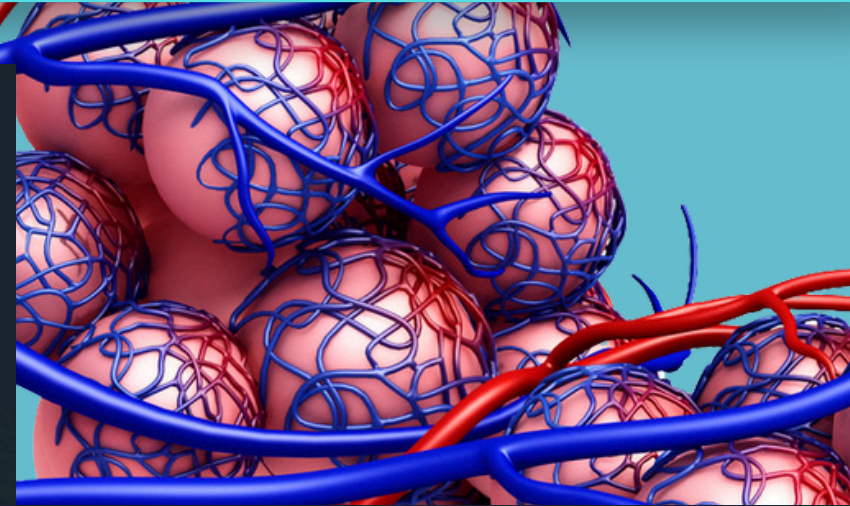
- **Respiratory Distress:** Persistent signs of distress (tachypnea, retractions, nasal flaring).
- **Radiological Findings:** Chest X-rays displaying hazy, emphysematous, or fibrous appearances.
- **The Transition:** Represents the chronic evolution from acute Respiratory Distress Syndrome (RDS) into long-term developmental lung arrest.



The anatomy of premature lung injury is multifactorial.

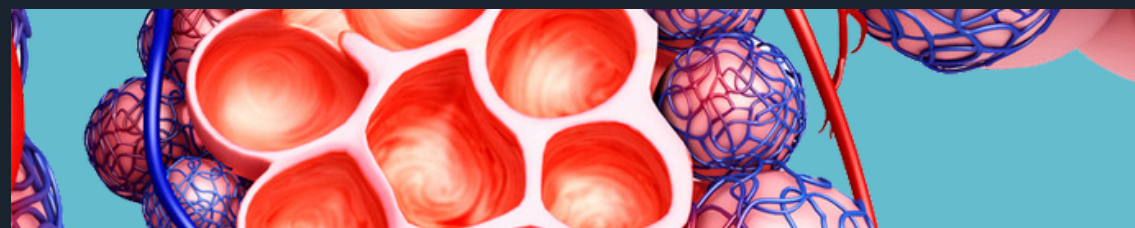
Biotrauma

Inflammatory insults, prominently intrauterine inflammation (Histological Chorioamnionitis) and postnatal infections.



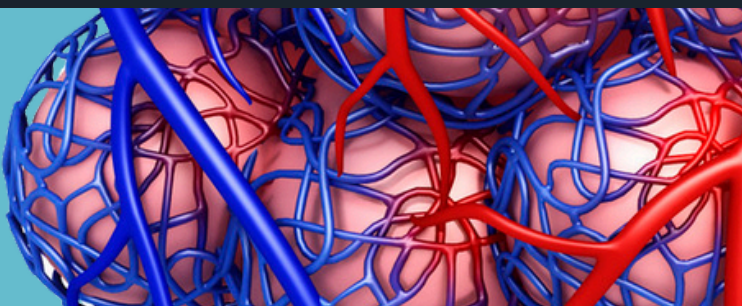
Volutrauma & Barotrauma

Mechanical damage to terminal bronchioles and alveoli induced by conventional mechanical ventilation.



Premature Alveolus (Canalicular/Saccular Stage)

Highly susceptible to external insults due to primary immaturity.

