



MINISTRY OF HEALTH BELIZE



# Neonatal Clinical Practice Guidelines



2018-2021

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*First Edition*

# FOREWARD



## ACKNOWLEDGEMENT

I am immensely grateful to the following persons for their priceless contribution in the development of this first edition of the Neonatal Clinical Practice Guidelines 2018-2021.

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I also want to extend my sincere gratitude to the following Medical Officers for their valuable time and feedback: Dr. Jenny Linares, MD; Dr. Dianélie Blanco, MD and Dr. Karina Catzim, MD.

Mr. Andrei Chell, MSc. Global Health and Development, I'll forever appreciate your commitment and amazing input throughout the guidelines.

To Dr. Natalia Beer, Maternal and Child Health Technical Advisor for the Ministry of Health, thank you for the opportunity and advice given in developing this challenging but enjoyable task.

To my supportive and understanding husband Dr. Edgar Caldeira, THANK YOU!



## PREFACE

These guidelines have been developed, at the request of the Ministry of Health, as an *aide-memoire* for all staff concerned with the management of neonates to work towards a better and more uniform standard of neonatal care across the country of Belize. The topics selected are the major and most frequent issues encountered in neonatology. The guidelines are based on the best available evidence and opinions from the most recent published literature and at points, directly from experts. It is quite straight forward, easy to read and understand. At the end of each topic, a further reading section is clearly highlighted for additional reference and in-depth explanation. Most articles stated are open access.

A guideline may not absolutely apply to every infant, even where the diagnosis is clear-cut; there will always be exceptions. Any deviation in practice should be recorded in the infant's notes with reasons for deviation. DO NOT attempt to carry out any of these procedures unless you have been trained to do so and have demonstrated your competence.

The care of at-risk newborns is a team effort, with neonatologists taking the lead position. This requires the coordination of care between a number of specialists, who only see one part of the picture. Therefore, it is the neonatologist's responsibility to oversee the infant's care and to ensure that the varied practitioners' activities come together for the best management and benefit of the infant. In neonatology, providing the adequate prompt management and care to the critically ill infant is priority since the first hours ("Golden Hours") of life will determine the infant's fate. Interest, concern, dedication and knowledge are very essential when caring for these newborns. There is so much to learn and neonatal care is constantly evolving; these changes should be embraced as they occur for the well-being of these precious infants. At the end, we should be conscious that the best for our patients is avoiding the least, and if possible, any complications or sequelae on these 'lil' warriors.

The intention of the guidelines is for it to be utilised as a valuable tool to raise the standards of the practice, to improve the duty of care and to achieve a desirable outcome that all newborns deserve.

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Kindly send your valuable comments or observations to [elsieconstanza@gmail.com](mailto:elsieconstanza@gmail.com).

About the cover:

Photo: Baby Arri Guardado, born extremely premature and with extremely low birth weight; today a healthy toddler. Photo courtesy of baby Arri's mother who granted consent to publish.  
Colour: Purple - pledging purple for preemies.



## ACRONYMS

AAP	American Academy of Pediatrics	IVH	Intra Ventricular Haemorrhage
ABG	Arterial blood gas	MAP	Mean airway pressure
ACV	Assisted control ventilation	nCPAP	Nasal continuous positive airway pressure
BID	Two times a day	NICU	Neonatal intensive care unit
bpm	beats per minute	NPO	Nothing per oral
BUN	Blood urea nitrogen	OD	Once daily
CBC	Complete blood count	PCO <sub>2</sub>	Partial pressure of carbon dioxide
CHD	Congenital Heart Disease	PO <sub>2</sub>	Partial pressure of oxygen
CPAP	Continuous positive airway pressure	PCV	Pressure controlled ventilation
CRP	C-reactive protein	PEEP	Positive end expiratory pressure
CSF	Cerebrospinal fluid	PIP	Peak inspiratory pressure
ECMO	Extracorporeal membrane oxygenation	PMA	Post menstrual age
ECG	Electrocardiogram	PO	Per oral
EEG	Electroencephalogram	PPV	Positive pressure ventilation
ELBW	Extremely low birth weight	PRN	As necessary
ESPGHAN	European Society of Paediatrics Gastroenterology, Hepatology and Nutrition	PSV q	Pressure support ventilation every
ETT	Endotracheal tube	RR	Respiratory rate
FIO <sub>2</sub>	Fraction of inspired oxygen	SatO <sub>2</sub>	Oxygen saturation
FRC	Functional residual capacity	SIMV	Synchronised Intermittent Mechanical Ventilation
GA	Gestational age	SIBEN	Sociedad Iberoamericana de Neonatología
GIR	Glucose infusion rate	Ti	Inspiratory time
HR	Heart rate	TPN	Total parenteral nutrition
Hb	Haemoglobin	UAC	Umbilical arterial catheter
Hto	Haematocrit	UVC	Umbilical venous catheter
I:E	Inspiratory:expiratory ratio	VLBW	Very low birth weight
IV	Intravenous	V/Q	Ventilation/perfusion



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### NEONATAL RESUSCITATION

Every birth should be attended by at least one qualified individual with neonatal resuscitation skills, including basic airway management and positive-pressure ventilation, whose only responsibility is providing care for the newly born infant.

Every high risk birth should have immediate access to a qualified team skilled in advanced airway management (endotracheal intubation and positive pressure ventilation) and vascular access.

Risk factors include:

1. Preterm delivery ( $\leq 35$  weeks)
2. Category 2 (indeterminate tracing) or 3 (abnormal tracing) foetal heart rate pattern
3. Maternal Septicaemia/Chorioamnionitis
4. Preclampsia/Eclampsia
5. Vaginal breech delivery
6. Obstetrical emergencies (shoulder dystocia, cord prolapse, placental abruption)
7. Thick meconium-stained amniotic fluid (MSAF)
8. Oligohydramnios
9. Foetal anomalies

Caesarean delivery is associated with an increased risk of problems with respiratory transition at birth requiring medical interventions especially for deliveries before 39 weeks gestation who have not had antenatal steroids.

#### NORMAL POSTNATAL CARDIORESPIRATORY TRANSITION

Initial breaths up to 100cmH<sub>2</sub>O negative pressure or ventilations → lungs aerate and alveolar fluid cleared → surfactant released → ↓alveolar surface tension → lung compliance and functional residual capacity established → ↓pulmonary vascular resistance → ↑pulmonary blood flow → ↑pulmonary venous return to left atrium → functional closure of patent foramen oval (PFO) and ceased ductal flow → right to left shunt shifts to left to right → ↑systemic vascular resistance. Being born and cessation of placental flow also increase systemic resistance; this occurs a little before PFO and ductal changes.

Goals of resuscitation

1. Minimise immediate heat loss.
2. Establish lung aeration and normal respiration.
3. Achieve normal postnatal oxygenation.
4. Assist normal postnatal cardiovascular adaptation.

Figure 1. Neonatal resuscitation equipment and supplies.



Source: Textbook of Neonatal Resuscitation. 7th ed. American Academy of Pediatrics and American Heart Association; 2016.



Table 1. Neonatal Resuscitation Equipment and Supplies

Suction equipment	<ul style="list-style-type: none"> <li>Bulb syringe</li> <li>Mechanical suction and tubing</li> <li>Suction catheters, 5F or 6F, 10F, 12F or 14F</li> <li>8F feeding tube and large syringe</li> <li>Meconium aspirator</li> </ul>
Positive-pressure ventilation equipment	<ul style="list-style-type: none"> <li>Device for delivering positive-pressure ventilation</li> <li>Face masks, newborn and preterm sizes</li> <li>Oxygen source</li> <li>Compressed air source</li> <li>Oxygen blender to mix oxygen and compressed air with flowmeter (flow rate set to 10 L/min) and tubing</li> <li>Pulse oximeter with sensor and cover</li> <li>Target oxygen saturation table</li> </ul>
Intubation equipment	<ul style="list-style-type: none"> <li>Laryngoscope with straight blades (Miller), No. 0 (preterm) and No. 1 (term). No. 00 (very preterm)</li> <li>Stylet (optional)</li> <li>Measuring tape</li> <li>Scissors</li> <li>Waterproof tape or tube-securing device</li> <li>Alcohol pads</li> <li>CO2 detector or capnograph</li> <li>Laryngeal mask (or similar supraglottic device) and 5-mL syringe</li> <li>5F or 6F orogastric tube if insertion port present on laryngeal mask</li> </ul>
Medications	<ul style="list-style-type: none"> <li>Epinephrine 1:10,000 (0.1 mg/ml)</li> <li>Normal saline solution for volume expansion - 100 or 250ml</li> <li>Dextrose 10%, 250 mL (optional)</li> <li>Normal saline for flushes</li> <li>Syringes (1-mL, 3-mL or 5-mL, 20- to 60-mL)</li> </ul>
Umbilical vessel catheterisation supplies	<ul style="list-style-type: none"> <li>Sterile gloves</li> <li>Antiseptic prep solution</li> <li>Umbilical tape</li> <li>Small clamp (hemostat)</li> <li>Forceps (optional)</li> <li>Scalpel</li> <li>Umbilical catheters (single lumen), 3.5F or 5F</li> <li>Three-way stopcock</li> <li>Syringes (3-5 mL)</li> <li>Needle or puncture device for needleless system</li> <li>Normal saline for flushes</li> <li>Clear adhesive dressing to temporarily secure umbilical venous catheter to abdomen (optional)</li> </ul>



Miscellaneous

Gloves and appropriate personal protection  
Radiant warmer or other heat source  
Temperature sensor with sensor cover for radiant warmer (for use during prolonged resuscitation)  
Firm, padded resuscitation surface  
Timer/clock with second hand  
Warmed linens  
Hat  
Stethoscope (with neonatal head)  
Tape, 1/2 or 3/4 inch  
Intraosseous needle (optional)  
Electronic cardiac (ECG) monitor leads and ECG monitor

For very preterm babies

Size-00 laryngoscope blade  
Food-grade plastic bag (1-gallon size) or plastic wrap  
Thermal mattress  
Transport incubator to maintain baby's temperature during move to the nursery

NEONATAL RESUSCITATION FLOW DIAGRAM (Figure 3)

Initial Assessment: Determine if the newborn can remain with the mother or should be moved to a radiant warmer for further evaluation. Maintain normothermia of 36.5 - 37.5 °C.

Airway (A): Perform the initial steps to establish an open Airway and support spontaneous respiration.

Breathing (B): Positive-pressure ventilation (PPV) is provided to assist Breathing for babies with apnoea or bradycardia. Other interventions (continuous positive airway pressure [CPAP] or oxygen) may be appropriate if the baby has laboured breathing or low oxygen saturation.

Circulation (C): If severe bradycardia persists despite assisted ventilation, Circulation is supported by performing chest compressions coordinated with PPV.

Drug (D): If severe bradycardia persists despite assisted ventilation and coordinated compressions, the Drug epinephrine is administered as PPV and chest compressions continue.

Note: Ventilation of the baby's lungs is the most important and effective action during neonatal resuscitation.

Free-flow oxygen can be given by

1. oxygen tubing
2. oxygen mask
3. the tail of a self-inflating bag with an open reservoir (Figure 2-A)
4. a flow-inflating bag and mask (Figure 2-B)
5. a T-piece resuscitator and mask (Figure 2-C)

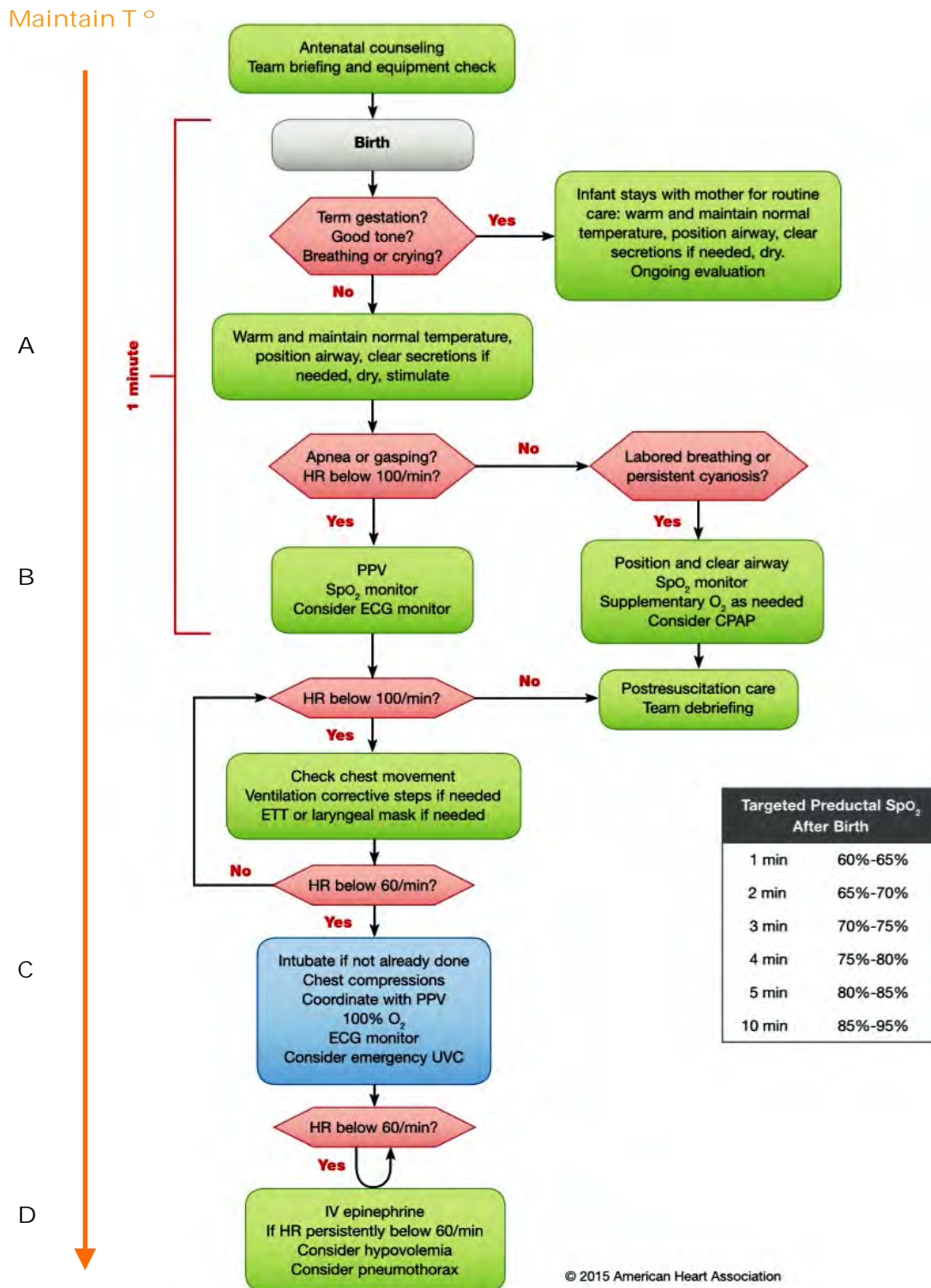
Figure 2. Ventilation Devices



Recommendation: For free-flow oxygen, the mask of a flow-inflating bag and T-piece resuscitator should NOT be held tightly against the face and do NOT attempt to administer free-flow oxygen through the mask of a self-inflating bag. Continuous positive airway pressure (CPAP) can be given using a flow-inflating bag or T-piece resuscitator when attached to a mask that is held tightly to the baby's face. CPAP cannot be given using a self-inflating bag. Initial respiratory support of all spontaneously breathing preterm infants with respiratory distress may be provided by CPAP, rather than routine intubation.



Figure 3. Neonatal Resuscitation Algorithm - 2015



Source: Textbook of Neonatal Resuscitation, 7th ed. American Academy of Pediatrics and American Heart Association; 2016.



Table 2. Ventilation Corrective Steps: MR. SOPA

M	MASK	CHECK MASK SEAL
R	REPOSITION	POSITION IN OPEN AIRWAY "SNIFFING" POSITION
S	SUCTION	SUCTION TO REMOVE OBSTRUCTING SECRETIONS
O	OPEN THE MOUTH	OPEN THE MOUTH TO DECREASE RESISTANCE
P	PRESSURE INCREASE	INCREASE THE PEAK INSPIRATORY PRESSURE
A	ADVANCED AIRWAY	PLACE A LARYNGEAL MASK AIRWAY OR INTUBATE

## INITIAL STEPS (A - Airway)

Firstly, evaluate three key components

1. Gestational age
2. Tone
3. Respiratory effort

1. Approximately 60 seconds "the Golden Minute" are allotted for completing the initial steps, reevaluating, and beginning ventilation if required.
2. If no risk, delay cord clamping (DCC) for 30 - 60 seconds for most vigorous term and preterm newborns.
  - a. If cord clamping is delayed, the baby should be placed skin-to-skin on the mother's chest or abdomen, or held securely in a warm, dry towel or blanket.
  - b. Do not delay cord clamping for high risk non-vigorous infants who need immediate resuscitation.
  - c. DCC improves mortality in newborns < 32 weeks GA. DCC has been associated with less intraventricular haemorrhage (IVH) of any grade, higher blood pressure and blood volume, less need for transfusion after birth, and less necrotising enterocolitis.
  - d. Cord milking is not recommended in infants  $\leq$  28 weeks gestation (more studies needed). Cord milking may be considered on an individual basis.
3. *Vigorous* term newborns should be placed skin-to-skin on mother's chest or abdomen to monitor transition.
  - a. Infant stays with mother for routine care: warm and maintain normal temperature (36.5 - 37.5 °C), position airway, clear secretions if needed, and dry.
  - b. Continue assessment.
4. Preterm and *non-vigorous* newborns should be carried to a radiant warmer. Preterm babies <32 weeks should be placed into a polyethylene wrap or bag and then placed under a radiant heater.
  - a. Remove wet towels and dry with warm towels/blanket.
  - b. Temperature of newly born *non-asphyxiated* infants should be maintained between 36.5 - 37.5°C after birth through admission and stabilisation.
  - c. Position the neck neutral or slightly extended in the 'sniffing' position.
  - d. Gently suction the mouth and nose with a bulb syringe if meconium stained fluid is present, the baby is not breathing, or the baby is having difficulty breathing.
    - (a) Routine intubation for tracheal suction in this setting is not suggested and should only be performed for suspected tracheal obstruction.



- (b) Routine suctioning and aggressive pharyngeal suctioning are not recommended.
5. Stimulate breathing. Overly vigorous stimulation is not helpful and can cause injury. Never shake a baby.
  6. If the baby is breathing and the heart rate (HR) is at least 100 bpm, but central cyanosis persists, use pre-ductal pulse oximetry (right hand or wrist) to assess the need for supplemental oxygen.
    - a. It is recommended that pulse oximetry be used when resuscitation can be anticipated, when PPV is administered, when central cyanosis persists beyond the first 5 to 10 minutes of life, or when supplementary oxygen is administered.
    - b. Visual assessment of cyanosis is not a reliable indicator of the baby's oxygen saturation and should not be used to guide oxygen therapy.
  7. Free-flow oxygen administration using a blender may begin at 30% oxygen and titrate to achieve the oxygen saturation target.
  8. To monitor HR: use stethoscope for auscultation at the cardiac apex or use an ECG monitor which has shown to be more accurate than pulse oximetry with HR monitor.
  9. If the baby is not breathing or the HR < 100 bpm by 1 min of age, proceed to positive pressure ventilation.

### POSITIVE PRESSURE VENTILATION (PPV) (B - Breathing)

Ventilation is the most important step for successful resuscitation of the newly born who has not responded to the initial steps.

1. Place the baby supine and standing at the head of the bed, hold the baby's head and neck in the 'sniffing' position for PPV.
2. Use appropriate size mask. Mask should not cover the eyes or extend beyond the chin. Hold to ensure an air-tight seal by using one or two hands.
3. PPV can be delivered effectively with a flow-inflating bag, self-inflating bag, or T-piece resuscitator. The self-inflating bag remains the only device that can be used when a compressed gas source is not available.
4. Begin PPV: Inflate lungs with 20 - 25 cm H<sub>2</sub>O peak inspiratory pressure (PIP). The first breath may require higher pressure of 30-40 cm H<sub>2</sub>O. Use positive end expiratory pressure (PEEP) of 5 cm H<sub>2</sub>O to help establish and maintain functional residual capacity (FRC).
5. The Neonatal Life Support (NLS) recommends that the first five positive pressure inflations maintain the initial inflation pressure for 2–3 seconds. Sustained inflation of greater than 5 seconds duration is not recommended. (more studies needed)
6. Ventilation rate: 40 - 60 breaths per minute.
  - ▶ *Breathe (squeeze), Two, Three (release); Breathe, Two, Three...*
7. Term babies: initiate ventilation with 21% oxygen (room air).
8. Pre-term babies < 35 weeks gestation: initiate ventilation with 21 -30% oxygen.
9. Use pre-ductal pulse oximetry (right hand or wrist) during PPV to evaluate oxygenation and adjust O<sub>2</sub> concentration (FIO<sub>2</sub>). Use the target oxygen saturation table to guide supplemental oxygen.

HR is the most sensitive indicator of a successful response to each step and should increase with PPV.

1. Evaluate HR. Ensure chest movement with PPV. If HR does not increase within 15 seconds and no chest movement, perform corrective steps - MR SOPA (Table 2).
2. Reassess the heart rate after 30 seconds of PPV that moves the chest.
3. Continue PPV until the HR is at least 100 bpm and the baby is breathing effectively.



4. If HR is not improving and chest movement cannot be achieved with face-mask ventilation, proceed to insert an alternative airway - endotracheal tube (ETT) or laryngeal mask airway (LMA).
  - a. Intubation should be completed within approximately 30 seconds.
  - b. Colorimetric and Capnograph devices are being used to confirm endotracheal tube placement by detecting exhaled CO<sub>2</sub>. Always confirm clinically by equal breath sounds and increase HR.

Table 3. Endotracheal tube size for babies of various weights and gestational ages.

Weight (g)	Gestational Age (wks)	Endotracheal Tube Size (mm ID)
Below 1,000	Below 28	2.5
1,000-2,000	28-34	3.0
Greater than 2,000	Greater than 34	3.5

Source: Textbook of Neonatal Resuscitation. 7th ed. American Academy of Pediatrics and American Heart Association; 2016.

Table 4. Initial endotracheal tube insertion depth ("tip to lip") for orotracheal intubation.

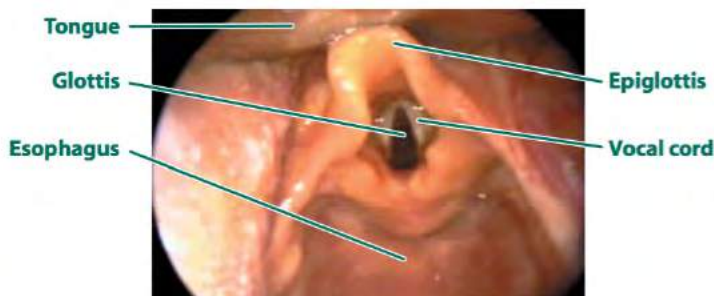
Gestation (weeks)	Endotracheal tube insertion depth at lips (cm)	Baby's Weight (grams)
23-24	5.5	500-600
25-26	6.0	700-800
27-29	6.5	900-1000
30-32	7.0	1,100-1,400
33-34	7.5	1,500-1,800
35-37	8.0	1,900-2,400
38-40	8.5	2,500-3,100
41-43	9.0	3,200-4,200

Source: Textbook of Neonatal Resuscitation. 7th ed. American Academy of Pediatrics and American Heart Association; 2016.

Methods to calculate ETT insertion depth:

- NTL (naso-tragus-length) method: distance (cm) from the baby's nasal septum to the ear tragus: NTL + 1 cm
- Baby's weight (kg) + 6 cm

Figure 4. Laryngoscopic view of vocal cords and surrounding structures.



Source: Textbook of Neonatal Resuscitation. 7th ed. American Academy of Pediatrics and American Heart Association; 2016.

5. LMA provides a rescue airway when PPV with a face mask fails to achieve effective ventilation and intubation is unsuccessful.



- a. Data are limited for the use of LMA in preterm infants delivered < 34 weeks of gestation or infants with birth weight < 2000 g.
  - b. If necessary, the laryngeal mask can be attached to a ventilator or CPAP device during transport.
  - c. Use of LMA has not been evaluated during chest compressions or for administration of emergency medications.
6. PPV may be discontinued when the baby has a heart rate continuously over 100 bpm and sustained spontaneous breathing.
    - a. Free-flow oxygen or CPAP may be required and can be weaned, as tolerated, based on pulse oximetry.
    - b. CPAP is NOT an appropriate therapy for a baby who is not breathing spontaneously or whose heart rate is less than 100 bpm.
  7. If HR remains < 60 bpm after 30 seconds of effective ventilation through a properly placed ETT or LMA, increase the FIO<sub>2</sub> to 100% and proceed to chest compressions.

### CHEST COMPRESSIONS (C - Circulation)

Less than 1% require extensive resuscitation measures such as cardiac compressions and medications.

1. Chest compressions should be performed if the HR remains < 60 bpm despite at least 30 seconds of effective ventilation.
2. In most cases, a baby that requires compressions should be intubated and with 100% FIO<sub>2</sub>. The supplementary oxygen concentration should be weaned as soon as the heart rate recovers.
3. Two thumbs encircling technique at the lower third of the sternum is recommended, and preferable from the head of the bed since it allows space for another provider to obtain emergency vascular access i.e. umbilical venous catheter (UVC) or intraosseous needle (ION).
4. Compress the chest by one third of the anteroposterior diameter.
5. Synchronised chest compressions and PPV at a ratio of (3:1) - 3 compressions to 1 ventilation are recommended since compromise of gas exchange is nearly always the primary cause of cardiovascular collapse in neonates.
  - a. Give one lung inflation after every third compression, for a total of 90 compressions and 30 ventilations per minute.
  - b. *One-and-Two-and-Three-and-(pause compression)-Breathe-and (PPV); One-and-Two-and-Three-and-Breathe-and...*
6. Check HR after 60 seconds of compressions.
7. Stop chest compressions when the heart rate is 60 bpm or higher. Once compressions are stopped, return to giving PPV at the faster rate of 40 to 60 breaths per minute.
8. If HR remains < 60 bpm despite compressions and effective ventilation, proceed to emergency medications.