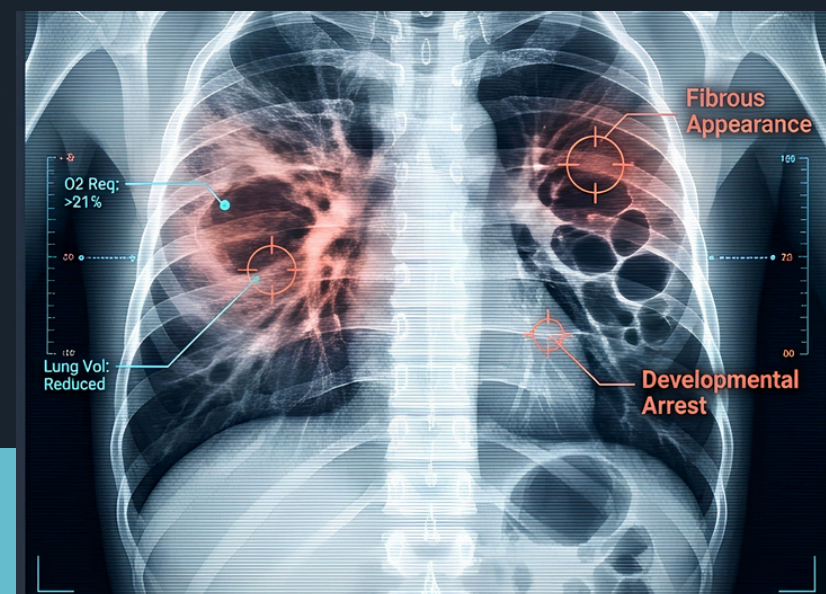


Atelectrauma

Alveolar collapse and shearing forces due to severe pulmonary surfactant deficiency.

Oxidative Stress

Cellular damage resulting from necessary but toxic exposure to high concentrations of supplemental oxygen.



Shifting from late diagnosis to early prognostic prediction

The Japanese Philosophy Proactive Prediction

By utilizing specific perinatal and early postnatal markers within the first 28 days of life, clinicians can predict long-term respiratory outcomes and intervene earlier in the lung injury cascade.

MICRO-TYPOGRAPHY
DATA LAEN

MICRO-TYPOGRAPHY
EARLY WINDOW

MICRO-TYPOGRAPHY
INTERVENTION POINT

Birth

Day 28

The Western Standard Retrospective Diagnosis

CLD severity is traditionally graded at 36 weeks Postmenstrual Age (PMA), after the primary windows for prevention have closed.

MICRO-TYPOGRAPHY
MIEGED

MICRO-TYPOGRAPHY
LATE STAGE

MICRO-TYPOGRAPHY
MISSED OPPORTUNITY

Day 28

36 weeks
PMA

The Three Pillars of the 2023 Revised Japanese Classification



MICRO-TYPOGRAPHY:
RISK FACTOR CLD

Pillar 1: **H-CAM** (Endotype)

Histological Chorioamnionitis:
The strongest proof of intrauterine infection.

This **inflammatory biotrauma** is a well-documented primary risk factor for CLD.



MICRO-TYPOGRAPHY:
PLACENTAL DYSFUNCTION

Pillar 2: **SGA** (Endotype)

Small for Gestational Age:
Defined as <10th percentile.

Suggests **placental dysfunction** and chronic in-utero hypoxia, which overwhelms alveolar growth and causes developmental arrest.

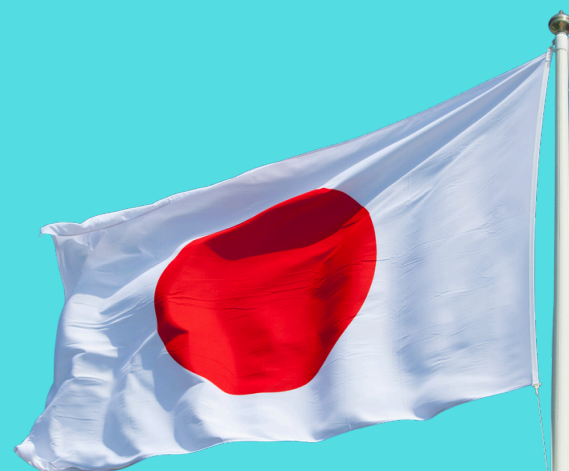


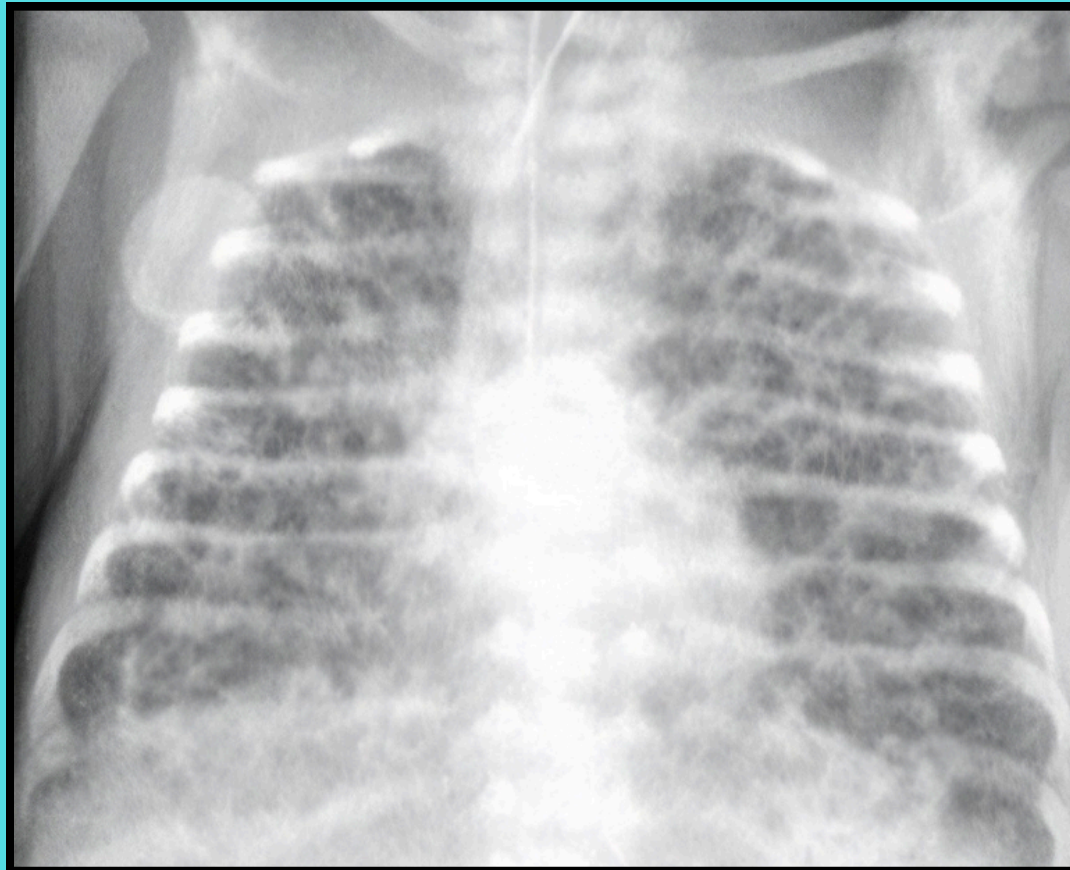
MICRO-TYPOGRAPHY:
PLACENTAL DYSFUNCTION

Pillar 3: **Bubbly/Cystic X-Ray** (Phenotype)

Radiological Appearance within 28 days: Diffuse, streaky infiltrates with small cystic areas (1-10 mm) across more than 3 lung areas.

Highly predictive of long-term **respiratory impairment** at school age.