### MEDICATIONS (D - Drugs)

1. Epinephrine (adrenaline)
  - a. Indication: HR < 60 bpm despite 60 seconds of compressions and effective ventilation.
  - b. Preparation: 1: 10,000 (0.1 mg/ml).
    - (a) Take one vial of 1 mg/ml and dilute in 10 ml NSS 0.9%.
    - (b) Use a 1 ml syringe for dosing.
  - c. Route: UVC or ION (rapidly infused)





- d. Dose: 0.01 to 0.03 mg/kg = 0.1 - 0.3 ml/kg of the preparation.
    - (a) Repeat every 3-5 min as needed if HR remains < 60 bpm.
    - (b) Flush with 0.5 or 1 ml NSS 0.9%.
  - e. Endotracheal absorption is less reliable and less effective. *Only* if ETT route is used (while vascular access is obtained), a higher dose of 0.05 to 0.1 mg/kg = 0.5 - 1 ml/kg is recommended.
    - (a) Follow the drug with several positive-pressure breaths to distribute the drug into the lungs. (Do not flush with NSS 0.9%.)
    - (b) Repeated ET administration is not recommended.
  - f. Clearly label the syringe: Epinephrin-IV or Epinephrin-ET ONLY
2. Volume expansion
- a. Routine volume expansion during and after resuscitation is not recommended.
  - b. Indication: Insufficient response to the previous steps of resuscitation with signs of shock or a history of acute blood loss.
  - c. Preparation: Normal saline solution (0.9% NaCl) or type O, Rh negative blood.
  - d. Route: UVC or ION
  - e. Dose: 10 ml/kg
  - f. Administration: over 5 - 10 minutes.
  - g. Avoid giving volume expanders rapidly in premature infants because rapid infusions of large volumes have been associated with IVH.
  - h. Ringer's lactate is no longer recommended for treating hypovolaemia.

Note: Administration of naloxone and sodium bicarbonate are not recommended as part of initial resuscitative efforts in the delivery room for newborns with respiratory depression.

Rapid administration of sodium bicarbonate may increase the risk of intraventricular haemorrhage in preterm newborns.

#### FAILURE TO RESPOND TO RESUSCITATION

1. Consider DOPE mnemonic if failure to respond to resuscitation or sudden deterioration after intubation. (Table 5)
2. Rule out pulmonary hypoplasia, congenital diaphragmatic hernia, pulmonary embolism, or septic/haemorrhagic shock.
3. Request chest x-ray.

Table 5. DOPE mnemonic

The <i>DOPE</i> mnemonic	
D	Displaced endotracheal tube
O	Obstructed endotracheal tube
P	Pneumothorax
E	Equipment failure

#### SPECIAL CONSIDERATION

*Prematurity:* Preterm newborns < 32 weeks gestation

1. Thermal management is particularly important.
2. Increase room temperature to 23 - 25 °C (74 - 77 °F).
3. Use a polyethylene plastic bag to wrap the newborn from feet to neck (without drying).
4. Place a cap on the head.
5. Use an exothermic (warming) mattress.



6. Use a servo-controlled radiant warmer when doing resuscitation.
7. Maintain an axillary temperature 36.5 - 37.5 °C of newly born *non-asphyxiated* infants.
8. There is insufficient current evidence to recommend a preference for either rapid (0.5°C/h or greater) or slow rewarming (less than 0.5°C/h) of unintentionally hypothermic newborns (< 36°C) at hospital admission.
9. Handle the baby gently. Do not position the baby's legs higher than the head (Trendelenburg position).
10. Use a 3-lead electronic cardiac monitor (ECG) with chest leads or limb leads to monitor heart rate if the pulse oximeter has difficulty acquiring a stable signal.
11. Monitor SpO<sub>2</sub> with a pulse oximeter.
12. Consider using CPAP immediately after birth as an alternative to routine intubation and prophylactic surfactant administration in spontaneously breathing preterm infants with respiratory distress.
  - ▶ Many preterm babies can be treated with early CPAP and avoid the risks of intubation and mechanical ventilation.
13. Consider administering surfactant if the baby requires intubation for respiratory distress or is extremely preterm.
  - a. If possible, remove the endotracheal tube immediately after surfactant administration and return to nCPAP for ongoing respiratory support "INTubate - SURfactant - Extubate" or "INSURE".
  - b. Some experts still recommend prophylactic surfactant for extremely premature newborns (< 26 weeks' gestation) because the likelihood of CPAP failure in this subgroup is relatively high.
14. PPV device for providing PEEP or CPAP are preferred. i.e. T-piece or flow-inflating bag
15. Avoid high PIP when giving PPV or CPAP.
16. Avoid rapid intravenous fluid infusions and hypertonic solutions such as sodium bicarbonate.
17. Resuscitation of newborns < 35 weeks gestation should begin with 21 - 30 % oxygen using a blender.
18. Monitor and control blood glucose.
19. Monitor for apnoea and bradycardia.

#### *Congenital Diaphragmatic hernia*

1. Avoid prolonged face-mask ventilation.
2. Quickly intubate the trachea in the delivery room and insert an orogastric tube (Reprogle) with suction to prevent gaseous distention of the stomach and intestines.

#### MAINTAINING NORMOTHERMIA IN RESOURCE-LIMITED SETTINGS

Recommendation to maintain body temperature or prevent hypothermia during transition (birth until 1 to 2 hours of life) in well newborn infants > 30 weeks of gestation:

1. Place them in a clean food-grade plastic bag up to the level of the neck and swaddle them after drying.
2. Nurse infant with skin-to-skin contact or kangaroo mother care.

#### DISCONTINUING RESUSCITATION

The decision to stop resuscitation should be individualised.

An Apgar score of 0 at 10 minutes is a strong predictor of mortality and morbidity in late preterm and term infants.



1. Infants with an Apgar score of 0 after 10 minutes of resuscitation, if the heart rate remains undetectable (asystole), it may be reasonable to stop assisted ventilation.
2. Prolonged bradycardia < 60 bpm without improvement and no respiratory efforts after 10 or 15 min of continuous and apparently adequate resuscitative efforts, the choice to withhold or to continue resuscitation is less clear.
3. Recent work by Dominic Wilkinson suggests that it may be completely appropriate to stop after 25 minutes of trying to get improvement.

## POST RESUSCITATION

Once effective ventilation and/or the circulation has been established, the infant should be maintained in or transferred to an environment where close monitoring and anticipatory care can be provided.

Abnormalities in multiple organ systems may occur following neonatal resuscitation. (Table 6)

Table 6. Clinical signs, laboratory findings, and management

Organ System	Clinical Signs and Laboratory Findings	Management Considerations
Neurologic	Apnea, seizures, irritability, poor tone, altered neurologic examination, poor feeding coordination	Monitor for apnea. Support ventilation as needed. Monitor glucose and electrolytes. Avoid hyperthermia. Consider anticonvulsant therapy. Consider therapeutic hypothermia. Consider delayed initiation of feedings and use of intravenous fluids.
Respiratory	Tachypnea, grunting, retractions, nasal flaring, low oxygen saturation, pneumothorax	Maintain adequate oxygenation and ventilation. Avoid unnecessary suctioning. Cluster care to allow periods of rest. Consider antibiotics. Consider x-ray and blood gas. Consider surfactant therapy. Consider delayed initiation of feedings and use of intravenous fluids.
Cardiovascular	Hypotension, tachycardia, metabolic acidosis	Monitor blood pressure and heart rate. Consider volume replacement or inotrope administration if baby is hypotensive.
Renal	Decreased urine output, edema, electrolyte abnormalities	Monitor urine output. Monitor serum electrolytes as indicated. Monitor weight. Restrict fluids if baby has decreased urine output and vascular volume is adequate.
Gastrointestinal	Feeding intolerance, vomiting, abdominal distention, abnormal liver function tests, gastrointestinal bleeding	Consider abdominal x-ray. Consider delayed initiation of feedings and use of intravenous fluids. Consider parenteral nutrition.
Endocrine-Metabolic	Metabolic acidosis, hypoglycemia (low glucose), hypocalcemia (low calcium), hyponatremia (low sodium), hyperkalemia (high potassium)	Monitor blood glucose. Monitor serum electrolytes as indicated. Consider intravenous fluids. Replace electrolytes as indicated.
Hematologic	Anemia, thrombocytopenia, delayed clotting, pallor, bruising, petechiae	Monitor hematocrit, platelets and coagulation studies as indicated.
Constitutional	Hypothermia	Delay bathing.

Source: Textbook of Neonatal Resuscitation. 7th ed. American Academy of Pediatrics and American Heart Association; 2016.



Infants born > 36 weeks of gestation with evolving moderate-to-severe hypoxic-ischaemic encephalopathy (HIE) should be offered therapeutic hypothermia. (See *guideline on Perinatal Asphyxia and HIE.*)

Briefing and debriefing techniques should be used whenever possible for neonatal resuscitation.

1. Pre-resuscitation Team Briefing:
  - a. Assess perinatal risk factors.
  - b. Identify a team leader.
  - c. Delegate tasks.
  - d. Identify who will document events as they occur.
  - e. Determine what supplies and equipment will be needed.
  - f. Identify how to call for additional help.
2. Performing a post-resuscitation team debriefing reinforces good teamwork habits and helps your team identify areas for improvement.

## ETHICS AND CARE AT THE END OF LIFE

Common ethical principles that apply to all medical care include respecting an individual's rights to make choices that affect his or her life (autonomy), acting to benefit others (beneficence), avoiding harm (non-maleficence), and treating people truthfully and fairly (justice).

If the responsible physicians believe that there is no chance for survival, initiation of resuscitation is not an ethical treatment option and should not be offered. In this case, *humane, compassionate, and culturally sensitive palliative care* focused on ensuring the baby's comfort is the medically and ethically appropriate treatment.

Parents are generally considered the best surrogate decision makers for their babies and should be involved in shared decision making whenever possible.

Parents should be supported by being honest and speaking in an empathic and caring manner.

The primary consideration for decisions regarding life-sustaining treatment for seriously ill newborns should be what is best for the newborn. Factors that should be weighed are:

1. The chance that the therapy will succeed.
2. The risks involved with treatment and non-treatment.
3. The degree to which the therapy, if successful, will extend life.
4. The pain and discomfort associated with the therapy.
5. The anticipated quality of life for the newborn with and without treatment.

## WITHDRAWING OR WITHHOLDING RESUSCITATION

1. Resuscitation may not be indicated:

When gestation, birth weight, or congenital anomalies are associated with almost certain early death and when unacceptably high morbidity is likely among the rare survivors. Examples include extreme prematurity (gestational age 23 weeks or birth weight 400 g), anencephaly, and some major chromosomal abnormalities, such as Trisomy 13 or 18.

2. Resuscitation is nearly always indicated:

In conditions associated with a high rate of survival and acceptable morbidity. This will generally include babies with gestational age 25 weeks or above (unless there is evidence of foetal compromise such as intrauterine infection or hypoxia-ischaemia) and those with most congenital malformations.



3. In conditions associated with uncertain prognosis in which survival is borderline, the morbidity rate is relatively high, and the anticipated burden to the child is high, parental desires concerning initiation of resuscitation should be supported.
4. When withdrawing or withholding resuscitation, care should be focused on the comfort and dignity of the baby and family.

## PROGNOSTIC TOOLS

The only prognostic tool widely used currently is the Apgar score. The Apgar score does not determine the need for neonatal resuscitation or any of its steps.

The Combined-Apgar has been shown to predict outcome in preterm and term infants better than the conventional Apgar score. (Table 7) In 2012 the Combined-Apgar score was introduced by Rüdiger et al. The use of this score seems promising in the future. More studies are ongoing before validating its use in clinical settings.

The Combined-Apgar consist of two numbers, such as 7–10 for the Expanded- and Specified-Apgar, respectively. The Combined-Apgar is calculated as the sum of the Specified- and the Expanded-Apgar.

1. Specified-Apgar: poor (0–3 points), fair (4–6 points) or good (7–10 points).
2. Expanded-Apgar: low (0–2 points), moderate (3–4 points), high (5–6 points) or no intervention (7 points).
3. Combined-Apgar: very low (0–5 points), low (6–9 points), moderate (10–13 points) or high (14–17 points).
  - a. A Combined-Apgar of 7–10 represents an infant without any clinical interventions (Expanded-Apgar of 7) and good clinical signs (Specified-Apgar of 10).
  - b. A Combined-Apgar of 0–10 represents an infant with full resuscitative interventions (Expanded-Apgar 0) and a good clinical response (Specified-Apgar of 10).
  - c. A Combined-Apgar of 0–0 represents an infant with full resuscitative interventions but no clinical response.

		Minutes		
		1	5	10
C	Continuous Positive Airway Pressure*			
O	Oxygen			
M-B	Mask and Bag Ventilation <sup>b</sup>			
I	Intubation and Ventilation			
N	Neonatal Chest Compression			
E	Exogenous Surfactant			
D	Drugs			
Sum of Expanded Apgar				
<u>Scoring Each Item:</u>				
0 = Intervention was performed ; 1 = No intervention was performed				
a : score 0 if "Mask and Bag" or "Intubation and Ventilation" is score 0				
b : score 0 if "Intubation and Ventilation" is scored 0				
A	Appearance (Skin Color) 2 = Completely pink 1 = Centrally pink with acrocyanosis 0 = Centrally blue or pale			
P	Pulse (HR) 2 = > 100 beats per minute 1 = < 100 beats per minute 0 = No heart beat			
G	Grimacing (Reflex) 2 = Appropriate for gestational age 1 = Reduced for gestational age 0 = No reflex response			
A	Activity (Muscle Tone) 2 = Appropriate for gestational age 1 = Reduced for gestational age 0 = No reflex response			
R	Respiration (Chest Movement) 2 = Regular chest movement 1 = Small of irregular chest movement 0 = No chest movement			
Sum of Specified Apgar				
Total (Sum of Expanded + Specified)				

Table 7. The Combined-Apgar scoring system, consists of the Expanded and Specified Apgar scoring systems.



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## ROUTINE CARE OF THE WELL NEWBORN

Avoid separation of mother and infant especially during the first hour of life (the “golden hour”) in order to promote immediate initiation of breastfeeding and early bonding through skin-to-skin contact.

Security in the nursery and mother’s room is necessary to protect the safety of families and to prevent the abduction of newborns.

### ROUTINE CARE

1. Transitional care of the newborn can take place in the mother’s room or in the nursery.
2. The infant should be evaluated every 30 to 60 minutes during the transitional period (first 4-6 hours after birth).
3. When disordered transitioning is suspected, a haemodynamically stable infant can be observed closely in the normal nursery setting for a brief period of time.
4. Infants with persistent signs of disordered transitioning require transfer to a higher level of care.
5. Rooming-in of healthy newborn should be encouraged during the infant’s hospital stay.
6. Well-appearing late-preterm infant of at least  $\geq 35$  weeks’ gestational age with birth weight of  $> 1800$  g -  $2000$  g may room in with mother.
7. Nursing ratios should not exceed 1:4 mother–baby couplets.
8. Record the infant’s weight, head circumference, and length.
9. Classify the infant according to gestational age and birthweight. (*See infant classification in Preterm Newborn guideline*)
10. Determine gestational age of the infant using Ballard score. (*See Appendix A. Ballard Score*)
11. Monitor heart rate, respiratory rate, and temperature; assess colour and tone; and observe signs of withdrawal from maternal medications.
12. The infant’s temperature is stabilised with one of the following modalities:
  - a. Skin-to-skin contact with the mother
  - b. Open radiant warmer on servo control
13. The first bath is given with warm tap water and non-medicated soap once thermoregulation has been achieved with a recorded axillary temperature  $> 97.5^{\circ}\text{F}$  ( $36.5 - 37.4^{\circ}\text{C}$ ) and vital signs are stable. This usually occurs on completion of the transitional period.
14. Umbilical cord care
  - a. Antiseptics, such as chlorhexidine 4%, alcohol 70% or topical antibiotics can be considered if there is concern for infection.
  - b. Clean, dry cord care is generally sufficient and has not been shown to increase infection rates in developed countries.
  - c. Keeping the cord dry also promotes earlier detachment of the umbilical stump.

### ROUTINE MEDICATIONS

1. All newborns should receive eye prophylaxis against gonococcal ophthalmia neonatorum within 1 to 2 hours of birth, regardless of the mode of delivery.
  - ▶ Prophylaxis is administered using antibiotic eye drops or ointment bilaterally in the conjunctival sac.



- ▶ Use: 0.5% Erythromycin (preferred), Gentamicin, or Chloramphenicol eye drops or ointment.
- 2. A single, intramuscular dose of 0.5 to 1 mg of vitamin K (phytomenadione) should be given to all newborns before 6 hours of age to prevent vitamin K deficiency bleeding - Haemorrhagic Disease of the newborn.
- 3. First dose of preservative-free, single-antigen hepatitis B vaccine (*HB Birth dose*) is recommended for all infants at birth, even if the mother's hepatitis B surface antigen (HBsAg) test is negative.
- 4. Hepatitis B vaccine is administered by 12 hours of age when the maternal HBsAg is positive or unknown. (See *TORCH guideline - Hepatitis B*)
- 5. Bacillus Calmette Guerin (BCG) should be administered before discharge or as soon as possible within the 1<sup>st</sup> month of life.

## SCREENING

1. Maternal prenatal screening tests typically include the following:
  - a. Blood type, Rh, antibody screen
  - b. Haemoglobin or haematocrit
  - c. Rubella antibody
  - d. HBsAg (Hepatitis B surface antigen)
  - e. Serologic test for syphilis (Venereal Disease Research Laboratory [VDRL] or rapid plasmin reagin [RPR])
  - f. Group B Streptococcus (GBS) culture
  - g. Human immunodeficiency virus (HIV)
  - h. Gonorrhoea and Chlamydia cultures
  - i. Glucose tolerance test (where applicable)
  - j. Antenatal testing results, including multiple marker screenings, and ultrasonography results
  - k. Cystic fibrosis carrier testing (where applicable)
2. Screening for neonatal sepsis risk (See *Neonatal sepsis guideline*)
 

All newborns should be screened for the risk of perinatally acquired GBS disease.
3. Cord blood screening
  - a. A blood type and direct Coombs test (also known as direct anti-globulin test or DAT) should be performed on any infant born to a mother who is Rh-negative, has a positive antibody screen, or who has had a previous infant with Coombs-positive haemolytic anaemia.
  - b. A blood type and DAT should be obtained on any infant if jaundice is noted within the first 24 hours of age or there is unexplained hyperbilirubinaemia.
4. Glucose screening
  - a. Infants should be fed early and frequently to prevent hypoglycaemia.
  - b. Infants of diabetic mothers, infants who are small or large for gestational age (SGA/LGA), and preterm infants should be screened for hypoglycaemia in the immediate neonatal period. (See *Hypoglycaemia guideline*)
5. Newborn metabolic screening
  - a. Universal newborn screening for specific disorders for which there are demonstrated benefits of early detection and efficacious treatment of the condition being tested, such as congenital hypothyroidism,





phenylketonuria, galactosemia, hemoglobinopathies, cystic fibrosis, as well as amino acid, fatty acid, and organic acid disorders.

b. Routine collection of the specimen for healthy term newborn is between 24 and 72 hours of life.

#### 6. Bilirubin screening

a. A pre-discharge serum bilirubin measurement combined with risk factor assessment best predicts subsequent hyperbilirubinaemia requiring treatment.

b. A total serum bilirubin measurement can be obtained at the time of the newborn metabolic screen.

c. Jaundice during the first 24 hours of life is considered pathologic and warrants a total serum bilirubin level.

d. The bilirubin result should be plotted and interpreted on an hour-specific nomogram to determine the need for phototherapy. (*See Hyperbilirubinaemia guideline*)

#### 7. Hearing screening

Routine screening for hearing loss in newborns (*See Hearing loss guideline*)

#### 8. Critical congenital heart disease screening (*See Evaluation in Suspected Congenital Heart Disease guideline*)

a. Screening for critical congenital heart disease (CHD) using pulse oximetry should be added to the uniform newborn screening panel.

b. A normal pulse oximetry reading does not rule out all congenital heart diseases. Conversely, a low pulse oximetry reading does not always signify congenital heart disease.

### ROUTINE ASSESSMENTS

1. Perform a complete physical examination within 24 hours of birth.
2. Evaluate vital signs, including respiratory rate, heart rate, and axillary temperature, every 8 to 12 hours.
3. First urination should occur by 24 hours of age. The first passage of meconium is expected by 48 hours of age.
4. Delayed urination or stooling is cause for concern and must be investigated.
5. Weight, length, head, chest and abdominal circumference are recorded in the infant's chart.

### FAMILY AND SOCIAL ISSUES

1. Sibling visitation is encouraged and is an important element of family-centred care.
2. However, siblings with fever, signs of acute respiratory or gastrointestinal illness, or a history of recent exposure to communicable diseases, such as influenza or chicken pox, are discouraged from visiting.
3. Social service involvement is helpful in circumstances such as teenage mothers; lack of, or limited, prenatal care; history of domestic violence; maternal substance abuse; history of previous involvement with child protective services or similar agency.

### FEEDINGS

1. The frequency, duration, and volume of each feed will depend on whether the infant is feeding breast milk or formula.
2. Exclusive breastfeeding for the first 6 months of a newborn's life is encourage.
3. Mothers should initiate breastfeeding as soon as possible after delivery, preferably in the delivery room, and then feed on demand, 8 to 12 times per day during the newborn hospitalisation.
4. Standard 19 or 20 cal/oz, iron-containing infant formula is offered to infants for whom breastfeeding is contraindicated, or at the request of a mother who desires to formula-feed.



5. Formula-fed infants are fed at least every 3 to 4 hours; 1 oz per feed.

#### NEWBORN CIRCUMCISION

1. Data are not sufficient to recommend routine neonatal circumcision.
2. Potential benefits are decreased incidence of urinary tract infection in the first year of life, decreased risk for the development of penile cancer, and decreased risk of acquiring sexually transmitted diseases, particularly HIV infection.

#### DISCHARGE READINESS

The hospital stay of the mother and her newborn should be long enough to identify early problems and to ensure that she is able and prepared to care for the infant at home.

All efforts should be made to promote the simultaneous discharge of a mother and her infant.

Ensure

1. Adequacy of oral intake, particularly for breastfed infants. This includes a minimum of eight feeds per day; one wet diaper per day of age, constant at the sixth day of life; and at least one stool per day.
2. Routine cord and skin care.
3. Routine post-circumcision care (if performed).
4. Parents can recognise signs of infant illness including fever, irritability, lethargy, or a poor feeding pattern.
5. Observation for neonatal jaundice.
6. Safe sleep environment, such as supine positioning for sleep, using tight-fitting crib sheets, having no loose blankets or materials in the crib, and sleeping in proximity but not bed sharing.
7. Appropriate installation and use of an infant car seat.
8. Other infant safety matters, such as maintaining a smoke-free environment, checking smoke detectors, lowering the hot water temperature at home, and hand hygiene.

Minimum discharge criteria to be met before any term newborn (37 0/7 to 41 6/7 weeks' gestation) is discharged from the hospital.

1. Clinical course and physical examination reveal no abnormalities that require continued hospitalisation.
2. The infant's vital signs are documented to be within normal ranges (with appropriate physiologic variations) and stable for 12 hours preceding discharge.
3. Axillary temperature of 36.5°C to 37.4°C (97.7–99.3°F, measured properly in an open crib with appropriate clothing), a respiratory rate below 60 per minute and no other signs of respiratory distress, and an awake heart rate of 100 to 190 beats per minute.
4. The infant has completed at least two successful feedings and adequately breastfeeding or formula feeding.
5. The infant has urinated regularly and passed at least one stool spontaneously.
6. There is no excessive bleeding at the circumcision site for at least 2 hours. (if performed)
7. The clinical significance of jaundice has been assessed and appropriate management and follow-up plans have been determined.
8. The infant has been adequately evaluated and monitored for sepsis based on maternal risk factors.
9. Maternal and infant laboratory tests have been reviewed.
10. The infant's BCG (Bacillus Calmette Guerin) vaccine has been administered. If not, indicate the nearest health centre for vaccination.



11. The infant's initial hepatitis B birth dose vaccine has been administered.
12. The mother's vaccine status has been updated, including influenza (during the flu season) and tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap).
13. Newborn metabolic, hearing, and CHD screenings have been completed.
14. Parental competency to care for the newborn has been demonstrated.
15. Appropriate car safety seat has been obtained, and the parent has demonstrated proper infant positioning and use.
16. Family members or other support persons are available to mother and infant after discharge.
17. A physician-directed source of continuing health care (well child visit) has been identified.
18. Family, environmental, and social risk factors have been assessed.

Late-preterm infants are usually not expected to meet the necessary competencies for discharge before 48 hours of age.

1. Accurate gestational age has been determined.
2. A physician-directed medical source has been identified, and a follow-up visit has been arranged within 48 hours of discharge.
3. A formal evaluation of breastfeeding has been documented in the chart by trained caregivers at least twice daily since birth.
4. The infant has demonstrated 24 hours of successful feeding with the ability to coordinate sucking, swallowing, and breathing while feeding.
5. A feeding plan has been developed and is understood by the family.
6. The infant has passed a car safety seat test to observe for apnoea, bradycardia, or oxygen desaturation with results documented in the chart.

## FOLLOW-UP

For infants discharged before 48 hours of life, an appointment with a health care provider should be arranged within 48 hours of discharge.

For newborns discharged between 48 and 72 hours of age, outpatient follow-up should be within 2 to 3 days of discharge.

Other visits include at 2 weeks of life and at one month of age.

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## PRETERM NEWBORN

### INFANT CLASSIFICATION

#### Infant classification by GA

1. Preterm: infants born at < 37 completed weeks of gestation
  - a. Extremely preterm: infants born < 28 weeks of gestation.
  - b. Early preterm: infants born < 34 weeks of gestation.
  - c. Late preterm: infants born between 34 0/7 and 36 6/7 weeks of gestation.
2. Term: infants born between 37 0/7 and 41 6/7 weeks of gestation.
  - a. Early term: infants born between 37 0/7 and 38 6/7 weeks of gestation.
  - b. Full term: infants born between 39 0/7 and 41 6/7 weeks of gestation.
  - c. Post-term: infants born after 42 weeks of gestation.

#### Infant classification by Birth weight

1. Normal birth weight (NBW): 2,500 to 4,000 g
2. Low birth weight (LBW): < 2,500 g
  - a. Very low birth weight (VLBW): < 1,500 g
  - b. Extremely low birth weight (ELBW): < 1,000 g



#### Infant classification by size

1. Average for gestational age (AGA): newborn whose growth measures are according to gestational age.
  2. Small for gestational age (SGA): newborn whose birth weight or birth crown-heel length is < 10th percentile for GA or < 2 standard deviations (SDs) below the mean for the infant's GA (approximately the 3rd percentile for GA).
  3. Large for gestational age (LGA): newborn whose birth weight is > 2 SDs above the mean for GA or > 90th percentile.
- ▶ LBW infants may be preterm or term SGA.