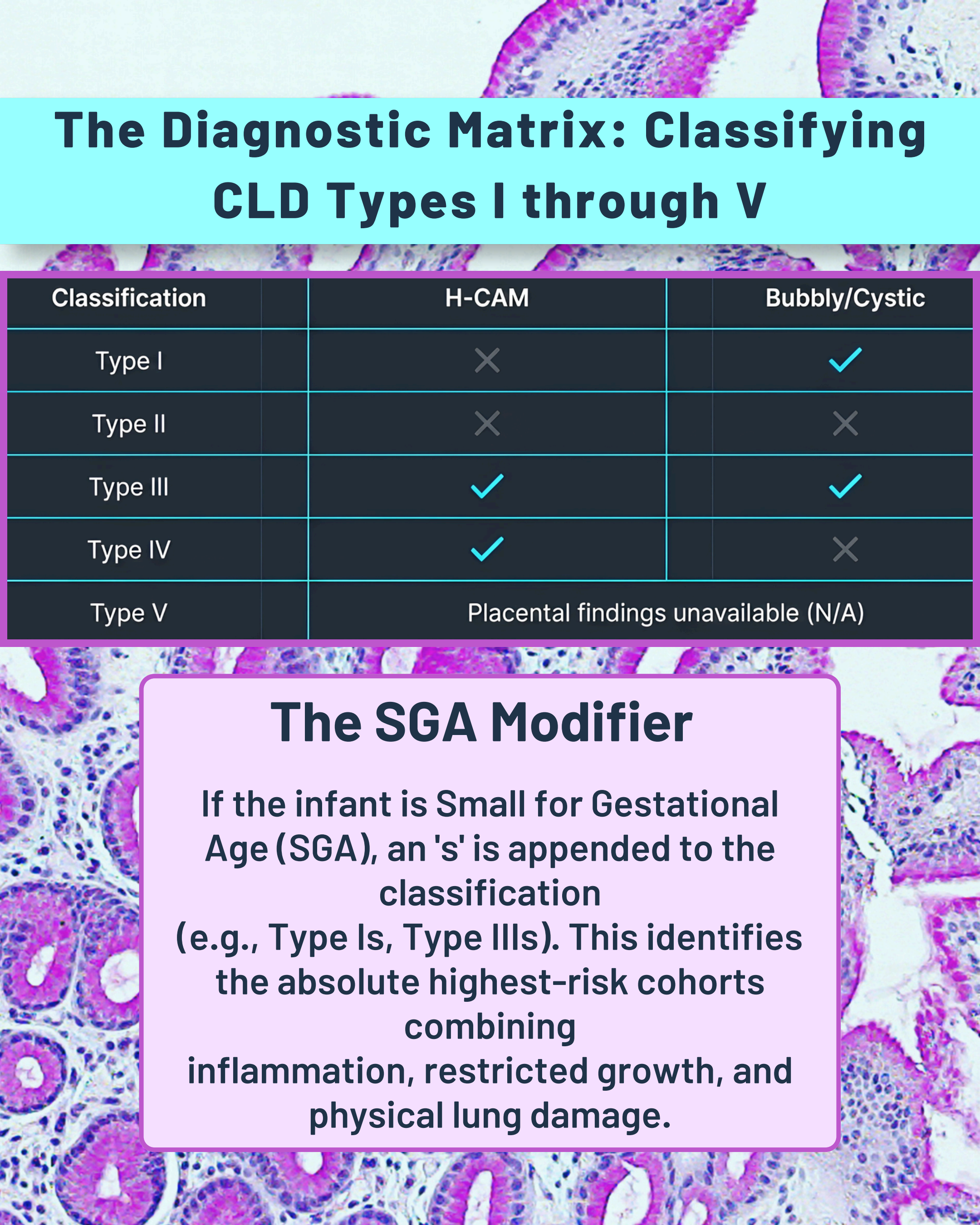
Images of bubbly/cystic appearance on chest X-ray, which have more than **three different areas with findings of diffuse, streaky infiltrates with small cystic areas (diameter 1-10 mm).**



**Images of nonbubbly/cystic appearance
on chest X-ray.**

Bubbly/cystic appearance is defined as follows:

The lungs are divided into four areas: left upper, right upper, left lower, and right lower. A diagnosis is made when more than three different areas exhibit findings of diffuse, streaky infiltrates with small cystic areas (diameter 1-10 mm), as determined by the attending neonatologists.



The Diagnostic Matrix: Classifying CLD Types I through V

Classification		H-CAM		Bubbly/Cystic
Type I		×		✓
Type II		×		×
Type III		✓		✓
Type IV		✓		×
Type V		Placental findings unavailable (N/A)		

The SGA Modifier

If the infant is Small for Gestational Age (SGA), an 's' is appended to the classification (e.g., Type Is, Type IIIs). This identifies the absolute highest-risk cohorts combining inflammation, restricted growth, and physical lung damage.

Postnatal Prevention Strategy: Delivery Room Resuscitation

First 30 Minutes



MICRO-TYPOGRAPHY:

FiO₂: 30-40%

Oxidative Stress Risk

Step 1: Strict Oxygen Limits

Initial resuscitation targets an FiO₂ of 30-40%. Hypoxia is managed closely to prevent oxidative stress and limit free radical damage to the fragile canalicular lungs.

MICRO-TYPOGRAPHY:

<28 Weeks

IVH Risk

Step 2: Securing the Airway

Unlike Western trends favoring LISA/INSURE, Japanese protocols favor prompt endotracheal intubation for infants <28 weeks to stabilize severe respiratory dynamics and avoid Intraventricular Hemorrhage (IVH).

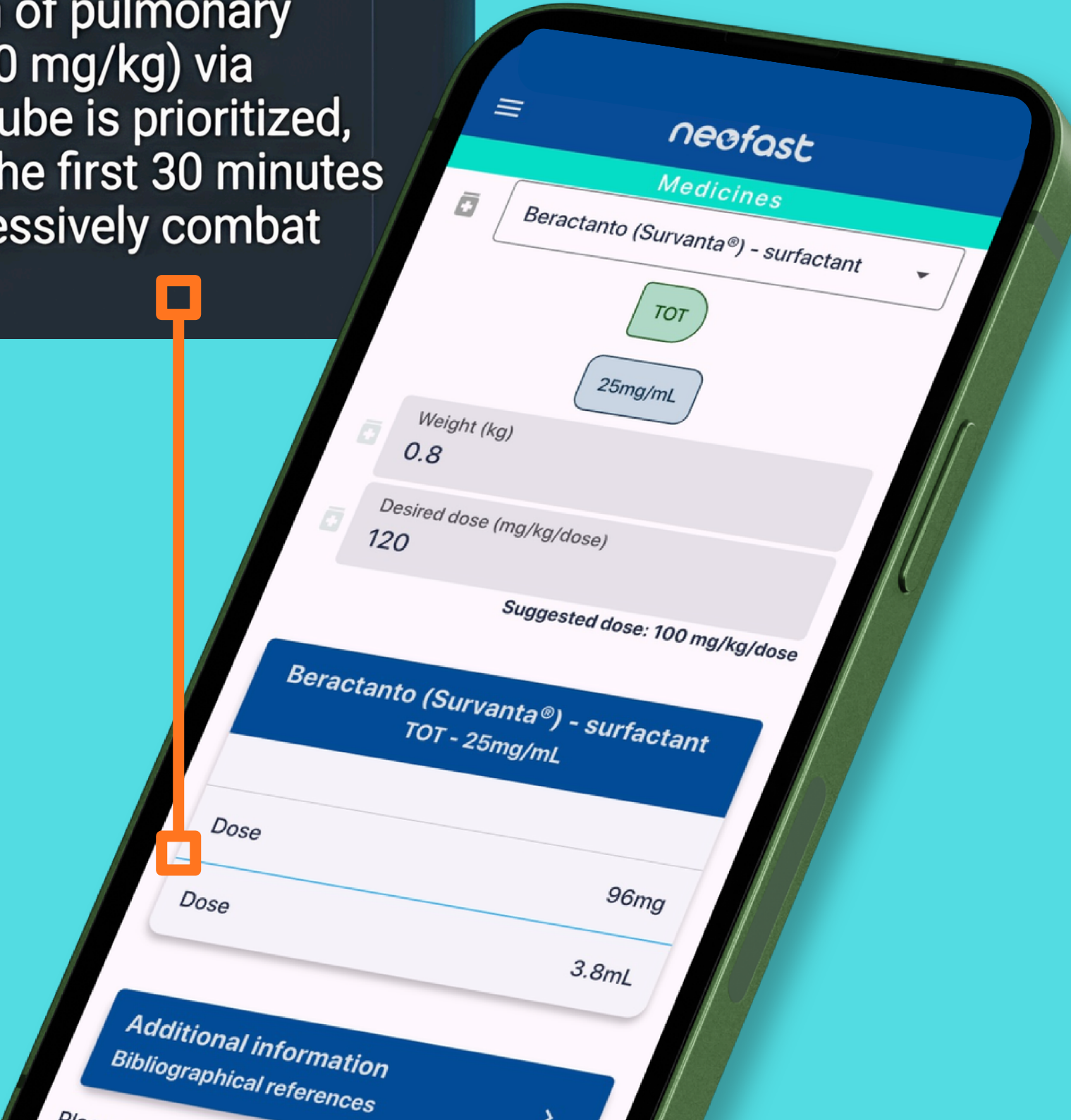
First 30 Minutes

MICRO-TYPOGRAPHY:

Dose: 120 mg/kg
Atelectrauma Combat

Step 3: Early Surfactant

Administration of pulmonary surfactant (120 mg/kg) via endotracheal tube is prioritized, ideally within the first 30 minutes of life, to aggressively combat Atelectrauma.



First-Line Respiratory Support: The HFOV Advantage

Conventional Mechanical Ventilation (CMV)



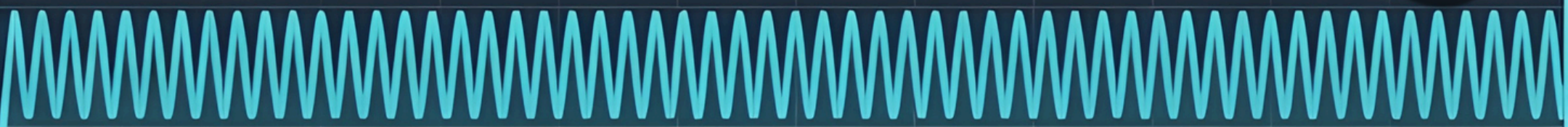
- Large pressure swings from peak inspiration to deep expiration.