### AETIOLOGY

1. Low socioeconomic status.
2. Women younger than 16 or older than 35 years.
3. Acute or chronic maternal illness.
4. Multiple-gestation births.
5. Maternal activity requiring long periods of standing or substantial amounts of physical stress.
6. Prior poor birth outcome.



7. Obstetric factors such as uterine malformations, uterine trauma, placenta previa, abruptio placentae, hypertensive disorders, preterm cervical shortening, previous cervical surgery, premature rupture of membranes, and chorioamnionitis.
8. Foetal conditions such as non-reassuring testing of foetal well-being, IUGR, or severe hydrops that may require preterm delivery.
9. Inadvertent early delivery because of incorrect estimation of GA.

#### NEONATAL COMPLICATIONS ASSOCIATED TO PREMATURITY

Problems associated with preterm birth are related to difficulty in extrauterine function due to immaturity of organ system.

Table 1. Neonatal Complications associated to prematurity

GENERAL	Thermoregulation- hypothermia
RESPIRATORY	Hyaline Membrane Disease/RDS Broncho Pulmonary Dysplasia (BPD) Persistent Pulmonary Hypertension of the Newborn (PPHN) Apnoea of Prematurity
CARDIOVASCULAR	Persistent Ductus Arteriosus (PDA) Neonatal Hypertension
GASTROINTESTINAL/NUTRITIONAL	Feeding Intolerance Necrotizing Enterocolitis (NEC) Malnutrition
HAEMATOLOGIC	Anaemia of prematurity Hyperbilirubinaemia Coagulation disorders
METABOLIC, WATER AND ELECTROLYTE IMBALANCES	Hypo/hyper Glycaemia Hypo/hyper Calcaemia Hypo/hyper Natremia Hyper Potassemia Metabolic acidosis Osteopenia of Prematurity



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## NEUROLOGICAL/VISION/AUDIO

Intra Ventricular Haemorrhage (IVH)

Peri Ventricular Leukomalacia (PVL)

Asphyxia

Retinopathy of Prematurity (ROP), blindness

Cerebral Palsy (CP)

Deafness

Hydrocephalus

## INFECTIONS

Early onset sepsis

Late onset sepsis

## MANAGEMENT OF THE PRETERM INFANT

### Resuscitation and stabilisation

1. Delivery in an appropriately equipped and staffed hospital is preferable.
2. Risks to the very premature or sick preterm infant are greatly increased by delays in initiating necessary specialised care.
3. Resuscitation and stabilisation require the immediate availability of qualified personnel and equipment.
4. Resuscitation of the newborn at delivery should be in accordance with the established Neonatal Resuscitation Program (NRP). (*See Neonatal Resuscitation guideline*)
5. Adequate oxygen delivery and maintenance of proper temperature are immediate postnatal goals.
6. Thermal regulation for the small preterm infant, this will require either an overhead radiant warmer (with the advantages of infant accessibility and rapid temperature response) or a closed incubator (with the advantages of diminished insensible water loss).
7. Weaning from an isolette/incubator should be considered when an infant with stable cardiopulmonary state reaches > 1600 grams and is able to be swaddled.

### Respiratory disorders

- ▶ Preterm infants have higher respiratory morbidity and mortality, with increased risk of RDS, Apnoea of prematurity, TTNB, PPHN, and BPD. (*See Respiratory disorders guidelines*)

### Fluid and electrolyte

- ▶ Therapy must account for relatively high insensible water loss while avoiding over-hydration and maintaining normal glucose and plasma electrolyte concentrations. (*See Nutritional Support guideline*)

### Hyperbilirubinemia

- ▶ Hyperbilirubinemia, which is inevitable in less mature infants, can usually be managed effectively by careful monitoring of bilirubin levels and early use of phototherapy. (*See hyperbilirubinaemia guideline*)

### Infection

- ▶ Infection may be the precipitant of preterm delivery. If an infant displays signs or symptoms that could be attributed to infection, the infant should be carefully evaluated for sepsis. (*See Neonatal Sepsis guideline*)

### Patent ductus arteriosus (PDA)



- ▶ PDA in preterm infants with birth weight >1,000 g often requires only conservative management with fluid restriction (usually 110 to 130 mL/kg/day) and supportive care. (See *PDA guideline*)

#### Nutrition

1. Nutrition has a direct impact in preterm newborn morbidity and mortality. (See *Nutritional Support guideline*)
2. Early nutrition mediates the influence of severity of illness on ELBW infants.
3. Early aggressive Total Parenteral and Enteral Nutrition support are associated with lower rates of death and short term morbidities and improved growth and neurodevelopmental outcomes.

#### The sensory environment of the intensive care nursery

- ▶ Unlike any other hospital patients, the preterm infant is going through a complex and vital stage of brain development in an environment far different from the expected norm. (See *Developmentally Supportive Care guideline*)

#### Immunisations

- ▶ Diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine; inactivated poliovirus vaccine (IPV); multivalent pneumococcal conjugate vaccine (PCV); and Haemophilus influenzae type b (Hib) vaccine are given in full doses to preterm infants on the basis of their chronologic age (i.e., weeks after birth). (See Appendix H. Schedule for immunisation of Preterm Infants)

#### ADMISSION CRITERIA

1. Admit infants less than 35 weeks' gestational age or less than 1800-2000 g birth weight.
2. If well late preterm infants are in their mothers' rooms in the first 24 hours, close monitoring is needed. (See *Routine Care of the Well Newborn guideline*)

#### CRITERIA FOR DISCHARGE

The 3 physiologic competencies that are generally recognised as essential before hospital discharge of the preterm infant are:

1. Oral feeding sufficient to support appropriate growth.
2. The ability to maintain normal body temperature in a home environment.
3. Sufficiently mature respiratory control.

#### Infant Readiness for Hospital Discharge

1. Daily sustained pattern of weight gain: 15-30 grams.
2. Has achieved a weight of at least 1800 grams.
3. Controlled axillary temperature, 36.5° to 37.4° C with the infant fully clothed in an open crib.
4. Competent suckle feeding, breast or bottle, without cardiorespiratory compromise.
5. If weight loss greater than 7 % in 48 hours, consider further assessment before discharge.
6. Cardio-Respiratory Stability.
7. Appropriate immunisations have been administered.
8. Appropriate metabolic screening has been performed.
9. CBC control before discharge has been assessed.
- 10.ROP screening has been performed. (See *Retinopathy of Prematurity guideline*)



11. Hearing screening has been performed. (See *Hearing Loss guideline*)
12. Transfontanellar US: indicated at 36 - 40 weeks post menstrual age.
13. Family/Parent orientation, education and preparation ensured to provide:
  - a. Basic infant care, including bathing; skin, cord, and genital care; temperature measurement; dressing; and comforting.
  - b. Understanding and detection of the general early signs and symptoms of illness as well as the signs and symptoms specific to the infant's condition.
  - c. Infant safety precautions, including proper infant supine positioning during sleep and proper use of car seats or car bed.
  - d. Administration of medications, specifically proper storage, dosage, timing, and administration and recognition of potential signs of toxicity.
  - e. The appropriate technique for each special care procedure required, including special dressings for infusion entry site, intestinal stoma, or healing wounds; maintenance of an artificial airway; oropharyngeal and tracheal suctioning; and physical therapy, as indicated.
  - f. Parents must 'know' their baby before discharge and have sufficient knowledge to continue care at home.
14. Follow up in the first week after discharge.

#### LONG TERM SEQUELAE OF PREMATURE INFANTS (Table 2)

Table 2. Long term impact of preterm birth on survivors.

Long-term outcomes		Examples:	Frequency in survivors:
<b>Specific physical effects</b>	Visual impairment	<ul style="list-style-type: none"> <li>• Blindness or high myopia after retinopathy of prematurity</li> <li>• Increased hypermetropia and myopia</li> </ul>	Around 25% of all extremely preterm affected [a] Also risk in moderately preterm babies especially if poorly monitored oxygen therapy
	Hearing impairment		Up to 5 to 10% of extremely preterm [b]
	Chronic lung disease of prematurity	<ul style="list-style-type: none"> <li>• From reduced exercise tolerance to requirement for home oxygen</li> </ul>	Up to 40% of extremely preterm [c]
	Long-term cardiovascular ill-health and non-communicable disease	<ul style="list-style-type: none"> <li>• Increased blood pressure</li> <li>• Reduced lung function</li> <li>• Increased rates of asthma</li> <li>• Growth failure in infancy, accelerated weight gain in adolescence</li> </ul>	Full extent of burden still to be quantified
<b>Neuro-developmental/ behavioral effectse</b>	Mild Disorders of executive functioning	<ul style="list-style-type: none"> <li>• Specific learning impairments, dyslexia, reduced academic achievement</li> </ul>	
	Moderate to severe Global developmental delay	<ul style="list-style-type: none"> <li>• Moderate/severe cognitive impairment</li> <li>• Motor impairment</li> <li>• Cerebral palsy</li> </ul>	Affected by gestational age and quality of care dependent [f]
	Psychiatric/ behavioral sequelae	<ul style="list-style-type: none"> <li>• Attention deficit hyperactivity disorder</li> <li>• Increased anxiety and depression</li> </ul>	
<b>Family, economic and societal effects</b>	Impact on family Impact on health service Intergenerational	<ul style="list-style-type: none"> <li>• Psychosocial, emotional and economic</li> <li>• Cost of care [h] – acute, and ongoing</li> <li>• Risk of preterm birth in offspring</li> </ul>	Common varying with medical risk factors, disability, socioeconomic status [g]

Source: WHO - The Global Action Report on Preterm Birth 2012; 15 million preterm births: priorities for action based on national, regional and global estimates; Chapter 2.





## NEURODEVELOPMENTAL FOLLOW UP CLINIC FOR HIGH RISK NEWBORNS

Criteria:

1. Birth weight < 1,500 grams.
2. Gestational age < 32 weeks.
3. Newborn with Severe Perinatal Asphyxia with hypoxic ischaemic encephalopathy.
4. Newborn with Hyperbilirubinaemia that required blood exchange transfusion.
5. Newborn with congenital anomalies.
6. Newborn with neonatal chronic pulmonary disease (Broncho-pulmonary dysplasia).
7. Newborn with meconium aspiration syndrome that required more than 2 weeks recovery.
8. Newborn with Meningitis.
9. Newborn with seizures.
10. Newborn with an abnormal head ultrasound (HUS).
11. Newborn who had a major surgery.

All discharged infants from the neonatal unit who fulfil these criteria should be given an appointment for the High Risk Infant Follow Up Clinic which is different from the regular follow up clinic of other infants discharged from the unit.

Most of these infants will require follow up with a multidisciplinary team.



Source: <http://www.marchofdimes.org>

Further reading:

American Academy of Pediatrics, Committee on Fetus and Newborn. Hospital Discharge of the High-Risk Neonate. *Pediatrics* 2008;122(5): 1119-26.

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## DEVELOPMENTALLY SUPPORTIVE CARE

### DEVELOPMENTAL CARE

Developmentally appropriate, individualised, and family-centred care is better neonatal care.

The developmental plan is complementary to the medical plan and uses developmental principles, techniques, and environmental modifications to reduce stressors that challenge an infant's physiologic stability through behavioural instability.

*Our patients can and do "talk" to us, can individually communicate what they can tolerate, and can indicate when and where they need help.*

### NEWBORN INDIVIDUALISED DEVELOPMENTAL CARE

#### Goals

1. Promote organised neuro-behavioural and physiological function.
2. Alter the physical environment to protect vulnerable developing sensory systems.
3. Family-centred care.

#### Outcomes

1. Improved physiological stability.
2. Reduced stress and pain.
3. Appropriate sensory experience.
4. Protection of postural development.
5. Improved sleep patterns.
6. Improved feeding.
7. Improved neuro-developmental outcomes.
8. Shorter hospital stay.
9. Decreased morbidity.
10. Confident parenting and attachment.
11. Staff satisfaction.

Note: Newborn Individualised Developmental Care and Assessment Program (NIDCAP) is a set of practices by which specially trained infant developmental specialists and NICU staff repeatedly assess an individual newborn preterm infant's developmental status and ability to withstand the stresses of NICU life before, during, and after caregiving procedures.

The NIDCAP approach is the most evidence-based, best organised, and best validated approach to developmental care for all infants, and it is especially powerful with very low- and extremely low-birth- weight preterm infants.

The formal NIDCAP evaluation involves detailed, systematic observations every 2 minutes, before, during, and after a caregiving intervention, making it possible to discern whether a child is thriving in, or merely coping with the environment's experiences and sensory load, or whether events overwhelm those coping skills and produce an unpleasant, stressful, or even unstable situation.



## ASSESSMENT

### STRESS RESPONSES

A priority of the individualised developmental care is for infants to experience auditory, visual, and social input without disrupting autonomic, motor, or state function and integration.

Cues

1. Autonomic
2. Motor
3. State organisational behaviour
4. Attentional/interactive signs of stress

1. Autonomic signs of stress include changes in colour, heart rate, and respiratory patterns, as well as visceral changes such as gagging, hiccupping, vomiting, and stooling.

*Supportive interventions:*

- a. Swaddling, hand-containment (facilitated tuck), and nesting with boundaries.
- b. A quiet, calm environment, swaddling to reduce motor arousal, and letting the infant guide the pace of a feeding are strategies that will elicit less stress behaviours during feeding and may result in better feeding tolerance.

2. Motor signs of stress include facial grimacing, gaping mouth, twitching, hyperextension of limbs, finger splaying, back arching, flailing, and generalised hyper- or hypotonia.

*Supportive interventions:*

Containment or “facilitated tuck” is useful for calming or support during care and/or procedures. Positioning aids may be needed when an infant cannot sustain a flexed, aligned posture with midline orientation that is also comfortable.

3. State alterations suggesting stress include rapid state transitions, diffuse sleep states, irritability, and lethargy.

*Supportive interventions:*

- a. Environmental modifications are made to promote quiet, focused attentional states and foster periods of well-defined, restful sleep with regular respirations and little movement.
- b. Avoid activities that cause abrupt state transitions, such as rousing an infant from sleep by suddenly repositioning for an examination.
- c. Letting an infant know when a caregiver approaches to perform care at the bedside by using soft speech (infant’s name), gentle touch, and containment while slowly repositioning can alleviate abrupt state disruption.

4. Changes in attention or interactional availability, exhibited by covering eyes/face, gaze aversion, frowning, and hyper-alert or panicky facial presentation, represent signs of stress in preterm infants.

Self-consoling behaviours to cope with stress include hand or foot bracing, sucking, bringing hands to face, flexed positioning, cooing, and grasping of linens, tubing, or own body parts.

The individual caregiver must learn to recognise and appropriately respond when an infant communicates stress, pain, or the need for attention.



## THE ENVIRONMENT

### SOUND

1. Increased noise levels in the NICU are associated with physiologic stress and autonomic instability.
2. Intense noise levels at 55 to 60 dB and above disrupt sleep and may impact brain development occurring during both active/light sleep and quiet sleep.
3. The American Academy of Pediatrics (AAP) recommends that NICU sound levels not exceed an hourly equivalent sound level of 45 dB.
4. Transient sounds should not exceed 65 dB.
5. The most natural source of sound for the infant is mother's voice.

#### *Supportive interventions:*

- a. Avoid personnel tapping on the incubator walls or using the top of the incubator as a shelf.
- b. To manage environmental sound: ensure low conversational tones, round away from the bedside, place pagers on vibrate mode, and have care in opening and closing portholes.
- c. Maintain quiet environment during oral feeding.
- d. Only use radios, portable music devices, musical toys etc. when clinically indicated and ensure other babies are not disturbed.
- e. Promote at least one 'rest time' or 'napping time' per day. Lower light and noise levels and suspend all routine procedures/ward rounds. Leave babies undisturbed to facilitate sleep. Encourage parents to view this as a quiet time to spend with baby.

### LIGHT

1. Reduced illumination is associated with increased autonomic stability in preterm infants and more frequent eye opening by both preterm and term infants.
2. An additional developmental benefit of reducing environmental light is a concurrent reduction in environmental noise and less handling of infants.
3. The AAP Guidelines for Perinatal Care recommend adjustable ambient light levels from 10 to 600 lux in infant areas.
4. Visual stimulation before 30 to 32 weeks' PMA is often accompanied by stress responses.
5. Cycled lighting may be beneficial for preterm infants, but the gestational age at which light intensity, day/night pattern, and light duration is safe and beneficial is not known.
6. Preterm infants who have been exposed to cycled lighting at 30 weeks' gestational age and beyond have greater weight gain, earlier oral feeding, and more regulated patterns of rest/activity after discharge than control groups.

#### *Supportive interventions:*

- a. Protection from light for the early preterm infant can be accomplished with thick, quilted covers that have dark material on the side facing the incubator.
- b. Lighting for staff needs to be at a level that allows safe and efficient functioning.
- c. Procedure lighting that can be controlled or reduced as needed is recommended for each NICU bed.
- d. During procedures, the infant's eyes should be protected from direct light using blanket tents or other methods that do not require tactile input.
- e. Daylight is preferable to artificial lighting. Protect babies from direct sunlight.



- f. Avoid direct bright light during feeding.
- g. Use dimmer switches and avoid sudden changes in light levels.
- h. Protect babies from bright light for a minimum of 18 hr following ROP screening.

## TEMPERATURE

1. Ambient temperature should be 22° to 26° C (72° to 78° F).
2. Relative humidity should be 30% to 60%.

## CARE PRACTICES

### POSITIONING

The goals of positioning are to facilitate flexed and midline positioning of extremities, stabilise respiratory patterns, and lessen physiologic stress.

#### *Supportive interventions:*

- a. Interventions include flexion, containment, midline alignment, and comfort.
- b. The use of “nesting materials” such as soft blanket rolls and commercially available positioning devices, or swaddling is useful in minimising the upper/lower extremity abduction, scapular retraction, and cervical hyperextension typical of preterm infants.
- c. More mature infants with congenital neuromuscular or skeletal disorders may also need positioning support.
- d. Nesting needs to allow sufficient room for the infant to push against boundaries, to facilitate continuing development of the neuromotor and skeletal systems.
- e. Use side-lying position for cares, including diaper changes. Promote a flexed position with limbs tucked in. Do not lift baby’s legs, place soles of feet together and roll side-to-side instead.
- f. Use containment and swaddling for transfers into/out of incubator/cot, weighing, and bathing. Move baby slowly, in flexed, side-lying position, close to carer’s body.

### FEEDING

1. Breastfeeding is the preferred method, and breast milk is recommended for both preterm and term infants.
2. The transition to oral feeding from tube feeding requires skilled assessment and judgment on the part of the caregiver.
3. Pre-non-nutritive suck (NNS) is characterised by weak suck and instability of motor, autonomic, and state regulation systems.
4. Nutritive suck typically begins at approximately 33 weeks’ PMA and progresses to full oral intake as autonomic stability and oral motor coordination improve.
5. As baby begins to take more enteral feeds (at around 33 weeks), NNS is no longer appropriate as it may mask feeding cues.
6. Leaving a gavage tube in place during initial feeding attempts or repeated insertions may cause discomfort and interfere with feeding progression or generate oral aversion and later feeding disorders.

#### *Supportive interventions:*

- a. NNS is characterised by more optimal suck patterns and should be encouraged during gavage feeds.
- b. Feed in a flexed, midline position, use paced techniques, and use slow-flow nipples.
- c. Remove gavage tube when initiating feeds.



## TOUCH

1. In the NICU, elements of both overstimulation and under-stimulation can be found, along with randomness and atypical, biologically unexpected stimuli.
2. Parents can be taught how to touch their infant in ways that are nurturing and won't create stress.
3. Kangaroo care sometimes referred to as skin-to-skin holding is a technique consistently associated with improved infant outcomes (i.e., fewer respiratory complications, improved weight gain, and temperature regulation) and maternal outcomes (i.e., improved maternal competence and longer breastfeeding duration).
4. Kangaroo holding impacts several developing sensory systems including tactile (skin), olfactory, and vestibular (rise/fall of chest).
5. Contraindication of Kangaroo: umbilical lines in situ

### *Supportive interventions:*

1. Hand containment or facilitated tuck can be done by parents soon after admission. This technique reduces pain responses during painful and non-painful events.
2. Kangaroo care can be initiated as soon as infants are medically stable - including those on CPAP with a stable oxygen requirement and medically stable ventilated babies.
  - a. Choose a mutually convenient time for parents and baby.
  - b. Provide privacy for parents to prepare clothing. Suggest parents wear a clean loose fitting, front fastening shirt.
  - c. Provide comfortable chair and foot rest if appropriate.
  - d. Infants are held on their mother or father's chest wearing only a diaper and are covered with a blanket and hat as needed.
  - e. A minimum of 1 hour is recommended for kangaroo holding.
  - f. Encourage mother to express breast milk following kangaroo time.
  - g. A NICU protocol for kangaroo holding ensures safety and minimises an infant's stress response to handling/positioning.

## PAIN AND STRESS

1. Pain assessment and management is a basic right of all patients.
2. Examples of potential high-stress conditions include delivery room care, transport to NICU, admission process, and diagnostic procedures that often produce pain or discomfort along with stress.
3. During stressful events, developmental support based on infant cues guides the NICU team's care and needs to be ongoing with every episode of care.

### *Supportive interventions:*

- a. Effective non-pharmacologic interventions incorporate developmental principles such as swaddling, NNS, kangaroo holding, hand containment/facilitated tuck, breastfeeding, and administration of an oral sucrose solution.
- b. Non-pharmacologic measures are used as an adjunct to pharmacologic treatment of moderate-to-severe pain.



## PARENT SUPPORT/EDUCATION

1. Enhancement of family involvement and direct care is thus a goal of many NICUs.
2. “Family-centred care” takes this to the next level, affirming that the family is the long-term constant and best (perhaps only) hope for the child’s ultimate success, and reinforcing the role of the family in directing the child’s care with full information and support from the health care team.
3. Family-centred NICU policies include welcoming families 24 hours per day, promotion of family participation in infant care, creation of parent advisory boards, implementation of parent support groups, and comfortable rooming-in areas for parents.
4. The family’s cultural background, spiritual beliefs, and wishes should be respected.
5. Family-centred care should be implemented during NICU stay as well as upon transition to home.
6. Parents must understand that their baby may not behave as a term baby would when he or she has reached 40 weeks’ PMA.

### *Supportive interventions:*

- a. Support groups for parents of preterm infants designed to provide long-term emotional and educational support should be available.
- b. Magazines, books, and web-based materials related to parenting preterm infants should be available.
- c. Ensure a follow-up programme to prevent or minimise developmental delay through early identification of risk factors and refer to appropriate treatment programs.

### *Further reading:*

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### RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome (RDS), formerly known as hyaline membrane disease (HMD), describes a disease typical of preterm infants <34 weeks gestation that is caused by insufficient pulmonary surfactant in alveoli.

Advances in preventive and rescue treatment strategies have greatly reduced the impact of RDS on neonatal morbidity and mortality:

1. antenatal glucocorticoids
2. exogenous surfactant
3. continuous positive airway pressure (CPAP)

#### RISK FACTORS

1. Prematurity: alveolar type II cells do not develop until early in the third trimester.
2. Sex: Male infants due to the presence of circulating weak foetal androgens that inhibit the production of surfactant phospholipids.
3. Maternal diabetes: due to enhanced production of foetal insulin which inhibits the production of proteins important for surfactant function.
4. Mutations in surfactant-related proteins: surfactant protein-B (SP-B), surfactant protein-C (SP-C). This is a rare condition and is not too associated with the typical RDS.

Labor lowers the risk of RDS due to the production of endogenous maternal glucocorticoids which enhance lung maturation.

#### DIAGNOSIS

Clinical manifestation of RDS:

1. tachypnea
2. retractions
3. flaring of the nasal alae
4. grunting
5. cyanosis

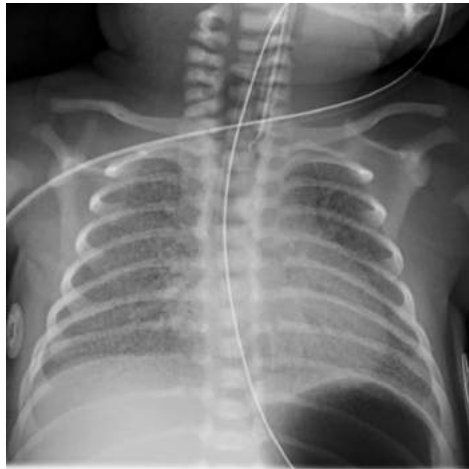
Typical Radiographic evidence: (Figure 1)

1. low lung volumes
2. homogeneous microatelectasis/diffuse reticulogranular pattern (ground glass)
3. air bronchograms highlighted by the surrounding microatelectasis





Figure 1. A typical radiographic features of RDS.



Source: Constanza E, 2013; HUC, Caracas.

Laboratory abnormalities: Arterial blood gas (ABG) with respiratory acidosis, metabolic acidosis, or mixed acidosis, hypoxaemia and hypercarbia.

#### OTHER DIAGNOSIS TO CONSIDER:

1. Transient tachypnea of the newborn
2. Pneumonia, especially due to group B Streptococcus
3. Genetic disorders of the surfactant system
4. Disordered lung development

#### MANAGEMENT OF RDS

##### Objective:

1. establish and maintain functional residual capacity (FRC)
2. lower alveolar surface tension
3. recruit atelectatic alveoli and in progressive atelectasis of recruited airspaces

##### Management:

1. Prenatal care
2. Delivery Room Stabilisation
3. Surfactant therapy
4. Respiratory support
5. Monitoring and supportive care

#### 1. PRENATAL CARE

Prevention: with use of antenatal corticosteroids (ANC)

1. A single course of ANC is recommended for pregnant women 24-34 weeks of gestation in preterm labor or who are at risk of delivery within 7 days, including for those with rupture membranes and multiple gestations.



May be considered for pregnant women at 23 weeks of gestation, who are at risk of preterm delivery within 7 days.

2. Betamethasone may be considered in pregnant women between 34 - 36 6/7 weeks of gestation who are at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.
3. A complete course of ANC is considered to be EITHER
  - a. Betamethasone at 12 mg intramuscular (IM) q24h × 2 doses OR
  - b. Dexamethasone 6 mg IM q 12h × 4 dosesDexamethasone is given every 12 hours due to its short acting half life and peak serum concentration.
4. Short term use of tocolytic drugs should be considered to delay birth and allow safe in-utero transfer to a specialised centre or to enable prenatal corticosteroids time to take effect.

Note: The optimal treatment to delivery interval is more than 24 hours and less than 7 days after the start of steroid treatment.

The WHO recommends that a single repeat course of steroids may be considered if preterm birth does not occur within 7 days after the initial course and subsequent assessment demonstrates that there is a high risk of preterm birth in the next 7 days.

ANC has shown to improve survival, reduce the risk of RDS, NEC and intra-ventricular haemorrhage.

## 2. DELIVERY ROOM STABILISATION

1. Babies with RDS have difficulty maintaining alveolar aeration after birth, although most try to breathe for themselves, and therefore any support of transition is 'stabilisation' rather than 'resuscitation'.
2. Umbilical cord clamping should be delayed 30- 60 seconds.
3. Cord milking may be a reasonable alternative if delayed cord clamping is not possible. (This practice is not yet recommended since more studies are needed, and as such remains controversial.)
4. Oxygen:
  - a. Administer using a blender.
  - b. Initial concentration of 30% oxygen for babies < 28 weeks gestation.
  - c. Concentration of 21–30% for those of 28–31 weeks gestation.
  - d. Adjustments should be guided by pulse oximetry from birth.
5. In spontaneously breathing babies:
  - a. Stabilise with CPAP: 6 cm H<sub>2</sub>O PEEP via mask or nasal prongs.
  - b. T piece device is a better choice than a self-inflating anaesthetic bag.
  - c. Peak inspiratory pressure (PIP): 20–25 cm H<sub>2</sub>O for persistently apnoeic or bradycardic infants.
6. Intubation should be reserved for babies who do not respond to positive pressure ventilation via face mask. Babies who require intubation for stabilisation should be given surfactant if the oxygen saturation remains low despite high FiO<sub>2</sub>.
7. Plastic bags or occlusive wrapping under radiant warmers should be used during stabilisation in the delivery suite for babies < 28 weeks gestation to reduce the risk of hypothermia.



Note: Delaying cord clamping until the lungs are aerated and left atrial blood flow is established results in smoother transition with less fluctuation in blood pressure. Promoting placento-foetal transfusion results in a higher haematocrit, transiently higher blood pressure with less need for inotropic support and fewer intra-ventricular haemorrhages.

### 3. SURFACTANT THERAPY

Surfactant *prophylaxis* is no longer indicated for babies receiving stabilisation using a non-invasive respiratory support as CPAP.

Early selective surfactant administration is reserved for babies showing signs of RDS with the condition that the baby required intubation for stabilisation.

INSURE (intubate-surfactant-extubate to CPAP): still recommended with surfactant administration when babies show signs of RDS and need more than 30% inspired oxygen.

#### SURFACTANT THERAPY ADMINISTRATION

1. Bolus administration via an endotracheal tube:
  - a. Use a sterile 5 Fr. feeding tube inserted into the ETT with the tip at or above the end of the ETT.
  - b. Give short period of ventilation using a T-piece or mechanical ventilation (MV) to distribute the drug followed either by continued MV or immediate (or early) extubation to CPAP when spontaneous breathing had resumed (INSURE method).
2. Dose in 2 to 4 aliquots and allow for recovery on MV between aliquots to help minimise obstruction of the ETT or large airways by the viscous surfactant preparation.
3. Positional maneuvers that were initially recommended to assist in surfactant distribution are not necessary.
4. Chest radiograph: not necessary prior to dosing if equal breath sounds can be confirmed by auscultation.

Note: Changes are ongoing shifting from the 'traditional' intubation to the use of a fine flexible catheter (small bore catheter or gastric tube) positioned in the trachea using laryngoscopy and Magill's forceps, whilst the baby is kept on nCPAP. This method is known as LIST (less invasive surfactant therapy).

Also used is a more rigid thin vascular catheter, stiff enough to be positioned in the trachea under direct laryngoscopy without forceps whilst the baby is kept on nCPAP. This is known as MIST (minimally invasive surfactant treatment).

Consider minimally invasive surfactant (*LIST* or *MIST*) as an alternative to *INSURE* if the unit has appropriate expertise. This approach has not shown to be clearly superior to *INSURE* and requires more experience and studies to recommend its practice.

Advantages of LIST and MIST: less ventilation, fewer pneumothoraces and reduction in severe intra-ventricular haemorrhage.

Nebulisation to deliver surfactant has not yet reached a stage where it can be recommended for routine clinical use.

Table 1. Animal derived surfactant available

Generic name	Trade name	Source	Manufacturer	Dose (volume)
Beractant	Survanta®	Bovine	Ross Laboratories (USA)	100 mg/kg/dose (4 ml/kg)
Bovactant	Alveofact®	Bovine	Lyomark (Germany)	50 mg/kg/dose (1.2 ml/kg)
Poractant alfa	Curosurf®	Porcine	Chiesi Farmaceutici (Italy)	100–200 mg/kg/dose (1.25–2.5 ml/kg)



Survanta®: can use up to 4 doses, given no more frequently than 6 hours  
Curosurf®: can use up to 2 subsequent dose of 100mg/kg (1.25ml/kg), given 12 hours apart  
Infasurf® (Calfactant) 3ml/kg: can use up to 3 doses, given 12 hours apart

#### WHEN TO TREAT

1. Babies with RDS should be given a natural surfactant preparation.
2. Occasionally, surfactant should be administered in the delivery suite, such as those who require intubation for stabilisation. Some experts recommend observation after stabilisation and withhold surfactant therapy until clinically indicated.
3. Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol: treat babies  $\leq 26$  weeks gestation when  $FiO_2$  requirements  $> 0.30$  and babies  $> 26$  weeks when  $FiO_2$  requirements  $> 0.40$ . Some centres use rescue surfactant when  $FiO_2 > 0.30$  in all preemies.
4. *Poractant alfa in an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or beractant for rescue therapy.*
5. INSURE should be considered for infants who are failing on CPAP.
6. LIST or MIST may be used as alternatives to INSURE for spontaneously breathing infants.
7. A second and sometimes a third dose of surfactant should be administered if there is evidence of ongoing RDS such as persistent oxygen requirement and need for MV.

#### 4. RESPIRATORY SUPPORT

##### 1. O<sub>2</sub> Target after stabilisation

Aim for a balance between avoiding negative effects of excess oxygen exposure such as retinopathy of prematurity (ROP) and potential negative effects of prolonged low-grade hypoxia such as increased mortality, necrotising enterocolitis (NEC) or adverse neurodevelopmental outcome.

- ▶ *SatO<sub>2</sub> target: 90 - 95 % in preterm babies (Alarm limits should be set at 89 and 96%)*

##### 2. Non-invasive respiratory support

Initiation of nCPAP from birth rather than routine intubation for stabilisation or prophylactic surfactant treatment is better at preventing lung injury.

- a. nCPAP for babies at risk of RDS i.e.  $< 30$  weeks gestation who do not need intubation for stabilisation. Where possible, nCPAP should be maintained without resorting to intubation.
- b. The system delivering nCPAP is of little importance.
- c. The interface should be short bi-nasal prongs or a mask.
- d. Starting pressure (PEEP): 6–8 cm H<sub>2</sub>O. Individualise PEEP depending on clinical condition, oxygenation and perfusion.
- e. nCPAP with early rescue surfactant should be considered the optimal management for babies with RDS.
- f. High flow nasal cannula (HFNC) may be used as an alternative to nCPAP for some babies during the weaning phase.

Note: Recent observational studies have confirmed that  $FiO_2 > 0.30$  by 2 hours of age on CPAP is predictive of CPAP failure by 6 h of age, and that those who fail CPAP have a poorer outcome.

##### 3. Invasive respiratory support

Mechanical Ventilation strategies:



- a. Volume targeted ventilation (VTV) compared to pressure limited ventilation (PLV):
  - ▶ Reduce BPD, death and intra-ventricular haemorrhage, and shorten duration of MV
- b. VTV/PLV - synchronised intermittent mandatory ventilation (SIMV) mode is not always preferred over assist/control (AC) or pressure support ventilation (PSV) as the primary mode. Data on VTV is weak and the use of this modality needs much more expertise.

Ventilator Parameters:

PEEP: 6-8 cm H<sub>2</sub>O (adjust PEEP based on FIO<sub>2</sub>, SpO<sub>2</sub>, and chest radiographs)

RR: 30-60 per minute

PIP: 8-16 cm H<sub>2</sub>O

Ti: 0.3-0.4 (adjust based on graphics)

Vt (tidal volume): 4-6 mL/kg

- c. When high pressures are needed to achieve adequate lung inflation, high-frequency oscillatory ventilation (HFOV) may be a reasonable alternative to MV.
- d. HFOV allows gas exchange with very low tidal volumes delivered at very fast rates in lungs held open at optimal inflation by a continuous distending pressure.

Over-distension should be considered if a baby is deteriorating on MV following surfactant administration, or when an increase in mean airway pressure (MAP) is followed by increasing oxygen requirement.

During ventilation hypocarbia and severe hypercarbia should be avoided - associated with an increased risk of: BPD, peri-ventricular leukomalacia and intra-ventricular haemorrhage.

Methods of continuous CO<sub>2</sub> assessment may be helpful during initiation of ventilation. Transcutaneous pulse CO<sub>2</sub> (TcPCO<sub>2</sub>) is preferred and more reliable than capnography.

Note: Weaning of ventilation should be started immediately when satisfactory gas exchange is achieved and spontaneous breathing is present.

Extubation may be successful from 7–8 cm H<sub>2</sub>O mean airway pressure on conventional modes and from 8–9 cm H<sub>2</sub>O continuous distending pressure on HFOV.

Extubating to a relatively higher level of CPAP pressure of 7–9 cm H<sub>2</sub>O will improve the chance of successfully remaining off the ventilator.

Monitoring of blood gases in the acute phase of recruitment may be necessary, but once adequate ventilation is achieved and recruitment has been established, noninvasive monitoring is usually sufficient to guide therapy.

WEANING STRATEGIES:

1. For the preterm infant > 32 weeks of gestation, discontinuation of CPAP can generally be considered at PEEP 4 to 5 and < 25% oxygen.
2. For infants born at < 32 weeks of gestation, poor chest wall compliance alone can lead to progressive atelectasis, and longer term use of low CPAP may be advantageous, even when oxygen supplementation is no longer needed.
3. Caffeine should be used when infant is ready to be extubated.
4. Early caffeine should be considered for all babies at high risk of needing MV, such as those < 1,250 g birth weight and < 32 weeks gestation, who are managed on non-invasive respiratory support.

Caffeine citrate IV or orally:

- Loading dose: 20 mg/kg/dose

- Maintenance: 5–10 mg/kg/dose once daily



5. Short-course of low-dose dexamethasone should be considered to facilitate extubation in babies who remain on MV after 1–2 weeks and who receive high O<sub>2</sub>.

Dexamethasone IV:

- 0.2 mg/kg/day given once daily and tapered every 3 days over 7 days for a total dose of 1mg/kg (BPD or ventilator wean) OR
- 0.25 mg/kg/dose given 4 hours prior to extubation then every 8 hours for a total of 3 doses (airway oedema or extubation)

6. Inhaled steroids: further study needed and cannot be recommended for routine use.

COMPLICATIONS:

A. *Respiratory*

1. Over distension: due to rapid changes in lung compliance as atelectatic regions are recruited.

Results in inadequate tidal volumes:

- a. Excessively high tidal volumes injure the lung and lead to hypocarbia - risk of periventricular leukomalacia or intra-ventricular haemorrhage.
  - b. Low tidal volumes, which can occur after a decrease in lung compliance can lead to hypercarbia and atelectasis.
  - c. Tamponade of the alveolar capillary bed, with ventilation–perfusion ( $\dot{V}/\dot{Q}$ ) mismatch leading to hypercarbia and hypoxaemia.
  - d. Poor venous return sufficient to reduce cardiac output.
2. Air-leak: due to rapid increase in lung compliance that occurs as surfactant lowers surface tension causing over distension and changes in airway pressure.
    - ▶ Pressure-limited mechanical ventilation may develop pneumothorax as delivered tidal volumes increase. This may be avoided using volume-limited mechanical ventilation at 4-6ml/kg of volume.
  3. Under distension: due to difficulty with the patient-device interface and/or an open mouth.
  4. Nasal septum trauma: due to interface device used in nCPAP. The need for occlusion may lead to pressure necrosis of the nasal septum.
    - ▶ Daily rounds should include a discussion of the interface and status of the nasal septum and thus alternate interface use (nasal prongs or nasal masks).
  5. Hemorrhagic pulmonary oedema: due to decrease in pulmonary vascular resistance as compliance improves. This is exacerbated by the presence of a patent ductus arteriosus.

B. *Cardiac*

1. Patent ductus arteriosus (PDA)
2. Congestive Heart Failure
3. Pulmonary hypertension (PPHN)

C. *Neurologic*

1. Intra-ventricular haemorrhage (IVH)
2. Periventricular leukomalacia (PVL)
3. Neurodevelopment impact

D. *Infectious*



1. Nosocomial or ventilator associated Pneumonia (VAP)
2. Sepsis

#### 5. MONITORING AND SUPPORTIVE CARE: IN NICU

1. Continuous Monitoring of:
  - a. SatO<sub>2</sub> by pulse oximetry
  - b. Heart rate by ECG monitoring
  - c. PaCO<sub>2</sub> monitoring (TcPCO<sub>2</sub>/capnography/ABG)
    - ▶ Mild respiratory distress - use pulse oximetry (assess pH and PCO<sub>2</sub> by ABG).
    - ▶ Moderate or severe respiratory disease: use pulse oximetry and ABG.
    - ▶ Respiratory acidosis requires assisted ventilation.
    - ▶ Serial blood gases should be performed to titrate respiratory support.
    - ▶ Administration of sodium bicarbonate to infants with respiratory acidosis is not indicated and could further increase the PCO<sub>2</sub>.
2. Maintain core temperature between 36.5 and 37.5°C at all times.

Note: WHO guidelines promote the use of kangaroo mother care in stable low-birth-weight babies as a means of maintaining temperature and reducing mortality in lower income settings. Kangaroo mother care is being used to maintain temperature and to maximise maternal-infant bonding, even in babies on MV who remain stable. This practice is not recommended in unstable infants.

3. Infant should be kept in a humidified incubator.
4. Start intravenous fluids of 80–90 ml/kg/day. Sodium intake should be restricted over the first 3 days of life. Fluids must be tailored individually according to serum sodium levels and weight loss. Monitor fluid balance and electrolyte levels.
5. Parenteral nutrition should be started from birth.
  - a. Protein should be started from day 1 at 2–2.5 g/kg/day and increase to 4g/kg/day.
  - b. Lipids should be started from day 1 at 0.5-1g/kg/day and increased to 4.0 g/kg/day. Some centres increase lipids to a maximum of 3 g/kg/day.
  - c. Avoid excessive non-nitrogen calorie, which can increase CO<sub>2</sub> production and exacerbate hypercapnia.
6. Enteral feeding with mother's milk should be started from the first day if the baby is haemo-dynamically stable.
7. Antibiotics should be used judiciously and stopped early when sepsis is ruled out.
8. Blood pressure should be monitored regularly.

Dopamine is more effective than dobutamine at increasing blood pressure and can improve cerebral blood flow in hypotensive infants.
9. Hb should be maintained at acceptable levels to support an adequate O<sub>2</sub> carrying capacity in infants with a high FIO<sub>2</sub> requirement (> 0.4).

A suggested Hb threshold for babies on respiratory support:

- a. 11.5 g/dl (haematocrit 35%) in week 1
- b. 10 g/dl (haematocrit 30%) in week 2



- c. 8.5 g/dl (haematocrit 25%) beyond 2 weeks of age
10. Monitoring pain and discomfort and consider non-pharmacological methods of minimising procedural pain and judicious use of opiates for more invasive procedures.
- a. Consider short-acting opiate, muscle relaxant and atropine to maximise comfort and improve the chances of successful intubation.
  - b. Once stable on ventilation there is usually no need for routine sedation.
11. There are no data supporting routine or rescue use of inhaled nitric oxide (iNO) in preterm babies.

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## APNOEA

Defined as the cessation of breathing or absence of airflow for > 15-20 seconds or shorter events if accompanied by bradycardia or hypoxaemia.

1. Hypoxaemia in neonates is defined by O<sub>2</sub> saturation < 85%.
2. Bradycardia in neonates is defined as HR < 100 beats per minute.

Apnoea of Prematurity: typically resolves by 37 weeks PNA but can take up to 44 weeks PNA for extreme prematures.

### CLASSIFICATION

1. Central Apnoea: absent of respiratory effort
2. Obstructive Apnoea: occurs when inspiratory efforts persist in the presence of airway obstruction
3. Mixed Apnoea: central and obstructive

### MANAGEMENT OF INFANTS WITH APNOEA

1. Bedside continuous non invasive monitoring: HR, RR and O<sub>2</sub> saturation (by pulse oximetry). *Cardiac alarms set at 100 beats per minute and Apnoea alarms set at 20 seconds.*
2. Documentation of apnoeic events, bradycardia/desaturation events as well as the duration of the period of observation before discharge.
3. Care in avoiding reflexes that may trigger apnoea i.e. suctioning of the pharynx. Tolerance of oral feedings when appropriate should be closely monitored.
4. Positions of extreme flexion or extension of the neck should be avoided to reduce the likelihood of airway obstruction. Prone positioning stabilises the chest wall and may reduce apnoea.

Note: Apnoeic spells occurring in late-preterm and term infants are always abnormal and associated with serious, identifiable causes, such as birth asphyxia, intracranial haemorrhage, seizures, depression from medication, PDA, anaemia, sepsis or metabolic disorders.

Active or rapid eye movement (REM) sleep is marked by irregularity of tidal volume and respiratory frequency. REM sleep predominates in preterm infants, and apnoeic spells occur more frequently in this state than in quiet sleep.

Active reflexes produced by stimulation of the posterior pharynx, lung inflation, fluid in the larynx, or chest wall distortion can precipitate apnoea in infants.

Passive neck flexion, pressure on the lower rim of a face mask, and sub-mental pressure (all encountered during nursery procedures) can obstruct the airway in infants and lead to apnoea, especially in a small premature infant.

Spontaneously occurring airway obstruction is seen more frequently when preterm infants assume a position of neck flexion.

Nasal obstruction can lead to apnoea, especially in preterm infants who usually do not switch to oral breathing after nasal occlusion.

5. O<sub>2</sub> target should be 90-95% in infants < 28 weeks gestation.
6. "Kangaroo" care, or skin-to-skin nursing has achieved widespread acceptance for high-risk infants, and provides an opportunity for greater parental involvement. (*See Developmentally Supportive Care guideline*)
7. For late preterm and term infants with apnoea:
  - a. Carry out history and physical examination.



- b. Laboratory: arterial blood gas measurement; complete blood count; and measurement of blood glucose, calcium, and electrolyte levels.
  - c. Cerebral US is indicated if neurologic findings present.
8. Methylxanthine therapy: Theophylline and Caffeine
- a. Increases minute ventilation, improves CO<sub>2</sub> sensitivity, decreases hypoxic depression of breathing, promotes broncho-dilation, enhances diaphragmatic activity, and decreases periodic breathing.
  - b. Indicated for preterm infants < 35 weeks gestation. Infants < 1,250 g birth weight, soon after birth. In preterm infants > 1,250 g birth weight who require mechanical ventilation, begin caffeine treatment prior to extubation. In other infants with apnoea of prematurity, begin caffeine to treat frequent and/or severe apnoea.
  - c. Toxic levels of aminophylline may produce tachycardia, cardiac dysrhythmias, feeding intolerance, and infrequently, seizures. These effects are rarely seen with caffeine at the usual therapeutic doses. Mild diuresis is caused by all methylxanthines.
  - d. Aminophylline IV:
    - Loading dose: 6-8mg/kg/dose
    - Maintenance dose: 2mg/kg/dose every 8 or 12 hours (start 8 hours after loading dose)
  - e. Caffeine is may be safer and effective in reducing the incidence of BPD and neurodevelopment impairment; more studies are needed. It is preferred because of its longer half-life, higher therapeutic index, and lack of need for drug-level monitoring.
    - Loading dose IV or orally: 20-15 mg/kg/dose.
    - Maintenance dose (start 24 hours after loading dose): 5-10 mg/kg/dose every 24 hours IV or orally.

Caffeine is generally discontinued at 34 weeks PMA if no apnoeic spells have occurred for 5 to 7 days.

Note: Prolonged use of Caffeine beyond 34 weeks corrected age decreases episodes of intermittent hypoxia.

Intermittent hypoxaemia defined as SpO<sub>2</sub> < 80% for ≥10 seconds and ≤3 minutes duration, has been associated with severe retinopathy of prematurity (ROP).

Recurrent hypoxaemia has been associated with ROP, necrotising enterocolitis (NEC), and periventricular leukomalacia.

Prolonged hypoxaemia events < 80% and lasting at least 1 minute during the first 2-3 months of life in infants < 28 weeks gestation were associated with developmental disability at 18 months.

Recommendation: Caffeine Citrate IV or orally is preferred over Aminophylline. Acquisition of caffeine citrate by health authorities should be considered.

9. Most apnoeic spells in preterm infants respond to tactile stimulation. Infants who fail to respond to stimulation should be ventilated during the spell with bag and mask.
10. Non-invasive respiratory support strategies
- a. Nasal continuous positive airway pressure (nCPAP) at 5-8cm H<sub>2</sub>O (most effective).
  - b. Heated, Humidified, high flow nasal cannula (HHFNC) at 3-8 LPM.
  - c. Nasal intermittent positive pressure ventilation (NIPPV).
- ▶ HHFNC produces less nasal trauma and it is easier to use than nCPAP but nCPAP has shown to be most effective of the three.



11. Red blood cell transfusion: if the haematocrit is <25% to 30% and the infant has episodes of apnoea and bradycardia that are frequent or severe while continuing treatment with caffeine.
  - ▶ This increases oxygen-carrying capacity, elimination of hypoxic respiratory depression, or an increase in intravascular volume.
12. Oxygen supplementation to avoid hypoxic respiratory depression.
13. Mechanical ventilation: may be required if the other interventions are unsuccessful.
14. Gastro-Oesophageal reflux (GER): is not associated with apnoea of prematurity.
  - ▶ The use of H2 blockers and proton pump inhibitors, and metoclopramide have been associated with increase morbidity such as late onset sepsis and necrotising enterocolitis, and should not be used.

*Discharge criteria:*

1. 5 to 7 day apnoea-free period after discontinuation of caffeine therapy without recorded apnoea events. May be extended to 10 days for extremely low gestation infants or those with severe events.
2. Severe events during feeding may suggest lack of discharge readiness.

Note: Intercurrent viral illness, anaesthesia, and ophthalmologic examinations may precipitate recurrent apnoea in preterm infants. These infants should be monitored closely at least until 44 weeks PMA.

Relationship between persistent apnoea of prematurity and sudden infant death syndrome (SIDS) is unlikely. Defined as "the sudden and unexpected death of an infant less than 1 year of age that cannot be explained after a thorough case investigation, autopsy, and review of the clinical history.

Risk factors of SIDS: non-supine sleep position, sleeping on a soft surface, bed sharing, the presence of soft objects and loose bedding in the crib, lack of prenatal care, maternal smoking during pregnancy, alcohol and illicit drug use, formula feeding instead of breastfeeding, overheating, failure to immunise, preterm birth and/or low birth weight, and male gender.

The use of a pacifier has been associated with a protective effect on the occurrence of SIDS.

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## MECONIUM ASPIRATION SYNDROME (MAS)

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Defined as respiratory distress in an infant born through meconium-stained amniotic fluid (MSAF) whose clinical findings cannot be otherwise explained.

MSAF can occur as a result of:

1. physiologic meconium passage, more often a maturational event in > 37 weeks gestation
2. due to antepartum or intrapartum compromise i.e. hypoxia or umbilical cord compression.

MAS occurs in 2-6% of newborns born through MSAF.

MAS leads to pulmonary changes:

1. airway obstruction → air trapping → pneumothorax (ball-valve effect)/atelectasis (complete obstruction)
2. airway oedema → surfactant deactivation → atelectasis → Ventilation/ Perfusion (V/Q) mismatch
3. pulmonary vascular remodelling → pulmonary vasoconstriction → PPHN

Outcome:

1. Acidosis
2. Hypoxemia
3. Hypercapnia

RISK FACTORS:

1. preeclampsia
2. chronic respiratory or cardiovascular disease
3. poor intrauterine foetal growth
4. post-term pregnancy
5. heavy smokers

DIAGNOSIS:

1. Signs of post maturity
2. Heavy staining of nails, skin, and umbilical cord with yellowish pigment (meconium)
3. Respiratory distress: cyanosis, grunting, flaring, retractions, and marked tachypnea
4. Neurologic depression

MANAGEMENT IN THE DELIVERY ROOM

Endotracheal intubation and intratracheal suctioning: vigorous infants, defined as those with strong cry, normal heart rate, and good tone, should not be intubated for MSAF regardless of its thickness.

Note: Neonatal Resuscitation Program (7th edition) guidelines no longer recommend routine intubation and intratracheal suctioning of depressed or non-vigorous infants but states that intubation and intratracheal suctioning may be performed if clinically indicated for non-vigorous MSAF infants with airway obstruction. The level of suction should be a pressure of 80 to 100 mm Hg.

MANAGEMENT IN NICU

1. Tactile stimulation: should be minimised.



2. Gastric suctioning: could prevent post-birth reflux or emesis and frank aspiration of MSAF.

3. Chest radiograph: (Figure 1)

- a. Diffuse, patchy infiltrates
- b. Consolidation
- c. Atelectasis
- d. Pleural effusions
- e. Air leak (pneumothorax and pneumomediastinum)
- f. Hyperinflation
- g. 'Wet lung' similar to TTNB
- h. Hypovascularity
- i. Apparently clear, virtually normal appearance

Figure 1. Typical radiograph features of MAS.



4. Chest physiotherapy (CPT): consists of postural drainage, percussion, vibration, saline lavage, and suctioning (nasopharyngeal, oropharyngeal, and intratracheal). CPT has potential adverse effect of exacerbating PPHN. Benefits are unproven for MAS.

5. Laboratory: ABG, CBC, blood glucose, electrolytes, calcium and renal function test. Correct if necessary.

6. Oxygen: Goal to maintain SpO<sub>2</sub> 92-96% and PaO<sub>2</sub> 60-80 Torr. Repeated hypoxic insults → pulmonary vasoconstriction → PPHN

7. If FIO<sub>2</sub> > 0.50 → CPAP or MV

8. Ventilation strategies

- a. Nasal cannula: low flow rate 1-2 L/m and high flow rate 3-7 L/m. High flow rates increase the propensity for gas trapping and air leaks.
- b. nCPAP: can be considered before MV if FIO<sub>2</sub> requirements exceed > 0.50-0.60.
- c. Conventional mechanical ventilation (CMV): Time-cycled, pressure limited MV. Mechanical ventilation is indicated for excessive carbon dioxide retention (PaCO<sub>2</sub> > 60 mm Hg) or for persistent hypoxaemia (PaO<sub>2</sub> < 50 mm Hg).