- Result: Repeated alveolar collapse and expansion, driving Volutrauma and Barotrauma.

HFOV (The Japanese Standard)



First-Line Respiratory Support: The HFOV Advantage

HFOV (The Japanese Standard)



- Maintains a constant Mean Airway Pressure (MAP) with micro-tilal volumes (1.0 - 2.0 mL/kg) at rapid rates (12-15 Hz).
- Result: Keeps the lung open consistently. Facilitates gas exchange while virtually eliminating the mechanical stress of volutrauma.

Diaphragm-type HFOV with Volume Guarantee (VG) is heavily preferred to automatically adjust high frequency tidal volume and prevent hyperventilation.

Weaning Pathway

Advanced Ventilation: Weaning to Non-Invasive Care

HFOV
(Acute Phase)

Conservative Extubation Philosophy

Japanese neonatologists often extubate **later** than Western counterparts. The priority is preventing frequent **hypoxic apnea** events rather than strictly minimizing days on a ventilator.

Direct to N-CPAP

Infants are frequently extubated directly from HFOV to moderate levels of Nasal CPAP (**4-7 cm H₂O**), utilizing the Coanda effect of Infant Flow systems to maintain lung recruitment.

Implementing NAVA

Neurally Adjusted Ventilatory Assist (NAVA) synchronizes support based directly on the electrical activity of the diaphragm (**EAdi**), adjusting dynamically to the infant's neural respiratory drive.

N-CPAP /
NAVA

Pharmacological Protocols for CLD Prevention

Systemic Corticosteroids (Hydrocortisone)

Protocol: 1.0 mg/kg/dose 8-hourly for 3 days (tapering down).
Rationale: Hydrocortisone is preferred over dexamethasone in the first week to balance anti-inflammatory benefits against neurodevelopmental risks.