Ventilator Parameters:

PIP: 15 to 25 cm H<sub>2</sub>O

PEEP: 4 to 6 cm H<sub>2</sub>O

Ti: 0.3 to 0.5 seconds

RR: 20 to 25 breaths per minute (when using assist control (AC) or pressure support ventilation (PSV))

Vt: 5-6 mL/kg

d. Some infants may respond better to conventional ventilation at more rapid rates with inspiratory times as short as 0.2 seconds.

e. Low lung volumes due to surfactant inactivation: PEEP 6 to 8 cm H<sub>2</sub>O.

f. High-frequency ventilation (HFV): high frequency oscillatory ventilation (HFOV) and high frequency jet ventilation (HFJV).

9. Surfactant therapy: Surfactant administration may be considered in severe cases.

10. PPHN: use pulmonary vasodilators - Sildenafil or milrinone. Inhaled nitric oxide (iNO) should be considered in infants with PPHN not responding to conventional therapy.



11. Extracorporeal membrane oxygenation (ECMO): last resort therapy

12. Others:

- a. Sedation if on MV.
- b. Paralysis if on MV remains controversial. Most experts prefer spontaneous breathing.
- c. Maintain adequate systemic blood pressure: dopamine, dobutamine, and fluid boluses.
- d. Broad-spectrum antibiotics (i.e. ampicillin and gentamicin) is usually indicated until sepsis is ruled out.
- e. Steroid therapy: could be administered systemically or inhaled. Not routinely recommended.
- f. Frequent clinical, radiographic, and laboratory assessments.

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## TRANSIENT TACHYPNEA OF THE NEWBORN (TTNB)

Defined as a common benign and self-limited, physiologic disorder (generally affecting infants born at late preterm or term gestation) resulting from transient pulmonary oedema secondary to inadequate or delayed clearance of foetal alveolar fluid.

This transient condition usually resolves by 48 to 72 hours.

At birth, the balance of fluid movement in the alveolus switches from chloride secretion to sodium absorption, causing resorption of intra-alveolar fluid. Sodium and fluid are cleared through the lymphatic and vascular systems through epithelial sodium channels (ENaC). Hormonal changes in spontaneous labor seem to increase the expression and activity of ENaC, thus, the higher incidence of TTNB in elective cesarean section.

### RISK FACTORS:

1. elective cesarean without labor < 39 weeks of gestation
2. vaginal delivery before completing 39 weeks of gestation
3. prematurity
4. male gender
5. large birth weight
6. maternal diabetes
7. maternal asthma
8. twin pregnancy

### DIAGNOSIS:

1. Signs present within the first 6 hours after birth.
2. Tachypnea - 60 to 120 breaths per minute.
3. Mild to moderate respiratory distress: retractions, grunting, nasal flaring, and/or mild cyanosis that usually responds to supplemental oxygen at < 0.40 FiO<sub>2</sub>.

### OTHER DIAGNOSIS TO CONSIDER:

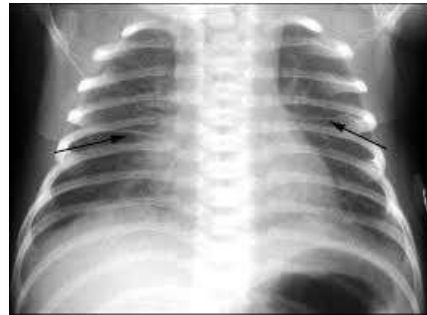
1. Pneumonia/sepsis
2. RDS
3. Pulmonary hypertension
4. Meconium aspiration syndrome
5. Cyanotic congenital heart disease
6. Respiratory congenital malformations - congenital diaphragmatic hernia, congenital pulmonary airway malformation
7. Central nervous system injury - subarachnoid haemorrhage, hypoxic-ischaemic encephalopathy
8. Polycythaemia
9. Metabolic acidosis
10. Inborn error of metabolism

### MANAGEMENT:

Chest radiograph: (Figure 1)

1. Peri-hilar streaking (sunburst pattern) - represents engorgement of the peri-arterial lymphatics.

Figure 1. Typical radiographic features of TTNB.



Source: Constanza E, 2017; NMSP, Belize.



2. Fluid-filled interlobar fissures. (Figure 1 - arrows)
3. Fluffy bilateral infiltrates - fluid-filled alveoli.
4. Atelectasis and pleural effusion.

Note: Radiographic changes are essentially resolved by 48 hours.

Ultrasound has recently been described to be useful in the diagnosis of TTNB. Some experts consider it as unnecessary.

The presence of increased pulmonary vascularity in the absence of cardiomegaly may represent total anomalous pulmonary venous return.

Laboratory:

1. complete blood count (CBC)
2. appropriate cultures
3. C-reactive protein (CRP)
4. arterial blood gas (ABG) - hypoxaemia, hypocapnea, and mild respiratory acidosis

Note: Persistent or severe hypoxaemia, and presumed TTNB for > 4 to 5 days: consider cardiac evaluation.

Treatment: *Supportive*

1. Supplemental oxygen as needed
2. Continuous positive airway pressure (CPAP): improve lung recruitment in severe cases.
3. Empiric antibiotic exposure may not be necessary if the infant is closely observed and there are no historical risk factors for infection.
4. If tachypnea and increased respiratory distress persist:
  - a. gavage feedings
  - b. intravenous fluids
  - c. fluid intake restriction

Complications: CPAP is associated with increased risk of air leak.

Prognosis: excellent

Note: Furosemide has no role in the treatment of TTNB.

Recommendation: Delay elective cesarean section until 39 to 40 weeks' gestation or until spontaneous labor starts to decrease the incidence of TTNB.

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# PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

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Defined as failure of normal pulmonary vascular adaptation at birth, and is characterised by elevated pulmonary vascular resistance (PVR) and right-to-left extrapulmonary shunting of deoxygenated blood through the foramen oval and ductus arteriosus, producing severe hypoxaemia.

Hypoxia:

1. reduces endothelial nitric oxide (NO) production
2. impairs NO release
3. induces vascular myocyte dysfunction

PATHOGENESIS AND RISK FACTORS :

1. Abnormally constricted pulmonary vasculature caused by lung parenchymal diseases
  - a. Meconium aspiration syndrome
  - b. Respiratory distress syndrome
  - c. Pneumonia
  - d. Perinatal asphyxia
  - e. Polycythaemia
  - f. Air leak syndrome
2. Lung with normal parenchyma and remodeled pulmonary vasculature
  - a. Idiopathic PPHN
  - b. In utero closure of ductus arteriosus (maternal aspirin use during late pregnancy remains a risk factor for PPHN)
  - c. Chronic in utero asphyxia
3. Hypoplastic vasculature
  - a. Congenital diaphragmatic hernia
  - b. Pulmonary hypoplasia
  - c. Congenital pulmonary adenomatoid malformation
  - d. Structurally abnormal heart disease (right to left shunt)
    - (a) total anomalous pulmonary venous return
    - (b) left ventricle outflow tract obstruction

DIAGNOSIS

1. History - presence of risk factor.
2. Clinical: non-specific - cyanosis, respiratory distress, low SatO<sub>2</sub>, pulse oximetry lability, prominent precordial impulse, accentuated second heart sound, systolic murmur consistent with tricuspid regurgitation.
3. Chest X-ray: non-specific - normal cardio-thymic silhouette, and normal or decreased pulmonary blood flow.
4. Arterial Blood Gas (ABG): hypoxia, hypercapnia, and acidosis.
  - ▶ *Correct ventilation and acid-base abnormalities before attributing hypoxaemia to PPHN.*



5. Hyperoxia test: Expose infant to 1.0 FIO<sub>2</sub> for 10-15 minutes. (This test is not recommended by some experts due to the risk of hyperoxia in increasing free radicals.)
  - a. Increase in PaO<sub>2</sub> (>80 to 150 mm Hg): parenchymal lung disease.
  - b. No change in PaO<sub>2</sub> (<50 mm Hg): Cyanotic congenital heart disease.
  - c. No changes or slight rise in PaO<sub>2</sub>: PPHN.
6. Pre-ductal and post-ductal oxygenation: Obtain simultaneous arterial blood gas samples from pre-ductal (right radial artery) and post-ductal (umbilical or posterior tibial artery). SatO<sub>2</sub> by oximetry may also be use.
  - a. A gradient 20 Torr or higher in the pre-ductal PaO<sub>2</sub> - right to left ductal shunt.
  - b. If both values are low - PPHN cannot be ruled-out (possible shunting).
  - c. If both values are high and essentially equal - PPHN is unlikely.
7. Hyperoxia-hyperventilation test: (This test is no longer recommended)
 

Hyperventilate the infant (mechanically or manually) using 1.0 Fio<sub>2</sub> for 10-15 minutes.

  - a. Attempt to decrease PaCO<sub>2</sub> (25-30 Torr) and increase pH to 7.5 range.
  - b. Obtain ABG: Dramatic increase in PaO<sub>2</sub> along with marked lability - suggests PPHN.

Note: Hypoxaemia and acidosis increase pulmonary vasoconstriction.  
 Alkalosis and hyperoxia decrease PVR.  
 Profound prolonged and rapid changes in PaCO<sub>2</sub> may alter cerebral blood flow.  
 Hyperoxia-hyperventilation test is not recommended by SIBEN or by other experts.

8. Oxygenation index (OI): Represents the relation between the amount of oxygen given and the amount of oxygen diffused in the blood. It's a marker of pulmonary function and of cardio-pulmonary capacity to respond.
 

The greater the OI, the greater the respiratory failure.

Normal value: <5

Moderate respiratory failure: OI 15 -25

Severe respiratory failure: OI >30

Formula:  $MAP \times Fio_2 / PaO_2 \text{ (mm/Hg)} \times 100$

$MAP = Ti \times \text{cycles}/60 \times (PIP-PEEP) + PEEP$  (modern ventilators automatically calculate MAP)

PaO<sub>2</sub> is usually post ductal from the umbilical arterial catheter.
9. Echocardiogram: GOLD STANDARD
  - a. Rule-out congenital heart disease
  - b. Evaluates myocardial function
  - c. Enable visualisation of shunting
  - d. Estimates pulmonary artery pressure (IMPORTANT - INFORMS GRADE OF PPHN IF PRESENT; PPHN: >30 mmHg)

OTHER DIAGNOSES TO CONSIDER:

1. Congenital heart disease



2. Sepsis
3. Severe pulmonary parenchymal disease

## MANAGEMENT

### Objective:

1. Reverse hypoxaemia
2. Improve pulmonary and systemic perfusion
3. Preserve end-organ function.

### 1. Prenatal:

- a. Identify maternal risk factors and refer to a higher-risk center
- b. Appropriate obstetrical management

### 2. Neonatal:

- a. Adequate resuscitation
- b. Avoid acidosis, hypoxia, and hypercarbia
- c. Avoid hypothermia, hypovolaemia, and hypoglycaemia (maintain glycaemia between 60 - 90 mg/dl).
- d. Avoid hypocalcaemia and hypomagnesaemia.

### 3. General supportive measures in NICU

- a. Continuous monitoring of vital signs. (HR,RR, SpO<sub>2</sub>, and blood pressure)
- b. Umbilical/peripheral arterial line is required for continuous ABG monitoring.
- c. Use appropriate ventilatory strategy.
- d. Maintain an initial negative liquid balance.
- e. Strict monitoring of total liquid balance, urine output and urine specific gravity, and electrolytes (especially serum sodium).
- f. Assure adequate systemic blood pressure:
  - (a) Dopamine: 4-7 mg/kg/min, may increase to 10-20 mg/kg/min.
  - (b) Dobutamine: 5-10 mg/kg/min, may require increase to 20 mg/kg/min (if decreased cardiac contractility).
  - (c) Blood pressure goal: 50 to 70 mm Hg (systolic) and 45 to 55 mm Hg (mean).
- g. Maintain adequate oxygen carrying capacity (haemoglobin >15mg/dl).
- h. Do not use diuretics such as furosemide without appropriate indication.
- i. ABG: Aim for desired pre ductal SpO<sub>2</sub>: 91-96%, PaCO<sub>2</sub>: 40 to 50 mm Hg, and pH 7.30 to 7.40.

Note: pH 7.25, PaO<sub>2</sub> 40-45 Torr, PaCO<sub>2</sub> 55-60 Torr are tolerated.

Excessive oxygen exposure releases free radicals that may worsen pulmonary hypertension.

- j. Polycythaemia: Partial exchange transfusion to reduce the haematocrit to 50% - 55% should be considered in the infant with PPHN whose central haematocrit exceeds 65% .
- k. Treat underlying disorder.



(a) Surfactant therapy can be useful when significant parenchymal disease exists.

(b) Correction of hypoglycaemia, hypocalcaemia and electrolyte imbalances.

l. Sedation y analgesia:

(a) Fentanyl: 1 to 4 µg/kg/hour infusion.

(b) Morphine sulfate: 0.05 to 0.1 mg/kg/hour infusion - alternative analgesic when the infant is not hypotensive.

m. Infants with PPHN rarely require neuromuscular blockade.

4. Ventilator strategies:

a. Conventional mechanical ventilation (CMV) and high frequency ventilation are recommended.

b. Avoid lung hyper expansion (contributes to PVR) and barotrauma.

c. Modest hyperventilation and alkalosis: produces pulmonary vasodilatory effect but may be risky.

Note: Decrease PaCO<sub>2</sub> (hypocapnia) decreases cerebral blood flow and is associated with neurodevelopmental impairment, including sensorineural hearing loss. AVOID ACIDOSIS AND HYPERCAPNIA.

d. Maintain adequate lung volume: functional residual capacity (FRC)

5. Pulmonary vasodilating agents

a. Inhaled nitric oxide (iNO)

(a) Primary treatment. (iNO is not recommended in premature infants but some experts may consider its use in premature infants with pulmonary hypertension.)

(b) The usual starting dose of iNO is 20 ppm, and it is delivered via the ventilator circuit. As the baby improves and FiO<sub>2</sub> is <50% to 60% and OI <15, iNO is tapered gradually at intervals no more frequent than every 4 - 6 hours in 24-48 hours: 20 to 15, 15 to 10, 10 to 5, 5 to 2, 2 to 1, and then off.

(c) The infant's oxygen saturation in response to each step down is observed before further weaning and/or discontinuing the medication.

(d) Rebound hypoxaemia can occur when iNO is discontinued abruptly.

(e) iNO has potential risks including methemoglobinaemia and increased bleeding time.

b. Sildenafil - adjuvant to iNO or as primary treatment in centres without access to iNO.

Dose: 1 to 2 mg/kg/dose every 6 hours orally or IV

c. Milrinone - may improve oxygenation in neonates with a poor response to iNO.

Use of milrinone should be avoided in infants with diastolic hypotension and with hypoxic-ischaemic encephalopathy undergoing therapeutic hypothermia.

d. Others: Bosentan, Epoprostenol (further studies needed).

6. Extracorporeal Membrane Oxygenation (ECMO) - last resource in the absence of pulmonary hypoplasia; rescue modality generally used when predicted mortality is high (80-85%) and when oxygenation index [OI] >30 on two ABGs ≥30 minutes apart.

7. Glucocorticoids: Brief courses of glucocorticoids may be beneficial.

Note: Close infant neurodevelopmental follow-up is required.



iNO is the drug of choice, effective, reduces morbi-mortality and the need for ECMO.

Acquiring iNO would be extremely beneficial and its rational use would be necessary.

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## BRONCHOPULMONARY DISPLASIA (BPD)

Defined as a form of chronic lung disease that develops in newborns treated with oxygen and mechanical ventilation for a primary lung disorder.

'New BPD' is characterised by alveolar arrest and disordered pulmonary vasculature and a smaller effective surface area resulting in diffusion abnormalities.

Presence at either 28 days of life or 36 weeks post menstrual age (PMA) of:

1. chronic respiratory signs
2. a persistent oxygen requirement
3. an abnormal chest radiograph

Table 1. Diagnostic criteria for establishing BPD: National Institutes of Health (NIH) consensus conference.

Gestational age	<32 weeks	>32 weeks
<b>time point of assessment-treatment with O<sub>2</sub> &gt; 21% for at least 28 days</b>	36 weeks PMA or discharge to home whichever comes first	>28 days but <56 days postnatal age or discharge to home, whichever comes first
<b>Mild</b>	breathing room air	breathing room air
<b>Moderate</b>	need for < 30% O <sub>2</sub>	need for < 30% O <sub>2</sub>
<b>Severe</b>	need for > 30% O <sub>2</sub>	need for > 30% O <sub>2</sub> , +/- PPV or CPAP

### FACTORS ASSOCIATED WITH BPD

1. Volutrauma and lung injury from mechanical ventilation or bag-and-mask ventilation.
2. Oxygen toxicity.
3. Increase pulmonary blood flow/lung oedema due to:
  - a. Excessive early intravenous fluid administration.
  - b. Persistent left-to-right shunt through the patent ductus arteriosus (PDA).
4. Inflammatory mediators due to intrauterine or perinatal infection.
5. Genetic factors.

### PATHOPHYSIOLOGIC CHANGES IN BPD:

1. Ventilation perfusion (V/Q) mismatch.
2. Decreased lung compliance.
3. Increased airway resistance.
4. Reduced functional residual capacity (FRC) in early stages and increased in later stages due to gas trapping and hyperinflation.
5. Pulmonary oedema and Pulmonary hypertension.
6. Airway and alveolar pathologic changes.



## PREVENTION

1. Administration of antenatal steroids. (Antenatal steroids do not reduce BPD because it increases survival.)
2. Reduce exposure to high airway pressures, tidal volumes, and FiO<sub>2</sub>.
3. Avoid fluid overload.
4. Avoid a prolonged symptomatic PDA.
5. Prevent pulmonary and systemic infections.
6. Proper nutrition.
7. Administration of substrates important for the antioxidant mechanisms i.e. vitamin A and vitamin E.
8. Administration of caffeine on extubation.
9. Administration of post-natal steroids.

## DIAGNOSES

1. Clinically: tachypnea, retractions, and rales
2. Chronic respiratory insufficiency with oxygen dependency: present intermittent cyanotic or life-threatening episodes ("BPD spells") when agitated, and poor growth.
3. Non-pulmonary causes of respiratory failure should be excluded.
4. ABG: hypoxaemia and hypercarbia, respiratory acidosis.
5. Chest radiograph: appearance changes as the disease progresses. (Figure 1)
  - a. With "new" BPD, the initial appearance is often diffuse haziness, increased density, and normal-to-low lung volumes.
  - b. In more severe disease, chronic changes may include homogeneous regions of opacification and hyperlucency with superimposed hyperinflation.

## MANAGEMENT - TREATMENT REMAINS MOSTLY SUPPORTIVE

### Objectives:

1. Maintain adequate gas exchange.
  2. Limit the progression of the lung damage.
  3. Maximise nutrition.
1. Oxygen therapy
    - a. Monitor SatO<sub>2</sub> using pulse oximetry.
    - b. Reduce the FIO<sub>2</sub> as quickly as possible to avoid oxygen toxicity.
    - c. Maintain O<sub>2</sub> saturation between 90-95% or the PaO<sub>2</sub> between 50-70 Torr. PCO<sub>2</sub> 45-55 mmHg can be tolerated.
    - d. Maintain haematocrit approximately 30% to 35% (haemoglobin > 10 g/dL) as long as supplemental O<sub>2</sub> or ventilator support is needed.
    - e. SpO<sub>2</sub> should remain > 90% during sleep, feedings, and active periods before supplemental O<sub>2</sub> is discontinued.
    - f. Supplemental oxygen is based on oxygen saturation (SpO<sub>2</sub>) during a room air challenge test performed at 36 weeks PMA (or 56 days for infants > 32 weeks PMA) or before hospital discharge.

Figure 1. Typical radiographic features of BPD.



Source: Constanza E, 2012; HUC, Caracas.



g. Persistent SpO<sub>2</sub> < 90% is the cutoff below which supplemental O<sub>2</sub> should be considered.

## 2. Non-invasive ventilation

a. nasal intermittent positive-pressure ventilation (NIPPV)

b. nasal CPAP (nCPAP)

c. high-flow nasal cannula (HFNC)

d. Goal: minimise V/Q mismatch and promote growth rather than the sole purpose of avoiding intubation.

e. In patients who are not adequately supported by noninvasive support methods, mechanical ventilation (MV), via either endotracheal tube or tracheostomy, needs to be considered.

## 3. Mechanical ventilation modes

- volume-targeted ventilation (VTV)

- synchronised intermittent mandatory ventilation (SIMV)

- assist/control ventilation (ACV)

- pressure support ventilation (PSV)

- flow-cycled ventilation (mainly used in PSV)

a. In early course in preterm infants: high rate, short inspiratory time (Ti), and low tidal volumes.

b. In severe BPD: slow-rate, long Ti ventilation plus adequate Pressure Support.

c. Patient with uniform lung disease: faster rate and shorter Ti.

d. Use lowest ventilation settings and limit the duration of mechanical support.

- tidal volumes: 5-8 ml/kg (VTV)

- Ti: 0.4-0.6 seconds

- PEEP: 4-8 cmH<sub>2</sub>O

- PIP: 12-14 cmH<sub>2</sub>O (PSV)

Note: Infants with established BPD have decreased lung compliance, increased resistance, reduced FRC, and obstructive lung disease.

Appropriate level of PEEP increases FRC, promote alveoli recruitment, reduce work of breathing, and improve V/Q matching.

When the set ventilator PEEP is less than inadvertent or intrinsic PEEP (PEEP<sub>i</sub>): BPD spells (desaturation episodes) can occur. Increase in lung volume and a buildup of pressure in the alveoli and distal airways is referred to as inadvertent PEEP or auto-PEEP.

Higher PEEP 6-8 cmH<sub>2</sub>O may help reduce expiratory airway resistance and improve alveolar ventilation in infants with unstable airways and severe obstruction.

## 4. Weaning must be done gradually

a. Reduce ventilator rate gradually to 10-15 breaths per minute.

b. During weaning from CMV it may be necessary to increase FIO<sub>2</sub> to maintain adequate O<sub>2</sub> saturation levels.

c. As long as pH > 7.25, hypercapnia should be tolerated to wean patients from the ventilator.





- d. Avoid hyperventilation and target arterial carbon dioxide tension (PaCO<sub>2</sub>) at  $\geq 55$  mm Hg, with pH  $\geq 7.25$ , and target SpO<sub>2</sub> at 90% to 95% and arterial oxygen tension (PaO<sub>2</sub>) 55 to 80 mm Hg.
  - e. Aminophylline or caffeine citrate (20 mg/kg loading dose and 5 mg/kg daily maintenance) can be used prior to extubation.
  - f. Extubate when: RR 10-15 breaths/min, PIP 12-15 cmH<sub>2</sub>O, FIO<sub>2</sub> < 0.3-0.4.
  - g. Extubate to nCPAP 6-8 cmH<sub>2</sub>O or nasal IPPV in smaller infants.
  - h. After extubation administer O<sub>2</sub> through nasal CPAP, hood or nasal cannula.
  - i. Chest physiotherapy is recommended post-extubation.
  - j. Chronically ventilated infants should be evaluated for tracheostomy placement at around or shortly after 40 weeks corrected gestation.
5. Fluid Management
- a. Pulmonary oedema has been associated with the development of BPD.
  - b. Fluids and sodium intake must be limited to the minimum required.
  - c. Maintain urine output at least 1 mL/kg/hour and serum sodium concentration of 140 to 145 mEq/L.
  - d. In the chronic phase, limit fluids to as low as 130 mL/kg/day.
  - e. Short term diuretic therapy can be useful and is only indicated for acute episodes of deterioration associated with pulmonary oedema.
  - f. Furosemide, thiazide, and spironolactone are commonly used in preterm infants to prevent or alleviate BPD.
  - g. Side effects of furosemide include hypercalciuria, nephrocalcinosis, ototoxicity, electrolyte imbalance, and nephrolithiasis.
  - h. Hydrochlorothiazide (2 to 4 mg/kg/day orally, divided BID) may be use to avoid furosemide toxicities.
  - i. Routine use of loop diuretics its not recommended.
6. Bronchodilators
- a. Reduce airway resistance, and should be limited to episodes of acute exacerbation of airway obstruction.
  - b. Inhaled bronchodilators: B-agonists ie. salbutamol or isoproterenol and anticholinergic agents i.e.. ipratropium bromide.
  - c. Others: Methylxanthines i.e. Aminophylline.
  - d. Have not been shown to prevent BPD, effectively treat BPD, or diminish the severity of BPD.
7. Corticosteroids
- a. Systemic corticosteroids reduces inflammation, increases surfactant production, accelerates lung cell differentiation, decreases vascular permeability, and increases lung fluid resorption.
  - b. The use of systemic steroids should only be considered after the first 2 weeks of life in infants who show clear evidence of severed and progressive pulmonary damage and who remain oxygen and ventilator dependent.
  - c. Duration of steroid therapy must be limited to 5-7 days.
  - d. Routine use of dexamethasone is discouraged and treatment reserved only for infants with progressive respiratory failure that is refractory to all other therapies.



BPD Outcome Estimator from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Neonatal:

<https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start>

If the risk of developing BPD is estimated at 2 weeks of age as  $\geq 60\%$  a preventive course of hydrocortisone may be considered as follows:

Hydrocortisone:

1.25 mg/kg/dose IV/PO q6h  $\times$  7 days

then q8h  $\times$  5 days

then q12h  $\times$  5 days

then q24h  $\times$  5 days

Post-extubation airway oedema, with stridorous obstruction:

1. Dexamethasone, 0.25 mg/kg/dose every 12 hours starting 8 to 12 hours before a planned extubation.
2. Oedema also may be acutely diminished with nebulised racemic epinephrine

Note: Complications of prolonged steroid therapy include: masking the signs of infection, arterial hypertension, hyperglycaemia, increased proteolysis, adrenocortical suppression, somatic and lung growth suppression, and hypertrophic cardiomyopathy.

The use of corticosteroids to treat or prevent BPD remains controversial.

Benefits and potential side effects should be discussed with the family before therapy.

Steroids may be administered by nebulisation (not enough evidence to recommend its use).

## 8. Nutrition

- a. Metabolic rate and energy expenditure are elevated in BPD.
- b. Ensure adequate calorie intake (at least 120-130 Kcal/kg/day) and protein intake 3.5 -4 g/kg/day.
- c. Providing more calories by the administration of lipids instead of carbohydrates lowers the respiratory quotient, thereby diminishing CO<sub>2</sub> production.
- d. Vitamin A regulates growth and differentiation of lung epithelial cells. Vitamin A : 5,000 IU intramuscular [IM], three times weekly for the first 28 days of age.
- e. Vitamin E and Trace elements such as copper, zinc, and selenium are vital to the functioning of antioxidant enzymes that may play a role in lung protection from inflammatory insults.
- f. Osteopenia may result from prematurity, inadequate calcium and phosphorus retention, and prolonged immobilisation. Supplementation with vitamin D, calcium, and phosphorus should be optimised.
- g. Gastro-oesophageal reflux is often observed in infants with BPD. Anti-reflux management and post-pyloric feeds in infants with severe BPD might be indicated to alleviate respiratory symptoms but is not routinely recommended.

## 9. Pulmonary vasodilators/Pulmonary Hypertension

- a. Oxygen therapy to prevent hypoxaemia is probably the most important first step to reduce pulmonary hypertension in these infants.
- b. iNO and Sildenafil use for pulmonary hypertension:



- c. There is no evidence to support the use of iNO nor Sildenafil in the prevention or treatment of BPD in preterm infants.

#### 10. PDA

- a. Treat hemodynamically significant PDA in infants who have respiratory decompensation or cannot be weaned from mechanical ventilation.
- b. Ibuprofen is as effective as indomethacin in closing a symptomatic PDA.

#### 11. Infection

- a. Complete blood count, blood culture, and chest radiograph (if pneumonia is suspected). Antibiotics is based on the sensitivity of the implicated organism, and treatment is continued until the infection has been controlled.
- b. Azithromycin may decrease the risk of developing BPD in infants with documented Ureaplasma colonisation or infection ( more investigation needed for recommendation).

#### 12. Medications for pain control

- ▶ Oral sucrose, morphine sulfate or fentanyl, and short-acting benzodiazepines (in term infants) may be used.

#### 13. Stem cell–based therapies is being investigated as a potential strategy to decrease BPD.

### DISCHARGE

#### 1. Supplemental O<sub>2</sub> should be weaned when:

- a. SpO<sub>2</sub> is consistently maintained >92%.
- b. No significant periods of desaturations occur during feedings and/or sleep.
- c. Good weight gain has been established. Recommended weight for discharge: > 2000 g for BPD.
- d. Respiratory status is stable.

#### 2. Involvement of parents in caregiving is vital to the smooth transition from hospital to home care.

#### 3. Document baseline value of:

- a. vital signs
- b. daily weight gain
- c. discharge weight and head circumference
- d. blood gases
- e. SpO<sub>2</sub> (SpO<sub>2</sub> monitoring should continue at home for infants with moderate to severe BPD receiving supplementary O<sub>2</sub> at discharge.)
- f. hematocrits
- g. electrolytes
- h. baseline appearance of the chest radiograph

#### 4. Follow-up eye examination and hearing screening should be scheduled as needed.

#### 5. Involves sub-specialist and multidisciplinary management.

#### 6. Infants with BPD should receive pneumococcal and influenza vaccines and palivizumab (Synagis).

#### 7. Parents of infants with BPD should be discouraged from smoking.

#### 8. Long-term follow-up is recommended.



## SEQUELAE

Cardio-pulmonary: asthma, pneumonia, pulmonary hypertension, chronic obstructive pulmonary disease (COPD).

Neurologic: Intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), neurodevelopmental delay/neurologic deficits: motor, cognitive, educational, and behavioral impairments.

Others: increase hospital readmission, failure to thrive, retinopathy of prematurity (ROP).

Death occurs usually as a result of respiratory failure, intercurrent infections, or intractable pulmonary hypertension and cor pulmonale.

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## PULMONARY AIR LEAK

Refers to a collection of gas outside the pulmonary space which arises from damage of the respiratory epithelium, usually by high trans-pulmonary pressures.

### TYPES:

1. Pneumothorax
2. Pneumomediastinum
3. Pneumopericardium (Figure 1)
4. Pulmonary interstitial emphysema (Figure 2)
5. Subcutaneous emphysema
6. Pneumoperitoneum

### RISK FACTORS

1. RDS
2. MAS
3. Pneumonia
4. TTNB
5. Pulmonary hypoplasia
6. Congenital diaphragmatic hernia
7. Pneumothorax

### *Pneumothorax*

#### CAUSES

1. Spontaneous
2. Secondary to a lung disease with uneven lung compliance and alveolar over-distention.
3. Direct injury by suctioning: ETT suctioning
4. Ventilatory support:
  - a. high PIP
  - b. long Ti
  - c. high MAP (>12 cm H<sub>2</sub>O)
  - d. low inspired gas temperature (<36.5C)
  - e. patient-ventilation dys-synchrony

#### DIAGNOSIS

1. Clinical signs
  - a. respiratory distress
  - b. cyanosis
  - c. decreased breath sounds

Figure 1. Pneumopericardium

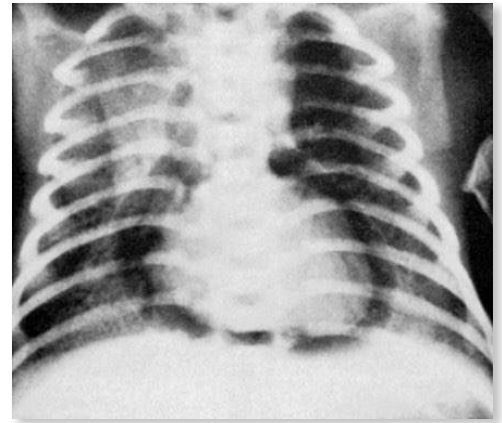


Figure 2. Pulmonary Interstitial Emphysema.

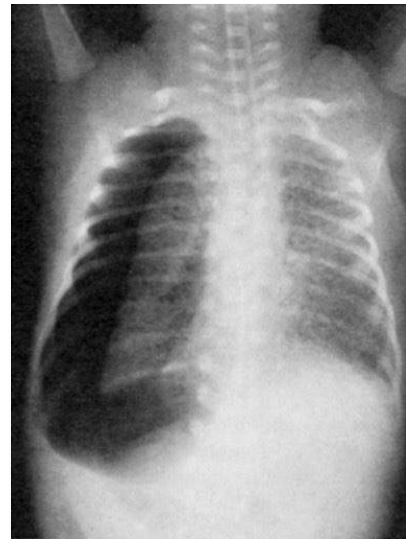


Source: Constanza E, 2014; HUC, Caracas.



- d. chest symmetry
  - e. apnoea
  - f. bradycardia
  - g. shift in cardiac point of maximal impulse
  - h. hypotension
  - i. cardio vascular collapse
2. ABG: hypoxaemia, respiratory or mixed acidosis
  3. Chest radiograph: GOLD STANDARD (Figure 3)
    - a. hyper-lucent hemithorax
    - b. flattening of the diaphragm
    - c. mediastinal shift

Figure 3. Right tension pneumothorax



#### MANAGEMENT

1. Nitrogen washout: administer 1.0 FIO<sub>2</sub> oxygen for 12-24 hours (NOT RECOMMENDED DUE TO INCREASE RISK OF OXIDATIVE DAMAGE.)
  - a. it is a conservative therapy
  - b. for small pneumothoraces
  - c. not to be used in preterm infants
  - d. not to be used if pneumothorax is under tension
2. Needle aspiration (thoracentesis): for symptomatic pneumothorax
  - ▶ On the second or third intercostal space in the mid-clavicular line of the affected side with a 23-gauge butterfly needle attached to a 20ml sterile syringe by a 3-way stopcock.
3. Chest tube placement (thoracostomy): for continuous drainage of pneumothoraces
  - a. Use 8 Fr, 10Fr or 12 Fr chest tubes depending on infant size
  - b. Position: on the fifth intercostal space in the anterior axillary line of the affected side
  - c. Once placed, attach the chest tube to an underwater drainage system under low continuous suction of -10 to -20 cmH<sub>2</sub>O.
  - d. Suture chest tube in place with 3.0 or 4.0 silk
  - e. Chest X-ray AP and lateral: confirm position and pneumothorax drainage
  - f. Complications: haemorrhage, lung perforation, cardiac tamponade, and phrenic nerve injury
  - g. Removal of a chest tube:
    - (a) When lung disease has improved and chest tube has not drained air for 24 to 48 hours.
    - (b) Then suction must be discontinued and the tube left under water seal.
    - (c) If chest x-ray shows no re-accumulation of extra-pulmonary air in the next 12 to 24 hours, the chest tube should be removed.
    - (d) Remove the chest tube during expiration in spontaneously breathing infants and during inspiration in mechanically ventilated infants.



(e) Cover the chest wound with a small occlusive dressing while removing the tube.

4. Ventilation:

- a. Rapid rate ventilation IMV ( $> 60$  breaths/min) has been utilised to decrease  $T_i$  and the duration of positive pressure (and hence tidal volume), and to produce less asynchronous breathing.
- b. SIMV or A/C, may reduce the incidence of air leak by avoiding patient-ventilator asynchrony.

## Pulmonary interstitial emphysema (PIE)

### DIAGNOSIS

1. Clinical signs: respiratory distress
2. ABG: respiratory acidosis, hypercarbia, hypoxaemia
3. Chest X-ray: characteristic cystic appearance or non confluent linear microradiolucencies, or large bullae formation

### MANAGEMENT

1. Ventilation:
  - a. Decrease PIP
  - b. decrease PEEP enough to maintain sufficient FRC
  - c. reduce  $T_i$
2. Supportive: position infant with the affected side down to minimise aeration of the affected lung and promote aeration of the unaffected lung.
3. Endotracheal suctioning and manual positive pressure ventilation should be minimised.
4. Severe cases: may require to collapse the affected lung by selective bronchial intubation of the unaffected lung. This procedure is very difficult to do and risky.

## Pneumomediastinum

### DIAGNOSIS

1. Clinical: tachypnea, cyanosis, distant heart sounds
2. Chest X-ray: GOLD STANDARD (best seen on lateral view)
  - characteristic "spinnaker sail" sign (Figure 4)

### MANAGEMENT

1. Nitrogen washout: infants are often placed in 100% oxygen for up to 24 hours.
2. Needle aspiration.
3. Mediastinal tube placement may be considered but avoiding intervention is better.
4. If ventilated, reduce mean airway pressure.

## Pneumopericardium

The majority of cases occur in infants ventilated with high PIP ( $>32$  cmH<sub>2</sub>O), high MAP ( $>17$  cmH<sub>2</sub>O), and/or long  $T_i$  ( $>0.7$  sec)

Figure 4. Pneumomediastinum.



Source: Constanza E, 2016; KMHM, Belize.



## DIAGNOSIS

1. Clinical
  - a. Cardiovascular compromise from cardiac tamponade (life-threatening).
  - b. (Hamman sign) or a characteristic mill wheel–like murmur (bruit de moulin) may be present.
2. Chest X-ray AP:
  - a. Air completely encircling the heart.
  - b. Air under the inferior surface of the heart is diagnostic.

## MANAGEMENT

1. Needle aspiration (pericardiocentesis).
  - a. Drain immediately at the subxiphoid area with a 20-22 gauge IV catheter attached to a short piece of IV tubing attached to a syringe via a stopcock.
  - b. Catheter must be inserted with the needle at a 30°-45° angle pointed toward the infant's left shoulder.
2. Pericardial tube placement: managed like a chest tube with less negative pressure for suction (-5 to -10 cmH<sub>2</sub>O).

## Subcutaneous emphysema

### DIAGNOSIS

1. Crepitus in the face, neck, or supraclavicular region upon palpation.
2. Can also be seen on radiograph.

### MANAGEMENT

Supportive

## Pneumoperitoneum

Distinguish the cause: due to trans-thoracic air leak or to bowel perforation

### MANAGEMENT

1. Needle aspiration
2. Peritoneal drain placement

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### EVALUATION IN SUSPECTED NEONATAL CONGENITAL HEART DISEASE

Note:

1. Congenital heart disease (CHD) should be raised in any symptomatic infant with prenatal history of cardiovascular disease (family history of CHD or syndrome associated with CHD) and no history of perinatal asphyxia.
2. The primary differential diagnosis of cyanotic CHD is persistent pulmonary hypertension of the newborn (PPHN).
3. General examination includes: vital signs of temperature, heart rate, respiratory rate, blood pressure and O<sub>2</sub> saturation by pulse oximetry, and observation of respiratory status, perfusion and colour.
4. The evaluation of the infant for critical cardiovascular disease should focus on the three cardinal signs of neonatal cardiovascular distress: cyanosis, decreased systemic perfusion, and tachypnea.
5. Heart murmurs may be present at birth in 0.6% of many normal asymptomatic infants (physiologic/innocent murmur) and are absent in about 50% of infants with symptomatic severe cardiovascular disease in the neonatal period.
6. A cardiovascular disease should be considered in any postnatal decrease in weight percentiles compared to length and head circumference.
7. Infants with unexplained failure to thrive, particularly in association with tachypnea and diaphoresis, should be evaluated for possible CHD.
8. In newborns with any findings suggestive of CHD, oxygen saturation should be measured in the right hand and one foot, and any abnormality should lead to further investigation.
9. The hyperoxia test is the single and perhaps the most sensitive and specific tool in the initial evaluation of the neonate with suspected disease.
10. Electrocardiogram (EKG) is of limited value in making a specific diagnosis at birth for many defects. Normal EKG does not exclude cardiovascular disease in the newborn; a superior axis however, suggests abnormality.
11. Echocardiography is the mainstay of the diagnosis of the newborn with symptomatic cardiovascular disease.
12. Urine output, serum electrolytes, and body weight must be monitored and used to guide water and electrolyte administration when managing newborns with CHD.

#### *Initial evaluation*

##### 1. Physical examination

###### 1. Inspection

Should focus on three cardinal signs - Cyanosis, Tachypnea, and decreased systemic perfusion.

###### (A) Cyanosis

- a. Cyanosis is caused by either CHD, PPHN or intra or extra-parenchymal lung disease.
- b. Peripheral cyanosis (acrocyanosis) is common in newborn infants and reflects their normally unstable peripheral vasomotor tone.



- c. Central cyanosis is important to recognise and is indicative of arterial oxygen desaturation.

## (B) Tachypnea

Tachypnea in the absence of cyanosis or decreased systemic perfusion often points to pulmonary disease.

## (C) Decreased systemic perfusion

- a. Signs to be assessed include temperature and colour of the skin, blood pressure, peripheral pulses, and capillary refill in each extremity.
- b. Blood pressure should be measured in the right upper and lower extremities.
- c. The differential diagnosis of decreased systemic perfusion includes sepsis, haematological abnormalities (anaemia/polycythaemia), and endocrine/metabolic disorders.
- d. Infants with cardiovascular disease are typically stable during the first hours of life, but eventually develop poor feeding, pallor, diaphoresis, and tachypnea with respiratory distress occurring as late as 3-4 weeks after birth.
- e. Mottling of the skin and/or an ashen, gray colour are important clues to severe cardiovascular compromise and incipient shock.

## 2. Palpation

- a. Palpation of the distal extremities with attention to temperature and capillary refill should be assessed.
- b. Diminished or absent lower limb pulses are suggestive of aortic arch obstruction.
- c. A precordial thrill may be present in the setting of at least moderate pulmonary or aortic outflow obstruction.
- d. A hyper-dynamic precordium may suggest a significant left-to-right shunt.

## 3. Auscultation

- a. Heart rate, heart sounds, rhythms, and murmurs should be assessed.
- b. Although difficult to find, the presence of a split second heart sound in a cyanotic infant strongly suggests total anomalous pulmonary venous connection.
- c. A systolic ejection click suggests aortic or pulmonary valve stenosis, and truncus arteriosus.
- d. Gallop rhythms may be present in newborn infants with severe left ventricular dysfunction.
- e. Murmurs are associated with (i) semilunar valve or outflow tract stenosis, (ii) shunting through a septal defect, or (iii) atrioventricular valve regurgitation. Diastolic murmurs are always indicative of cardiovascular pathology.
- f. Presence and intensity of systolic murmurs do not necessarily suggest the type and severity.
- g. Murmur heard in the left axilla strongly suggests left pulmonary artery branch stenosis.

## 2. Four-extremity blood pressure

- a. Measurement of blood pressure should be taken in bilateral upper and lower extremities.
- b. A systolic pressure that is 10–15 mm Hg higher in the upper body compared to the lower body is abnormal and suggests coarctation of the aorta, aortic arch hypoplasia, or interrupted aortic arch.
- c. A systolic blood pressure gradient not be present in the neonate with an arch abnormality in whom the ductus arteriosus is patent and nonrestrictive.

## 3. Pulse oximetry



- a. The primary approach includes pre- (right hand/wrist) and post-ductal extremity pulse oximetry measurement >24 hours after birth.
  - b. Values < 95% would result in further evaluation with echocardiography.
4. Chest x-ray
- a. A frontal and lateral view should be requested.
  - b. In addition to heart size, visceral and cardiac situs should be observed (dextrocardia and situs inversus are frequently accompanied by congenital heart disease).
  - c. A right-sided aortic arch is associated with congenital heart disease in > 90% of patients.
  - d. Dark or poorly perfused lung fields may suggest decreased pulmonary blood flow, whereas diffusely opaque lung fields may represent increased pulmonary blood flow or significant left atrial hypertension.
5. Hyperoxia test
- a. The neonate who “fails” a hyperoxia test is very likely to have congenital heart disease involving ductal-dependent systemic or pulmonary blood flow and should receive prostaglandin until anatomic definition can be accomplished. A failed hyperoxia test is also seen in PPHN.
  - b. In intra-cardiac right-to-left shunt, the arterial oxygen tension should be measured in room air (if tolerated) followed by repeat measurements with the patient receiving 100% inspired oxygen (the “hyperoxia test”).
  - c. When a patient breathes 100% oxygen, an arterial PO<sub>2</sub> of > 250 torr in both upper and lower extremities virtually eliminates critical structural cyanotic heart disease (a “passed” hyperoxia test).
  - d. An arterial PO<sub>2</sub> of < 100 in the absence of clear-cut lung disease (a “failed” hyperoxia test) is most likely due to intra-cardiac right-to-left shunting and is virtually diagnostic of either a cyanotic congenital heart disease or PPHN.
  - e. If possible, the arterial partial pressure of oxygen (PO<sub>2</sub>) should be measured directly through arterial puncture or a properly applied transcutaneous oxygen monitor (TCOM) values for PO<sub>2</sub>.
  - f. Pulse oximetry may be used for documentation although it is preferable that measurements be made by arterial blood gas or TCOM at both “pre-ductal” and “post-ductal” sites.
  - g. Markedly higher oxygen content in the upper versus the lower part of the body may be an important diagnostic clue to PDA and all forms of critical aortic arch obstruction or left ventricular outflow obstruction.
  - h. ‘Reverse differential cyanosis’ with elevated lower body saturation and lower upper body saturation occurs only in children with transposition of the great arteries with an abnormal pulmonary artery to aortic shunt due to coarctation, interruption of the aortic arch, or supra-systemic pulmonary vascular resistance (“persistent foetal circulation”).

### *Stabilisation and transport*

Initial resuscitation: volume resuscitation, inotropic support, and correction of metabolic acidosis may be required with the goal of improving cardiac output and tissue perfusion.

#### Prostaglandin1 (PGE1) indication

1. In neonates who present in shock in the first few weeks of life have duct-dependent systemic blood flow until proved otherwise, and resuscitation will be successful if the ductus arteriosus is opened.
2. PGE1 is also indicated in congenital lesions resulting in ductal-dependent systemic or pulmonary blood flow or have a PDA that aids in inter-circulatory mixing.
3. PGE1 causes apnoea in 10% to 12% of neonates, usually within the first 6 hours of administration.



4. Discuss with the receiving hospital before initiating PGE1. The infant who will be transferred to another institution while receiving PGE1 should be intubated for maintenance of a stable airway before leaving the referring hospital.
5. PGE1 typically causes peripheral vasodilation and subsequent hypotension in many infants.
6. A separate IV line should be secured for volume administration in any infant receiving PGE1, especially those who require transport.

#### Inotropic agents:

1. Dopamine can be expected to increase mean arterial pressure, improve ventricular function, and improve urine output with a low incidence of side effects at doses  $<10 \mu\text{g}/\text{kg}/\text{minute}$ .
2. Combination of low-dose dopamine (up to  $5 \mu\text{g}/\text{kg}/\text{minute}$ ) and dobutamine may be used to minimise the potential peripheral vasoconstriction induced by high doses of dopamine while maximising the dopaminergic effects on the renal circulation.

#### Transport:

1. Ensure a reliable vascular access.
2. Umbilical lines placed for resuscitation and stabilisation should be left in place for transport.
3. The neonate with congenital heart disease may potentially require cardiac catheterisation (if possible) through umbilical lines.
4. The umbilical venous catheter should be at the inferior vena cava (IVC)—right atrial junction to ensure that access to the heart via this route is possible. (Not in the atrium since it is associated with pericardial effusion.)
5. All neonates receiving a PGE1 infusion should be intubated for transport.
6. Acid–base status and oxygen delivery should be checked with an arterial blood gas before transport.
7. Supplemental oxygen at or near 100% is often not the inspired oxygen concentration of choice for the neonate with congenital heart disease except in case of Hypoplastic left heart.
8. Hypotension is a late finding in shock. Tachycardia and poor tissue perfusion, are important to note and treat before transport.

### Diagnosis confirmation

#### Echocardiography:

- ▶ Two-dimensional echocardiography, supplemented with Doppler and colour Doppler has become the primary diagnostic tool for anatomic definition in paediatric cardiology.

Cardiac catheterisation: rarely necessary for anatomic definition of intra-cardiac structures.

- ▶ Catheterisation is performed for catheter-directed therapy of congenital lesions.

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# PATENT DUCTUS ARTERIOSUS

A patent ductus arteriosus (PDA) occurs when the ductus arteriosus fails to completely close after birth.

## Ductus arteriosus in Fetal Circulation

In the foetal circulation, the ductus arteriosus provides a connection between the pulmonary artery and descending aorta, through which deoxygenated blood returning to the right heart is diverted to the placenta for re-oxygenation (right to left shunt).

In the normal term infant, the ductus arteriosus constricts soon after birth 12 -72 hours (*functional closure*), stimulated by the rapid postnatal increase in arterial oxygen tension and pulmonary clearance of prostaglandin.

After several weeks to months permanent *anatomic closure* takes place resulting in the formation of the *ligamentum arteriosum*.

## FACTORS ASSOCIATED WITH DELAYED CLOSURE

1. Prematurity (significant PDA affects approximately 30% of very-low-birth- weight babies)
2. Lack of antenatal corticosteroid prophylaxis
3. Surfactant-deficient lung disease
4. Hypoxaemia
5. Foetal inflammation or infection
6. Use of furosemide especially in the first week of life in preterm infants
7. Volume overload

## ADVERSE EFFECTS OF PDA

Left-to-right shunting through the PDA → excessive pulmonary blood flow due to diversion of aortic flow into the lungs ('ductal steal') → increased volume work for the left heart → ventricular enlargement and myocardial dysfunction → decreased systemic cardiac output ('diastolic steal') → systemic end-organ ischaemia.

Hypotension may be present in the early stages.

## PROLONGED PDA IN PRETERM INFANTS IS ASSOCIATED WITH:

1. Severe respiratory distress syndrome (RDS)
2. Prolonged assisted ventilation
3. Pulmonary haemorrhage
4. Bronchopulmonary dysplasia (BPD)
5. Necrotising enterocolitis (NEC)
6. Renal impairment
7. Intraventricular haemorrhage (IVH)
8. Periventricular leukomalacia (PVL)
9. Cerebral palsy
10. Death

## CLINICAL MANIFESTATION

Clinical signs usually appear after 4 days of age in VLBW infants.



1. Characteristic ejection systolic murmur (heard best along the left sternal border)
2. Characteristic continuous 'machinery' murmur may be heard (once pulmonary pressures have fallen). This appears later and is more common in post-term infants.
3. Large PDA may have no audible murmur
4. Increased precordial impulse
5. Arterial pulses are prominent and bounding on palpation
6. The larger the PDA and shunting the more haemodynamically unstable the infant:
  - a. heart failure
  - b. respiratory distress
  - c. apnoea
  - d. broncho-pulmonary dysplasia
  - e. pulmonary haemorrhage
  - f. poor feeding
  - g. failure to thrive

Haemodynamically significant PDA is suspected because of signs of excessive pulmonary perfusion resulting in:

1. increase alveolar-arterial oxygen gradient followed by an increase in PaCO<sub>2</sub>
2. decrease lung compliance
3. inability to wean the infant from supplemental oxygen
4. need for distending airway pressure
5. need for positive pressure ventilation

#### DIFFERENTIAL DIAGNOSIS

1. Other cardiac pathology (congenital heart disease, including duct-dependent lesions, arrhythmias or cardiomyopathy)
2. Infection/pneumonia
3. Bronchopulmonary dysplasia (may cause increased oxygen requirements and increased CO<sub>2</sub>)

#### DIAGNOSTIC

1. Chest radiographs
  - a. Enlarged cardiac silhouette, prominent pulmonary vascular markings, or evidence of pulmonary oedema.
  - b. These signs are nonspecific and insensitive.
2. Electrocardiogram: can be normal or show left ventricular hypertrophy and left-atrial dilatation. (poor sensitivity)
3. Biomarkers (presently not in use but ongoing studies seem to be promising)
  - a. B-type natriuretic peptide (BNP)
  - b. Cardiac troponin T (cTnT)
  - c. Aminoterminal B-type natriuretic peptide (NT-proBNP)
4. Color Doppler echocardiography: GOLD STANDARD



- a. An echocardiograph should be done prior to starting treatment.
- b. Findings that correlate with a large shunt include:
  - a. increased left atrial to aortic root diameter (LA : Ao) ratio > 1.5
  - b. large ductal diameter > 1.5 mm
  - c. left ventricular distention
  - d. reduced or reversed diastolic flow in cerebral, renal, or mesenteric arteries or descending aorta.

## MANAGEMENT

The initial treatment of choice is medical, however some symptomatic infants may require surgical ligation if medical treatment fails or is contraindicated.

## IMMEDIATE TREATMENT

### General measures

1. Ventilation
  - a. Optimise oxygenation by appropriate ventilatory support
  - b. Increase PEEP (i.e.  $\geq 5$  cmH<sub>2</sub>O) can help minimise effects of pulmonary oedema and risk of pulmonary haemorrhage. PEEP of 5 to 8 cm H<sub>2</sub>O reduces ductal shunting without adversely affecting cerebral perfusion or oxygenation.
  - c. Increase PIP
2. Treat anaemia – maintain Hb  $\geq 10.0$  g/dL with blood transfusion (considering a dose of IV furosemide after transfusion has not shown to be effective)
3. Before starting medication, restrict fluid intake i.e. from 150 mL/kg/day to 90–120 mL/kg/day). Some experts would recommend maximum 150 ml/kg/day on either enteral or parenteral nutrition.
4. If fluid overload or pulmonary oedema, give one IV dose of furosemide: 1 mg/kg/dose. (not much evidence except in congestive heart failure)
5. Avoid use epinephrine and dopamine (these increase left to right shunting).
6. Enteral feedings can be safely continued in the presence of a PDA.