Inhaled Corticosteroids

Protocol: Fluticasone propionate (50 µg per actuation) delivered via valved spacer.
Rationale: Targets lung inflammation directly. Highly effective in infants with H-CAM (intrauterine infection), reducing oxygen dependence without systemic side effects.

Sivelestat (Targeted Therapy)

Protocol: 0.1 - 0.2 mg/kg/hour continuous infusion for 7-14 days.
Rationale: A selective neutrophil elastase inhibitor utilized early to prevent acute lung injury and subsequent fibrosis by stopping neutrophil-mediated alveolar destruction.

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Medicines

Hydrocortisone

IV bolus or IM

Intermittent IV

100mg Powder

250mg Powder

500mg Powder

Without BSA

BSA (height)

BSA (without height)

Weight (kg)

Desired dose (mg/kg/dose)

Additional information

Bibliographical references

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Medicines

Hydrocortisone

IV bolus or IM

Intermittent IV

100mg Powder

250mg Powder

500mg Powder

Without BSA

BSA (height)

BSA (without height)

Weight (kg)

1.5

Desired dose (mg/kg/dose)

1

Suggested dose: 0.25 to 0.5 mg/kg/dose

Hydrocortisone

IV bolus or IM - 100mg Powder

Dose

1.5mg

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Medicines

Hydrocortisone

IV bolus or IM - 100mg Powder

Dose

1.5mg

Interval

12/12h

Reconstitution

Or PRN

Reconstitute with SWFI or own diluent

2mL

Concentration after reconstitution

50mg/mL

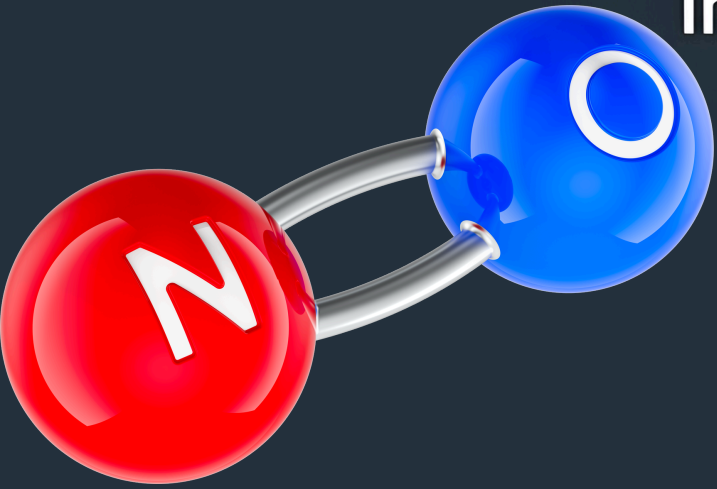
Dose after reconstitution

0.03mL

Infusion rate

30s

Managing CLD-PH with Inhaled Nitric Oxide (iNO)

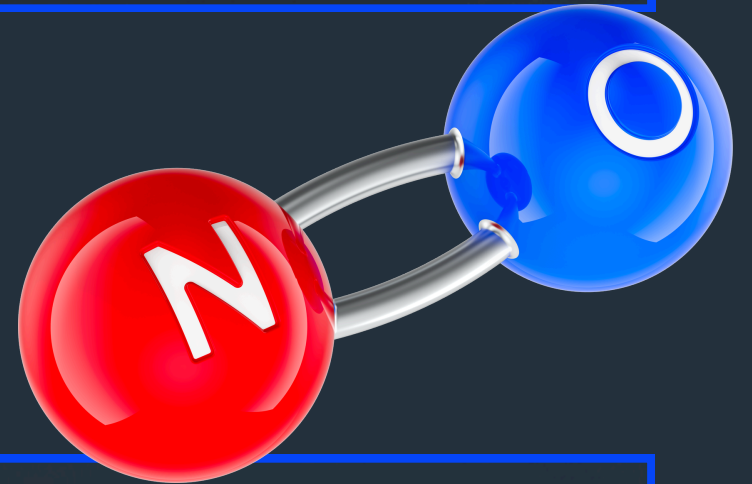


The Complication

Pulmonary Hypertension (CLD-PH) occurs in 20-40% of severe CLD cases, drastically impacting mortality and long-term neurodevelopment.