### Preterm Infants

1. Not all preterm infants with a PDA will require treatment.
2. The duct will close spontaneously in the majority of preterm infants.
3. Medical interventions may be indicated in the first 3 or 4 weeks and direct surgical management thereafter; most PDAs close spontaneously.
4. Fluid restriction: maximum 150 ml/kg/day.
5. Loop diuretics i.e. Furosemide should be avoided in preterm infants since it stimulates synthesis of prostaglandin E<sub>2</sub>, which can promote ductal patency.
6. Pharmacologic treatment should be considered when there is:
  - a. Persistent need of significant ventilatory support
  - b. Cardiac failure
  - c. Compromised gut perfusion with or without feed intolerance
  - d. A significant shunt on echocardiograph



## INDICATIONS FOR PHARMACOLOGIC TREATMENT

1. Babies born < 34 weeks' gestation with significant PDA – on clinical and/or echocardiographic assessment.
2. Includes ventilatory/CPAP dependent babies or PDA with haemodynamic effects (i.e. cardiac failure or poor perfusion).
3. Monitor babies with non-significant PDA carefully and treat if becomes significant.

NSAIDs, now called cyclooxygenase inhibitors (COIs), induce constriction and closure of the ductus arterioles.

Indomethacin and ibuprofen are equally effective in reducing rates of persistent PDA but ibuprofen has a better side effect profile than indomethacin.

### 1. Ibuprofen

Dose: 10 mg/kg OD followed by 5 mg/kg at 24 and 48 hours IV/PO

A second and a third course may be considered if the previous have failed to close the duct and it is still thought to be clinically significant.

### 2. Indomethacin (difficult to source)

Dose: 0.2 mg/kg OD for 3 doses OR 0.1 mg/kg/day OD for 6 doses IV/PO

### 3. Paracetamol (Acetaminophen) - as yet unproven but appears promising (is not a COI)

Dose: 15mg/kg/dose every 6 hours for 3 days IV/PO

## Monitoring while on Ibuprofen

1. Platelet, serum creatinine, urea and electrolytes before and during treatment.
2. Consider withholding if creatinine > 1.5 mg/dl.
3. A platelet count of < 50,000/mm<sup>3</sup>. Consider platelet transfusion.
4. Daily weight, vital signs and fluid balance.
5. Careful monitoring of gastrointestinal and renal status is required.
6. Enteral feeds should not be increased rapidly during treatment.
7. Infants given steroids while on Ibuprofen are at increased risk of focal gut perforation. Therefore, it is not recommended to give steroids while on ibuprofen.
8. Echocardiography (if clinically indicated), repeated after 2–3 days of completion.

## Contraindications to Ibuprofen

1. Duct-dependent cardiac lesion
2. Poor renal function (creatinine > 1.5 mg/dl)
3. Necrotising enterocolitis
4. Acute sepsis
5. Active bleeding i.e. gastrointestinal, significant intraventricular haemorrhage

## PERSISTENT SIGNIFICANT PDA AND SURGICAL REFERRAL

If PDA is still significant and infant is ventilatory or CPAP dependent, refer to a cardiac centre for surgical ligation when:





1. prostaglandin inhibitor contraindicated (Table 1)
2. prostaglandin inhibitor not indicated ( $\geq 34$  weeks with cardiac failure not controlled by diuretics)
3. prostaglandin inhibitor ineffective (usually after giving second course)

After surgical ligation, keep baby nil-by-mouth for 24 hr before gradually increasing up feeds (because of risk of necrotising enterocolitis).

Immediate post-ligation complication includes: Post-ligation cardiac syndrome (PLCS), characterised by systolic hypotension and ventilation/oxygenation failure beginning 4 to 12 hours after surgery. Treatment: dobutamine or milrinone to increase LV systolic performance and reduce afterload.

Other surgical complications include: chylothorax, pneumothorax, phrenic or recurrent laryngeal nerve injury, and scoliosis in late childhood.

Table 1. Cardiac lesions dependent on PDA

Duct-dependent systemic blood flow (left-sided obstructed lesions)	Duct-dependent pulmonary blood flow
Aortic stenosis	Pulmonary stenosis
Coarctation of aorta	Pulmonary atresia
Interrupted aortic arch	Tricuspid atresia
Hypoplastic left heart syndrome	Tetralogy of Fallot
	Ebstein anomaly

## DISCHARGE

If infant is stable and PDA persistent clinically or echocardiographically at discharge, arrange further follow-ups in cardiac clinic.

If PDA is still persistent at 1 yr of age or if clinically significant during follow-up (cardiac failure or failure to thrive), refer to paediatric cardiologist to consider closure (first option is usually catheter closure).

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### BLOOD COMPONENTS TRANSFUSION

1. Routine blood components consist of packed red blood cells (RBCs), platelets, fresh frozen plasma, cryoprecipitate, and granulocytes.
2. Blood components are preferred over whole blood because each component has a specific optimal storage condition, which maximises the use of blood donations.
3. Neonates, especially premature infants tend to receive multiple transfusions during hospitalisation due to many contributing factors and critical health conditions.
4. Donor exposures and acute transfusion reactions can be minimised by reserving a fresh unit of packed RBCs for a neonate at his or her first transfusion and transfusion of aliquots of that unit for each subsequent transfusion.

### RED BLOOD CELLS TRANSFUSION

#### INDICATIONS

1. Acute blood loss with haemodynamic compromise,  $\geq 10\%$  blood volume loss or hypovolaemic shock.  
In emergency:
  - a. bolus of crystalloid solution can be given initially
  - b. use group O Rh negative blood
  - c. transfuse 10 mL/kg over 30 min
  - d. further transfusion based on haemoglobin (Hb)
2. For infants requiring respiratory support: See Table 1.
  - ▶ Some experts recommend not to wait until infants are symptomatic and transfuse for any Hct  $<24\%$  (Hb 7 g/dl) especially in preterm infants.

NOTE: Growing premature infants may manifest a need for transfusion by exhibiting poor weight gain, apnoea, tachypnea, or poor feeding.

Sick infants (i.e. with sepsis, pneumonia, or bronchopulmonary dysplasia) may require increased oxygen-carrying capacities and therefore need transfusion.



Table 1. Suggested haemoglobin levels and haematocrit thresholds for transfusing infants with anaemia of prematurity

Postnatal Age	Respiratory Support	No Respiratory Support
Week 1	11.5 (35)	10.0 (30)
Week 2	10.0 (30)	8.5 (25)
Week 3 and older	8.5 (25)	7.5 (23)

Data presented as hemoglobin (g/dL) (hematocrit %). Respiratory support is defined as  $FiO_2 > 25\%$  or the need for mechanical increase in airway pressure  
 Source: Adapted from Whyte R, Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. *Cochrane Database Syst Rev* 2011;(11):CD000512.

For newborns on week 3 and older recommended threshold to transfuse is  $Hb \leq 9$  (Hto 27) for babies with respiratory support and  $Hb \leq 8$  (Hto 24) for babies without respiratory support.

### PRE-TRANSFUSION

Communication:

1. If clinical condition permits before transfusion, inform parents that baby will receive blood transfusion.
2. Document discussion.
3. If parents refuse transfusion (i.e. Jehovah's Witness) follow hospital/local policy.

### CROSSMATCH

1. On admission of any infant requiring intensive care take red topped (preferable without gel separator) specimen for Group and save. (Purple top may also be used when requesting blood group.)
2. Ensure specimen of maternal blood has been sent for Group, antibody screening and cross-match.
3. For first transfusion, send samples of baby's and mother's blood.
4. Crossmatch against maternal serum and neonatal serum.

### COOMBS' TESTING

1. The laboratory will perform Indirect Coombs' test (Indirect Antiglobulin Test or IAT) on maternal serum for any atypical antibodies.
2. If maternal IAT negative, blood issued will be crossmatched once against maternal serum.
  - ▶ No further maternal blood samples are necessary for repeat top-up transfusions.
3. If maternal IAT positive, crossmatching of donor red blood cells against maternal serum is required every time.

### MULTIPLE TRANSFUSIONS

1. Donor exposures can be minimised by reserving a fresh unit of RBCs for a neonate at his or her first transfusion.
2. Subsequent transfusions can utilise aliquots of that unit until it is depleted or expires. This is useful for premature infants who are expected to require multiple simple transfusions for anaemia of prematurity.
3. In babies <29 weeks who may need multiple transfusions, use paediatric satellite packs ('Paedipacks') from one donor (if available) to reduce multiple donor exposure.



### *Use of Multipacks*

1. This is a unit from a single donor divided into multiple small volume units that are reserved for one infant to minimise donor exposure.
2. For any infant who likely needs multiple transfusions i.e. infants < 1000 g requiring intensive care a multipack or satellite-pack should be ordered.
3. Make sure to check on the expiry date.

### TYPES OF BLOOD PREPARATION

#### *When to use irradiated blood*

1. Transfusion-associated graft-versus-host disease (TA-GVHD) occurs when transfused lymphocytes mount an immune response against the patient and the patient is unable to destroy the transfused lymphocytes.
2. Irradiation of the blood component prevents proliferation of lymphocytes and thus prevents TA-GVHD.
3. It is preferred practice for all blood given to babies to be irradiated.
4. Irradiated blood MUST always be given for those:
  - a. who are receiving an intra-uterine transfusion or a large-volume transfusion (i.e. double volume exchange transfusion)
  - b. with suspected or proven immunodeficiency
  - c. receiving blood from a first- or second- degree relative, or an HLA-matched donor

#### *When to use CMV-free blood*

- ▶ CMV-seronegative blood should be used for neonatal transfusions if available. If not available, or testing not performed, an adequately leukoreduced blood product is considered CMV-safe and can be used.

#### *Leuko-reduced blood*

1. Blood products should be preferably leuco-depleted to <math>< 5 \times 10^6</math> leucocytes/unit.
2. Leuko-reduction filters remove approximately 99.9% of the white blood cells from RBCs and platelets.
3. Benefits of leuko-reduction include the following:
  - a. Decreased rate of febrile transfusion reactions.
  - b. Decreased rate of CMV transmission to a negligible rate.
  - c. Potential to reduce a possible immunomodulatory effect of blood transfusions.
  - d. Decreased immunisation to antigens on leukocytes such as histocompatibility antigens (HLA).

#### *Whole blood*

1. Whole blood may be used for neonatal exchange transfusions.
  - ▶ In these cases, the whole blood should be < than 5 days old.
  - ▶ For neonatal exchange transfusions, fresh packed RBCs (<5 days old) reconstituted with compatible FFP down to a Hct. of 40-50% is best recommended. This product should be irradiated, leukoreduced, CMV-negative, and warmed prior to infusion.
2. Whole blood may be useful for neonates immediately following disconnection from a cardiopulmonary bypass circuit for cardiac surgery.
  - ▶ In these cases, the blood should be no more than 2 to 3 days old.



3. Platelets in whole blood will be cleared rapidly following transfusion, and reconstituted whole blood lacks significant quantities of platelets.

#### WITHHOLDING FEEDS DURING TRANSFUSION

- ▶ Some units withhold enteral feeds during the 3–4 hr duration of transfusion in preterm neonates at risk for NEC (<34 wks post-conceptual age). This practice is NOT recommended for full term neonates.
- ▶ Some units withhold enteral feeds 4 hours before starting the transfusion and restart enteral feeds 4 hours after ending the transfusion.
- ▶ There has been controversy about whether feedings should be withheld when a baby receives a transfusion, but the evidence for this practice is not very well substantiated.

#### TRANSFUSION

The volume of transfusion may be calculated as follows:

1. Generally: 10–20 mL/kg of red cell is transfused irrespective of pre-transfusion Hb. If 20 ml/kg is being transfused, it is recommended for it to be divided into 2 aliquots (10 ml/kg each) given 8 hours apart especially in ELBW infants.
2. Volume of blood (ml) = 3 x desired rise in Hb (g/dl) x weight (kg)
3. Volume of transfusion = [(desired Hct - Hct observed) x weight (kg) x blood volume (ml/kg)]/Hct to be given.
  - ▶ The average newborn blood volume is 80 mL/kg; the Hct of packed RBCs is 60% to 80% and should be checked before transfusion.

#### *Rate of administration*

1. Administer blood at 10 mL/kg over 3-4 hrs or 15 mL/kg over 4 hr.
2. Increase rate in presence of active haemorrhage with shock.
3. Via peripheral venous or umbilical venous line (not via long line or arterial line)

#### *Use of furosemide*

1. Routine use not recommended after a transfusion.
2. May be considered soon after blood transfusion for babies: (1 – 2 mg/kg/dose IV)
  - a. with chronic lung disease
  - b. with haemodynamically significant PDA
  - c. in heart failure
  - d. with oedema or fluid overload

#### DOCUMENTATION AND GOOD PRACTICE

1. The use of blood products should always be discussed with the parents in advance and their informed, verbal consent given. The only exception to this should be a life threatening emergency.
2. Clearly document indication for transfusion.
3. Document pre- and post-transfusion Hb levels.
4. Ensure blood transfusion volume and rate is prescribed in appropriate infusion chart.
5. Monitor and record vital signs and SatO<sub>2</sub> before, during and after transfusion.
6. Ensure positive identification of baby using accessible identification.



7. Appropriate labelling of syringes to ensure compliance with current best practice.
8. Unless clinically urgent, avoid transfusion out-of-hours.
9. To reduce need for blood transfusion, minimise blood sampling in babies (micro-techniques, non-invasive monitoring) and avoid unnecessary testing.
10. Ensure donor exposure is minimised by using satellite packs from same donor.

SIDE EFFECTS (The first three are common in adults and rare in neonates.)

1. Acute haemolytic transfusion reactions: hypotension, fever, tachycardia, infusion site pain, and haematuria.
2. Allergic transfusion reactions: hives and possibly wheezing; severe reactions can present as anaphylaxis.
3. Febrile non-haemolytic transfusion reactions.
4. Volume overload
5. Hypocalcaemia
6. Hypothermia
7. Transfusion-associated acute lung injury (TRALI): due to antibodies in donor plasma that react with the patient's histocompatibility (HLA) antigens. Suspect TRALI in any infant who experiences respiratory decompensation with higher oxygen or ventilator requirements and pulmonary oedema on chest X-ray during the transfusion or within the 6 hours following transfusion. Contact the blood bank for work up if suspected.
8. Hyperkalaemia: more frequent secondary to large transfusions such as exchange transfusions or transfusions for major surgery.
9. Bacterial contamination
10. TA-GVHD: Lymphocytes from donor blood components can induce an immune response against the patient.
11. Necrotising enterocolitis is likely NOT due to transfusions but rather to the severity of the pre-transfusion anaemia (Hct. < 25%).

## PLATELETS TRANSFUSION

Platelets can be prepared from whole blood donations or collected by aphaeresis.

If collected by aphaeresis, an aliquot is obtained for a neonatal transfusion.

Aliquots of aphaeresis platelets are relatively RBC free, thus, there should be limited to no concern for Rh sensitisation.

A standard unit of platelets, prepared from a single donation of whole blood contains at least  $5.5 \times 10^{10}$  platelets in 50 to 70 mL of plasma.

Platelets are stored with agitation at  $22 \pm 2$  °C for up to 5 days.

### TRANSFUSION INDICATION

1. Threshold for platelet transfusion:
  - a.  $\leq 30,000/\mu\text{L}$  for healthy or stable term and preterm infants without other risk factors.
  - b.  $\leq 50,000/\mu\text{L}$  for VLBW neonates within the first week of life, and clinically unstable neonates.
2. Patients at increased risk for intracranial haemorrhage with platelet count of 50,000 to 100,000 platelets/ $\mu\text{L}$ .
3. Patients with active bleeding and platelet count < 80,000 - 100,000/ $\mu\text{L}$ .



4. Patients with HIE receiving therapeutic hypothermia with platelet count < 100,000/ $\mu$ L.

Do not transfuse in stable infants with 50,000 - 99,000 or > 99,000 platelet count with no evidence of bleeding.

To calculate platelet doses in neonates:

1. based on mL/kg: 10 to 15 ml/kg over 30 - 60 minutes.
2. based on equivalent units/kg: 1 EU/5 to 10 kg of weight (for children > 5kg)
  - a. An equivalent unit (EU) is the volume of a platelet aliquot that has a minimum platelet content of  $5.5 \times 10^{10}$ .
  - b. This amount yields a platelet increment of 50,000/ $\mu$ L to 100,000/ $\mu$ L if no predisposing risk factors exist.

It is important to account for device-related dead space (10-30mL) when issuing the product.

#### SIDE EFFECTS

- ▶ Bacterial contamination.
- ▶ ABO incompatible plasma in a platelet unit. This rarely can cause a haemolytic transfusion reaction.

Nonetheless, some blood banks remove plasma from platelet units containing antibodies that are incompatible with the patient or avoid platelets with high titers of these antibodies. This is mandatory if maternal platelets are used in neonates with Neonatal Alloimmune Thrombocytopenia. If maternal platelets are used for transfusion in a baby who is not responding to random platelet transfusions and IVIG, then the platelets need to be volume-reduced (preferred) or washed to eliminate the antibodies in the plasma.

## FRESH FROZEN PLASMA TRANSFUSION

Plasma can be prepared by either whole blood separation or by aphaeresis.

Plasma product is frozen to  $-18^{\circ}$  C or colder within 8 hours of collection and labeled as fresh frozen plasma.

FFP can be stored at  $-18^{\circ}$ C for up to 1 year.

Plasma should be separated into a system of multiple satellite bags and frozen as aliquots for use in neonates. This conserves plasma inventory and limits donor exposures.

FFP contains:

1. all plasma proteins including albumin and antibodies (Ig), coagulation factors, Fibrinogen, and vitamin K dependent factors (II, VII, IX, X).
2. 160 to 170 mEq/L sodium and 3.5 to 5.5 mEq/L potassium

#### INDICATIONS

1. Acquired coagulation factor deficiencies due to:
    - a. DIC, liver failure, vitamin K deficiency from malabsorption, biliary disease, and warfarin therapy.
    - b. Dilutional coagulopathy from massive transfusion.
  2. To reconstitute blood for blood exchange transfusion.
  3. For congenital factor deficiencies when specific factor concentrate is unavailable.
- ▶ FFP is not indicated for volume expansion, enhancement of wound healing, or as first-line treatment for congenital factor deficiencies.



## TRANSFUSION

1. FFP: 10 to 20mL/kg IV in 30-60 minutes.
  2. May be repeated every 8 to 12 hours depending on the clinical situation.
- ▶ Plasma transfusions should be ABO-compatible with the neonate's RBCs to avoid passive transfer of iso-haemagglutinins from ABO-incompatible plasma, which may result in haemolysis.

### Further reading:

Lemus-Varela MA, Sola A, Golombeck SG, integrantes del IV Consenso SIBEN y la experta de opinión Martha Sola-Visner. Manual Práctico para toma de Decisiones en Hematología Neonatal. Consenso SIBEN 2010: Hematología Neonatal; Buenos Aires, Argentina; Edimed-Ediciones Medicas; 2011.

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# ANAEMIA

Anaemia is defined by a haemoglobin or haematocrit value that is more than two standard deviations below the mean for age.

## AETIOLOGY OF ANAEMIA IN THE NEONATE

In the neonate, the causes of anaemia can be divided into two broad categories:

1. anaemia resulting from accelerated loss or destruction of red blood cells
2. anaemia caused by a defect at some stage of red blood cell production

Table 1. Causes of anaemia in the neonatal period.

Accelerated Loss	Accelerated Destruction	Diminished Red Blood Cell Production
Hemorrhage <ul style="list-style-type: none"> <li>• Fetal</li> <li>• Fetal-maternal</li> <li>• Placental</li> <li>• Traumatic delivery</li> <li>• Coagulation defects</li> </ul> Early umbilical cord clamping Twin-twin transfusion Excess phlebotomy losses	Hemolytic anemia <ol style="list-style-type: none"> <li>1. Immune                             <ul style="list-style-type: none"> <li>• Alloimmune: Rh, ABO, minor blood group</li> <li>• Autoimmune</li> </ul> </li> <li>2. Nonimmune</li> </ol> Hemoglobinopathy Thalassemia Unstable hemoglobin Red blood cell enzyme defect Structural defect of red blood cell membrane Mechanical destruction Microangiopathic hemolytic anemia Infection Vitamin E deficiency	Congenital <ul style="list-style-type: none"> <li>• Diamond-Blackfan anemia</li> <li>• Pearson syndrome</li> <li>• Fanconi anemia</li> <li>• Congenital dyserythropoietic anemias</li> <li>• Anemia of prematurity</li> </ul> Acquired <ul style="list-style-type: none"> <li>• Parvovirus B19</li> <li>• Transient erythroblastopenia of childhood</li> <li>• Human immunodeficiency virus</li> <li>• Syphilis</li> <li>• Iron deficiency</li> <li>• Lead toxicity</li> <li>• Infection</li> </ul>



Table 2. Classification of anaemia in the newborn

Reticulocytes	Bilirubin	Coombs Test	RBC Morphology	Diagnostic Possibilities
Normal or ↓	Normal	Negative	Normal	Physiologic anemia of infancy or prematurity; congenital hypoplastic anemia; other causes of decreased production
Normal or ↑	Normal	Negative	Normal	Acute hemorrhage (fetomaternal, placental, umbilical cord, or internal hemorrhage)
↑	↑	Positive	Hypochromic microcytes	Chronic fetomaternal hemorrhage
			Spherocytes	Immune hemolysis (blood group incompatibility or maternal autoantibody)
Normal or ↑	↑	Negative	Spherocytes	Hereditary spherocytosis
			Elliptocytes	Hereditary elliptocytosis
			Hypochromic microcytes	α- or γ-Thalassemia syndrome
			Spiculated RBCs	Pyruvate-kinase deficiency
			Schistocytes and RBC fragments	Disseminated intravascular coagulation; other microangiopathic processes
			Bite cells (Heinz bodies with supravital stain)	Glucose-6-phosphate dehydrogenase deficiency
			Normal	Infections; enclosed hemorrhage (cephalohematoma)

RBC, red blood cell; ↓, decreased; ↑, increased.  
 Source: Adapted from the work of Dr. Glader Bertil, director of Division of Hematology-Oncology, Children's Hospital at Stanford, California, 1991.

Table 3. Haemoglobin changes in babies in the first year of life

Week	Hemoglobin Level		
	Term Babies	Premature Babies (1,200–2,500 g)	Small Premature Babies (<1,200 g)
0	17.0	16.4	16.0
1	18.8	16.0	14.8
3	15.9	13.5	13.4
6	12.7	10.7	9.7
10	11.4	9.8	8.5
20	12.0	10.4	9.0
50	12.0	11.5	11.0

Source: From Glader B, Naiman JL. Erythrocyte disorders in infancy. In: Taesch HW, Ballard RA, Avery ME, eds. *Diseases of the Newborn*. Philadelphia, PA: WB Saunders; 1991.



Table 4. Haemoglobin nadir in babies in the first year of life

Maternity of Baby at Birth	Hemoglobin Level at Nadir	Time of Nadir (week)
Term babies	9.5–11.0	6–12
Premature babies (1,200–2,500 g)	8.0–10.0	5–10
Small premature babies (<1,200 g)	6.5–9.0	4–8

*Source:* From Glader B, Naiman JL. Erythrocyte disorders in infancy. In: Taeusch HW, Ballard RA, Avery ME, eds. *Diseases of the Newborn*. Philadelphia, PA: WB Saunders; 1991.

## CLINICAL FINDINGS

1. Acute blood loss: shock, cyanosis, poor perfusion, and acidosis
2. Chronic blood loss: pallor, mild symptoms of respiratory distress or irritability
3. Chronic haemolysis: pallor, jaundice, and hepatosplenomegaly

## DIAGNOSTIC APPROACH TO ANAEMIA IN THE NEWBORN

### Initial testing:

1. Complete blood cell count
2. Reticulocyte count
3. Blood smear
4. Coombs test and bilirubin level

### Other testing according to findings:

1. Apt test (differentiate foetal or neonatal blood from maternal blood)
2. Kleihauer-Betke test (measures foetal Hb in mother's blood)
3. Ultrasound of abdomen and head
4. Sepsis workup
5. Bone marrow study

## MANAGEMENT

TRANSFUSION: See *RBC Transfusion Guideline*

The only absolute indications for rapidly correcting anaemia by RBC transfusion are:

1. to restore tissue oxygenation
2. to expand blood volume after severe, acute loss

## PROPHYLAXIS

### Term infants

According to the 2010 American Academy of Paediatrics (AAP) recommendation:

1. Breastfed infants should be started on iron supplementation at the age of 4 months.
2. Non breastfed infants should be sent home from the hospital on iron-fortified formula (2 mg/kg/day).



Premature infants (preventing or ameliorating the anaemia of prematurity):

#### *Iron supplementation*

Should be started between 4 and 6 weeks of age at the onset of reticulocytosis or once full enteral feeding is achieved at 100 ml/kg/day in preterm infants < 34 weeks.

Dose: 2 mg/kg/day of elemental iron for formula-fed preemies, and 4 mg/kg/day of elemental iron for breastfed preterm infants.

#### *Vitamin E*

Dose: 5 to 25 IU of water-soluble form once daily until the baby is 38 to 40 weeks' post conceptional age.

This is usually stopped at discharge from the hospital.

#### *Vitamin D*

Dose: 200-400 IU daily for premature infants.

For full term infants, Fe and vitamin D is not needed if the infant is formula-fed (all formulas are supplemented), but yes if the infant is completely or mostly breastfed. Full term infants and preterm infants with a weight >1,500 g should receive 400 IU/day of vitamin D.

#### *Recombinant human erythropoietin (rh-EPO)*

The association with ROP is weak but related with an increased risk for retinopathy of prematurity (ROP) when rh-EPO is started in the first week of life.

Currently, EPO it is not routinely use nor recommended for prophylaxis for anaemia.

Nevertheless, there may be utility in this option for families who withhold consent to transfusion of blood products.

#### Further reading:

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## POLYCYTHAEMIA

Defined as peripheral venous haematocrit (Hct) > 65% or Hb greater than 22g/dL.