Strategic Impact

Surging adoption in Japan due to its critical ability to improve oxygenation and allow for decreased ventilator support in fibrotic, hyperinflated lungs.

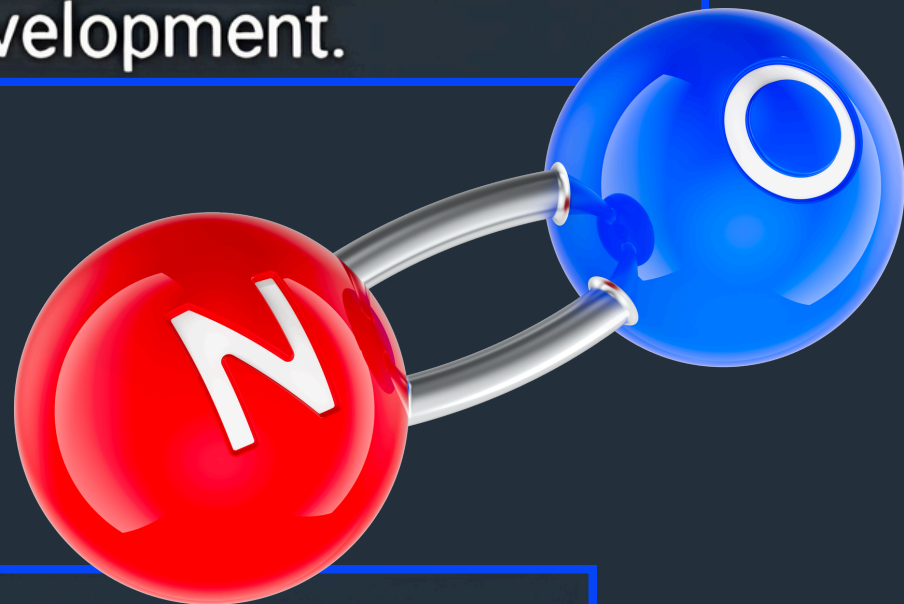


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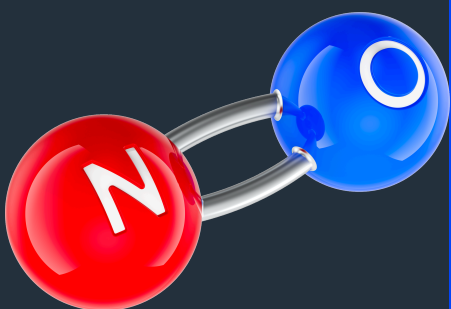
Mechanism

Diffuses rapidly across the alveolar membrane to relax smooth muscle via cGMP, causing selective pulmonary vasodilation without systemic hypotension.



Protocol & Weaning

Initiated at 5 ppm for severe hypoxemic hypoxemic respiratory failure. Tapered by 1-2 ppm increments once SpO₂ is stabilized at 85-95% on an FiO₂ < 0.40.



Synthesis: The Japanese NICU Precision Blueprint

The Premature Infant (<28 Weeks)

Acute Resuscitation

- Strict O2 targets + Intubation + Early Surfactant (<30 mins)

Diagnostic Classification Lens

Predict prognosis <28 days using the 2023 Matrix: H-CAM, SGA, Bubbly/Cystic X-Ray

Mechanical

First-line HFOV to eliminate volutrauma -> Wean to NAVA/N-CPAP

Pharmacological

Targeted systemic/inhaled steroids + **Sivelestat** for inflammation

Rescue

iNO for **CLD-PH** and extreme **hypoxia**

Improved Long-Term Outcomes

Precision engineering applied to human physiology: Japan's 60% survival rate at 22 weeks is the result of relentless, standardized protocol execution.



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Neonatal Prescription



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