1. Capillary haematocrit may be up to 20% higher than venous.
2. Hct peaks at 2 hr after birth and then decreases with significant changes occurring by 6 hr .
3. Symptoms rarely occur with peripheral Hct of < 70%.

### CAUSES

Polycythaemia is mostly seen in babies with intrauterine growth restriction (IUGR), small for gestational age (SGA), and post-term infants.

Table 1. Causes of polycythaemia.

Intra-uterine increased erythropoiesis	Erythrocyte transfusion
Placental insufficiency: SGA and IUGR infants	Maternal-fetal
Post maturity	Twin-to-twin transfusion
Maternal diabetes	Delayed cord clamping
Maternal smoking	Unattended delivery
Maternal hypertension	Holding the baby below the mother at delivery
Chromosomal abnormalities: trisomy 21, 18, 13	
Beckwith–Wiedemann syndrome	
Congenital adrenal hyperplasia	
Neonatal thyrotoxicosis	
Congenital hypothyroidism	

### CLINICAL MANIFESTATION

Commonly plethoric but asymptomatic.

Table 2. Clinical signs.

Cardiorespiratory	Respiratory distress
	Persistent pulmonary hypertension of the newborn (PPHN)
	Congestive cardiac failure
CNS	Lethargy, hypotonia within 6 hr
	Difficult arousal, irritability
	Jittery
	Easily startled
	Seizures



Cardiorespiratory	Respiratory distress Persistent pulmonary hypertension of the newborn (PPHN) Congestive cardiac failure
GASTROINTESTINAL	Poor feeding Vomiting NEC Hypoglycaemia Hypocalcaemia Jaundice
Haematological	Thrombocytopenia
Renal	Renal vein thrombosis Renal failure

## CLINICAL CONSEQUENCES

Hyper viscosity leads to → decreased blood flow and decreased glucose in plasma → impaired tissue perfusion → thrombus formation.

## COMPLICATIONS

1. Cerebral micro-infarction and adverse neuro-developmental outcome
2. Renal vein thrombosis
3. Necrotising enterocolitis (NEC)

## MANAGEMENT

Objective:

1. to maintain an adequate hydration state
2. to correct metabolic and electrolytes imbalances
3. to treat associated complications

### *Investigations*

To unstable, symptomatic, and at-risk babies who look plethoric:

- ▶ CBC/Hct (peripheral venous sample)

If Hct > 65%: check blood glucose and serum calcium

### *Immediate Treatment*

Partial exchange transfusion (PET) to reduce hematocrit should be considered for symptomatic newborns with peripheral venous Hct levels > 65%.

1. PET is not recommended to asymptomatic patients with Hct > 65%.
2. Administer adequate fluid intake.



Asymptomatic babies with Hct >70% :

1. Repeat peripheral venous Hct after 6 hr.
2. If still high, discuss with consultant.
3. Many neonatologists perform an exchange transfusion when the peripheral venous hematocrit is >70% in the absence of symptoms. (current evidence does not show any benefit of PET in asymptomatic babies)
4. If Hct is 60% - 70%: increase fluid intake and repeat the haematocrit in 4 to 6 hours.

Symptomatic babies with Hct > 65%

1. PET is indicated.
2. Explain to parents the need for exchange and possible risks before procedure.
3. Monitor vital signs: HR, RR, SatO<sub>2</sub>, BP.
4. Use normal saline solution (NSS) 0.9%.
5. Perform exchange via:
  - a. If one umbilical catheter is available:
    - (a) Blood is taken from umbilical vein catheter or umbilical artery catheter and replaced with NSS via a peripheral vein: Iso-volumetric exchange (preferred method).
    - (b) Blood is taken from the umbilical catheter (artery or vein) interchanged with administration of NSS in aliquots of 5-10 ml.
  - b. If both umbilical catheters are available:

Blood is taken from umbilical artery catheter and replaced with NSS via umbilical vein catheter: Iso-volumetric exchange.
  - c. If no umbilical catheter available: use two peripheral access
    - (a) Blood is taken from a peripheral arterial puncture and replaced with NSS via a peripheral vein.
    - (b) Central line placement should be avoided if not needed for other purpose in care.
6. Take 5–10 mL aliquots and complete procedure over 15–20 min.

7. Volume of exchange in mL:

$(\text{blood volume ml/kg} \times \text{weight kg}) \times (\text{observed Hct} - \text{desired Hct}) / \text{Hct observed}$

*Desired Hct: 50-55%.*

i.e. A 2.5 kg infant, Hct 75%, blood volume 80 mL/kg (to bring Hct to 50%):

Vol of exchange:  $(80\text{ml} \times 2.5 \text{ kg}) \times (75-50)/75 = 200 \times 25/75 = 67 \text{ ml of blood}$

(replace with 67 - 70 ml of NSS 0.9%)

The total volume exchanged usually corresponds to 15 - 20 mL/kg of body weight.

## RISK OF PET

Infection, NEC, cardiac arrhythmia, thrombosis, embolus, haemorrhage, hypothermia, hypotension, death

► Partial exchange transfusion increases risk of NEC: monitor for NEC

## SUBSEQUENT MANAGEMENT

Babies who required PET require long- term neuro-developmental follow-up.



Further reading:

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### GASTRO-OESOPHAGEAL REFLUX (GOR)

Gastro-oesophageal reflux (GOR) is a normal physiological event that occurs in healthy infants after eating.

GOR is the passage of gastric contents into the oesophagus.

Gastro-oesophageal reflux disease (GORD) occurs when the effect of GOR leads to symptoms severe enough to merit medical treatment.

#### PATHOPHYSIOLOGY

1. In both preterm and term infants, GOR is generally associated with transient relaxations of the lower oesophageal sphincter (LES) independent of swallowing, which permits gastric contents to enter the oesophagus.
2. Reflux occur commonly in preterm newborn infants but is generally non-acidic and improves with maturation.
3. Acid GER predominates pre-prandially, and non-acid GER predominates post-prandially.
4. The majority of GER events in infants are non-acid.
5. Regurgitation and vomiting are common and often non-pathologic complications of GER.
6. Regurgitation is generally assigned as effortless, painless and non-projectile in a healthy-appearing infant with normal growth - called 'happy spitter'.
7. In the NICU population, preterm and term patients with nasogastric or orogastric feeding tubes may experience more reflux episodes because of mechanical impairment of the competence of the LES.

Note: Gastro-oesophageal reflux (GOR)

1. Is very common (it affects at least 40% of infants).
2. Usually begins before the infant is 8 weeks old.
3. May be frequent (5% of those affected have 6 or more episodes each day).
4. Usually becomes less frequent with time (it resolves in 90% of affected infants before they are 1 year old).
5. Does not usually need further investigation or treatment.

#### MANAGEMENT

1. Positioning of infant:
  - a. Keep infant upright for 30 minutes after feeds, if possible.
  - b. Elevate the head and upper body 30°, in either a prone or right side down position.
  - c. Prone positioning is suggested to be beneficial in children older than 1 year with either GER or GERD.
2. Feeding intervals:
  - a. Temporary reductions in the feeding volume and shortening the interval between feeds.
  - b. Lengthening the duration of the feeding, especially in gavage fed infants.
  - c. Avoid overfeeding.



3. Specialised thickened or commercial anti-regurgitation formulas should only be used for short periods of time in formula fed infants. (Due to possible association between thickened feedings and necrotising enterocolitis in preterm infants.)
4. When milk protein allergy is thought to be mimicking or triggering GERD consider:
  - a. Dairy free diet for a breastfeeding mother.
  - b. Change to elemental formula.
5. Radiographic studies indicated:
  - a. Unless feeding problems have persisted for 2 or more weeks or unless bilious emesis occurs.
  - b. To rule out anatomic abnormalities that may mimic GERD.

#### DIFFERENTIAL DIAGNOSIS

1. Gastrointestinal obstruction
2. Motility abnormalities
3. Infection
4. Inborn errors of metabolism
5. Adrenal insufficiency and other hormonal abnormalities
6. Neurologic abnormalities, including increased intra-cerebral pressure
7. Cow's milk protein allergy

#### THERAPEUTIC INDICATION

Anti-acids and pro-motility medications:

1. Proton pump inhibitors (PPIs) or H2 receptor antagonists are not recommended to treat regurgitation in infants occurring as an isolated symptom.
2. PPIs and H2 receptor antagonists are associated with an increased risk of necrotising enterocolitis in preterm infants.
3. Pro kinetic agents: metoclopramide, domperidone, cisapride or erythromycin are not recommended to treat GOR or GORD in neonates.

Other considerations:

1. Apnoea:
  - a. Studies have not shown an association between GER and apnoea episodes.
  - b. Treatment with pro-motility agents should not be used.
2. Consider enteral tube feeding to promote weight gain in infants and children with overt regurgitation and failure to thrive if:
  - a. other explanations for poor weight gain have been explored and/or
  - b. recommended feeding and medical management of overt regurgitation is unsuccessful.
3. Infants With Recurrent Vomiting and Poor Weight Gain consider:
  - a. A 2-week trial of extensively hydrolysed formula or amino acid – based formula to exclude cow's milk
  - b. Allergy.
  - c. Increased caloric density of formula and/or thickened formula.



- d. Education as to appropriate daily formula volume required for normal growth.

#### FOLLOW-UP

If symptoms worsen or do not resolve by 12 to 18 months of age or “warning signs” develop, referral to a paediatric gastroenterologist.

#### Further reading:

Vandenplas Y, Rudolph CD, Di Lorenzo C, et al; North American Society for Pediatric Gastroenterology Hepatology and Nutrition; European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2009;49(4):498–547.

National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease in children and young people: diagnosis and management. NICE guideline; 2015. Available at: <http://www.nice.org.uk/guidance/ng1>.

Lightdale JR, Gremse DA and SECTION ON GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION. Gastroesophageal Reflux: Management Guidance for the Pediatrician. *Pediatrics* 2013;131:e1684.

Hamilton T, Smithers J, Nurko S. Chapter 7, Part 7.10: Gastroesophageal Reflux. In: Hansen AR, Puder M, editors. *Manual of Neonatal Surgical Intensive Care*. Third ed. Shelton, Connecticut; PMPH-USA; 2016. p. 363-78.

Anderson DM, Poindexter BB, Martin CR. Chapter 21: Nutrition. In: Eichenwald E, Hansen AR, Martin CR, Stark AR, editors. *Cloherty and Stark’s Manual of Neonatal Care*. Eight ed. Philadelphia, PA; Wolters Kluwer; 2017. p. 279-81.

Gibbs AM. Chapter 91: Gastroesophageal Reflux and Gastroesophageal Reflux Disease in the Neonate. In: Martin RJ, Fanaroff AA, Walsh MC, editors. *Fanaroff and Martin’s Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 10th ed. Philadelphia, PA; Elsevier Saunders; 2015. p. 1371-76.



## NEONATAL HYPERBILIRUBINEMIA (JAUNDICE)

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Defined as an elevated total serum bilirubin (TSB) concentration of > 5 mg/dl in the newborn.

Unconjugated hyperbilirubinaemia: defined as an indirect-reacting bilirubin concentration of 2.0 mg/dL or greater.

Conjugated hyperbilirubinaemia: defined as an elevation of the direct-reacting fraction greater than 1.5 mg/dL provided it comprises more than 15% of the total bilirubin (TB) concentration.

Bilirubin exists in four different forms in circulation:

1. Unconjugated bilirubin reversibly bound to albumin.
2. Unconjugated bilirubin not bound to albumin (unbound bilirubin).
3. Conjugated bilirubin which are readily excretable through the renal or biliary systems.
4. Conjugated bilirubin covalently bound to albumin.

### *Unconjugated Hyperbilirubinaemia*

Note:

1. Early-onset hyperbilirubinaemia (less 24 hours of age) is a medical emergency.
2. Visual inspection is not a reliable indicator of TSB level but a clinical guide for management.
3. Do not subtract direct bilirubin from TSB. Use value of TSB for management.
4. Newborns have a lower plasma-binding capacity for bilirubin.
5. The consequence of hyperbilirubinemia in premature infants is more severe than in term infants, with mean peak TB levels approaching 10 to 12 mg/dL.
6. Cutaneous icterus in the newborn will not become evident until TB concentrations exceed 5 to 6 mg/dL.
7. Unbound bilirubin fraction is thought to be a more sensitive predictor of bilirubin-induced neurologic dysfunction (BIND) than the TB.
8. The degradation of 1 g of haemoglobin forms 34 mg of bilirubin.
9. 1 gram of albumin binds 8.2 mg of unconjugated or indirect bilirubin.

### NON-PATHOLOGIC HYPERBILIRUBINEMIA: (Physiologic jaundice)

Physiologic jaundice in term newborns, is characterised by a progressive rise in TB of 5-6 mg/dL to 10-14 mg/dl between 48 and 120 hours of age.

Physiologic jaundice in premature neonates is more severe than in term neonates with mean peak TB concentrations of 10 to 12 mg/dL by the fifth day of life.

Physiologic jaundice is attributed to:

1. Increased RBC volume per kilogram and decreased RBC survival (90 days vs. 120 days) in infants compared to adults.
2. Defective uptake of bilirubin from plasma caused by decreased ligandin and binding of ligandin by other anions.
3. Increased ineffective erythropoiesis and increased turnover of non-haemoglobin heme proteins.
4. Due to decreased UGT activity.



5. Decrease hepatic excretion of bilirubin.
6. Increased enterohepatic circulation.

Note: The two most common pathologic causes of unconjugated neonatal hyperbilirubinaemia include:

1. Isoimmune haemolytic disease caused by mother-foetus blood group incompatibility.
2. Glucose-6-phosphate dehydrogenase deficiency (G6PD).

Some countries have introduced neonatal screening for G6PD deficiency.

Clinical burden is confounded by:

1. prematurity
2. delayed enteral feeding
3. neonatal sepsis
4. use of drugs that impede bilirubin binding to albumin
5. cholestasis due to parenteral nutrition

Visual assessment of jaundice progress: Kramer's Rule (Figure 1)

- ▶ Do not use as an indicator to measure TSB levels.
- ▶ Should be assessed when vital signs are taken or at least every 8-12 hours in the first 24 hours of life then at 24 or 48 hours.

Neurotoxicity risk factors include:

1. haemolytic disease
2. Glucose-6-phosphate dehydrogenase deficiency
3. asphyxia
4. temperature instability
5. sepsis
6. acidosis
7. albumin < 3.0 g/dl

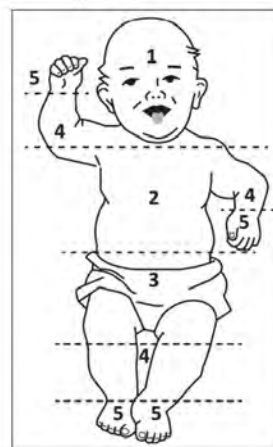
#### RISK FACTORS FOR DEVELOPMENT OF SEVERE HYPERBILIRUBINAEMIA IN INFANTS $\geq 35$ WEEKS OF GESTATION

Major Risk Factors

1. Pre-discharge TB or TcB level in the high-risk zone
2. Jaundice observed in the first 24 hours
3. Blood group incompatibility with positive DAT, other known haemolytic disease (i.e. G6PD deficiency)
4. Gestational age 35 to 36 weeks
5. Previous sibling received phototherapy
6. Cephalo-hematoma or significant bruising

Figure 1. Kramer's Scale

Area of the Body	Level	Range of Serum Bilirubin	
		$\mu\text{mol/L}$	mg/dL
Head and neck	1	68 - 133	4 - 8
Upper trunk (above umbilicus)	2	85 - 204	5 - 12
Lower trunk and thighs (below umbilicus)	3	136 - 272	8 - 16
Arms and lower legs	4	187 - 306	11 - 18
Palms and soles	5	$\geq 306$	$\geq 18$



7. Exclusive breastfeeding, particularly if nursing poorly and weight loss is excessive
8. East Asian race

#### Minor Risk Factors

1. Pre-discharge TB or TcB in the high intermediate-risk zone
2. Gestational age 37 to 38 weeks
3. Jaundice observed before discharge
4. Previous sibling with jaundice
5. Macrosomic infant of diabetic mother
6. Maternal age  $\geq 25$  years
7. Male sex

#### Factors Associated with Decreased Risk of Significant Jaundice

1. TB or TcB in the low-risk zone
2. Gestational age  $\geq 41$  weeks
3. Exclusive bottle feeding
4. Black race
5. Discharge from hospital after 72 hours

#### HYPERBILIRUBINAEMIA IS DUE TO:

1. Conditions Associated with Increased Erythrocyte Destruction
2. Disorders of Conjugation
3. Disorders of Excretion
4. Disorders of Enterohepatic Circulation

#### 1. Conditions Associated with Increased Erythrocyte Destruction: Haemolysis

##### - Immune

##### Iso-immunisation

Rh incompatibility

ABO incompatibility

Other blood group incompatibilities

##### - Non-immune

##### a. Erythrocyte Biochemical Defects

Glucose-6-phosphate dehydrogenase deficiency (G6PD)

Pyruvate kinase deficiency

Hexokinase deficiency

Congenital erythropoietic porphyria

Other biochemical defects



b. Structural Abnormalities of Erythrocytes

Hereditary spherocytosis

Hereditary elliptocytosis

Infantile pyknocytosis

Other

c. Infection

Bacterial

Viral

Protozoal

d. Polycythaemia

e. Sequestered Blood

Subdural hematoma, cephalo-hematoma, and subgaleal hematoma

Ecchymoses

Hemangiomas

### ISO-IMMUNISATION - ABO/RH INCOMPATIBILITY

Note: The hallmark of iso-immunisation is a positive Direct antiglobulin test (DAT) or Coombs test.

Direct test refers to the antiglobulin adhered to the RBCs.

Indirect test refers to the antibody being detected in the serum.

The Rh blood group proteins are a highly antigenic group of proteins capable of causing severe iso-immunisation with a high risk for foetal hydrops and death.

All newborns born to Rh negative mother must be tested for blood group, Rh and DAT, and be closely monitored.

Maternal prophylaxis with high titer anti-D immunoglobulin G (RhoGAM) has decreased the incidence of Rh disease.

ABO incompatibility is the most prominent cause of immune haemolytic disease in the neonate.

It is essential to closely observe any newborn born to a blood group O mother and to perform a TB measurement, blood group and DAT at the first appearance of jaundice to rule out ABO incompatibility.

Some or all of the following criteria are necessary to support the diagnosis of ABO haemolytic disease:

1. Indirect hyperbilirubinaemia, especially during the first 24 hours of life.
2. Mother with blood group O, infant with blood group A or B
3. Spherocytosis on blood smear
4. Increased reticulocyte count
5. Evidence of haemolysis based on increased endogenous production of carbon monoxide (CO).

## 2. Disorders of Conjugation

1. Crigler-Najjar Syndrome Type I



- a. Consist of severe unconjugated hyperbilirubinaemia that develops during the first 3 days of life and progresses in an unremitting fashion, with TB concentrations reaching 25 to 35 mg/dL during the first month of life.
- b. Kernicterus often occurs in the neonatal period.
- c. Stools are pale yellow.
- d. Should be considered if unconjugated hyperbilirubinaemia at TSB concentrations of greater than 20 mg/dL persist beyond the first week of life, or repeated need for phototherapy in the absence of obvious haemolysis.

## 2. Crigler-Najjar Syndrome Type II

## 3. Pyloric Stenosis

## 4. Hypothyroidism

## 3. Disorders of Excretion

Due to decreased UGT1A1 activity.

## 4. Disorders of Enterohepatic Circulation

Increased enterohepatic circulation.

Jaundice Associated with Breastfeeding.

1. Breastfeeding Failure Jaundice: appears to be associated with poor feeding practices.
2. Breast Milk Jaundice: related to a change in the composition or physical structure of the milk.

## SEQUELAE OF UNCONJUGATED HYPERBILIRUBINAEMIA

1. Acute bilirubin encephalopathy (ABE): defined as the acute manifestations of bilirubin induced neurologic dysfunction (BIND).
2. Kernicterus: defined as chronic bilirubin encephalopathy (CBE) and permanent disabling neurologic sequelae of ABE due to bilirubin neurotoxicity.

Note: ABE is characterised by lethargy, poor feeding, hypotonia, and a high-pitched cry in a severely jaundiced infant. Hyperextension of the extensor muscles and back arching may appear.

BIND occurs when the TB level exceeds an infant's neuro-protective defences.

BIND syndrome represents a spectrum of neurologic manifestations among infants with a previous history of moderate to severe hyperbilirubinaemia of varied duration where impaired cell function has occurred.

The spectrum of neurologic impairment from BIND may manifest as disturbances of myriad processes, including visual-motor, auditory, speech, cognition, and language.

CBE or Kernicterus is characterised by chronic manifestations of the acute syndrome of ABE, including dystonia, athetoid cerebral palsy, gaze paralysis, and sensorineural hearing loss.

Risk of cell death occurs when bilirubin neurotoxicity is irreversible (>23 mg/dl).

The classic tetrad signs of kernicterus:

1. Choreo-athetoid cerebral palsy
2. Upward gaze palsy
3. Sensorineural hearing loss
4. Dental dysplasia during later infancy and childhood





## MANAGEMENT

All TB measurements should be plotted on the hour-specific Bhutani et al. nomogram (Figure 4)

Consider four groups of newborns when making decisions regarding laboratory evaluation and therapy of unconjugated hyperbilirubinaemia:

1. healthy term
2. sick term
3. healthy premature
4. sick premature neonates

Initial studies that may be indicated include:

1. Determination of maternal blood group and Rh type
2. A screen for antibodies directed against minor erythrocyte antigens
3. Determination of neonatal blood group and Rh type
4. Direct Coombs test or DAT
5. Haemoglobin or hematocrits
6. Smear of peripheral blood for RBC morphology
7. Reticulocyte count
8. Bilirubin panel

Note: In the presence of significant jaundice with a potential ABO incompatibility (type O mother and type A or B infant), the DAT should be repeated at least once if originally negative because initial false-negative results have often been noted.

Bilirubin panel includes:

1. Total serum bilirubin
2. Rate of production of TSB for age in hours
3. Serum albumin
4. Bilirubin: Albumin molar ratio (BAMR) to measure bilirubin binding capacity (BBC)
5. Hb/Hto (COHB/ETCO)

Further laboratory investigation is required when TSB concentration is:

1.  $\geq 4$  mg/dL in cord blood
2. increasing at a rate of  $\geq 0.3$  mg/dL/hour over a 4- to 8-hour period
3. increasing at a rate of 5 mg/dL or greater per day
4.  $\geq 13$  to 15 mg/dL in full-term infants at any time
5.  $\geq 10$  mg/dL in premature neonates at any time
6. when associated signs of illness such as vomiting, lethargy, poor feeding, excessive weight loss, apnoea, tachypnea, or temperature instability are present
7. when clinical jaundice persists beyond 10 to 14 days of life



Note: With prolonged jaundice, tests for liver disease, congenital infections, sepsis, metabolic defects, or hypothyroidism are indicated.

G6PD measurement may be helpful, especially in infants of African, East Asian, Mediterranean, or Middle Eastern descent or if the TB is  $\geq 18$  mg/dL.

Transcutaneous Bilirubinometry: allows a noninvasive estimate of TB levels.

- ▶ Currently commercially available are: BiliChek<sup>®</sup> and JM-103<sup>®</sup> Jaundice Meter.

End-Tidal Carbon Monoxide (ETCOc) Measurements:

- ▶ Measurement of CO in the end-tidal breath, corrected for ambient CO to derive ETCOc, can be used as an index of in vivo heme degradation and bilirubin production and, hence, haemolysis.

Bilirubin-to-Albumin Molar Ratio (BAMR)

1. The molar ratio of bilirubin (mg/dL) to albumin (g/dL) correlates with unconjugated bilirubin levels in newborns and therefore can be used as a surrogate for unbound bilirubin or residual binding capacity of albumin.
2. BAMR may be estimated by dividing TB (mg/dL) by serum albumin (g/dL).
3. The BAMR may be used as an adjunct to measurements of TB in determining the need for exchange transfusion. (Table 1)
4. In term infants, BAMR values  $>0.8$  (TSB mol/L/albumin mol/L) or 7.0 (TSB mg/dL/albumin g/dL) are considered dangerous because bilirubin/albumin binding is unpredictable at these levels.
5. Sick infants have an impaired albumin binding of bilirubin and can have ratios of 0.7 (TSB mol/L/albumin mol/L), and it is recommended that the ratio should not exceed 0.5 (TSB mol/L/albumin mol/L).
6. The fraction of free bilirubin (unbound bilirubin) increases as bilirubin approaches the binding capacity of albumin.

Table 1. Risk category and BAMR values for blood exchange transfusion in infants  $\geq 35$  weeks GA.

Risk Category	BAMR at Which Exchange Transfusion Should Be Considered	BAMR at Which Exchange Transfusion Should Be Considered
	TSB (mg/dL)/albumin (g/dL)	TSB (mol/L)/albumin (mol/L)
Infants $\geq 38$ wk	8.0	0.94
Infant 35 to 37 wk and well or $\geq 38$ wk if higher risk or isoimmune haemolytic disease or G6PD deficiency	7.2	0.84
Infant 35 to 37.6 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.80

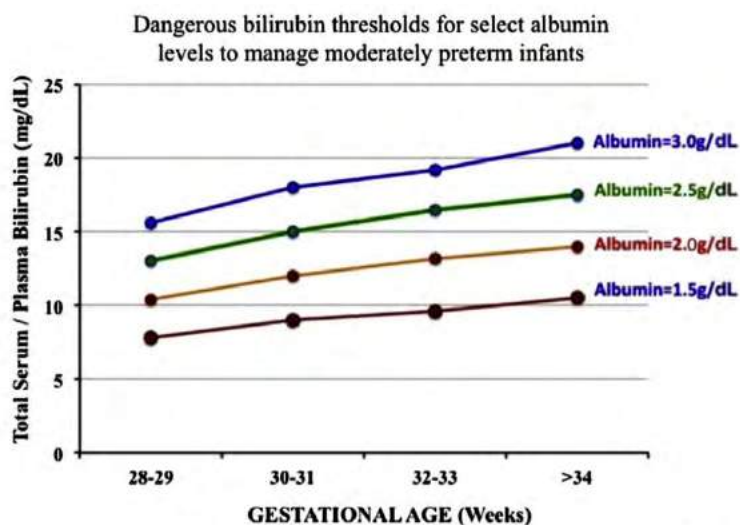
Source: From AMERICAN ACADEMY OF PEDIATRICS, Subcommittee on Hyperbilirubinemia. CLINICAL PRACTICE GUIDELINE. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics* 2004;114;297.



Note: If TB is at or is approaching the exchange level, send blood for immediate type and crossmatch. Blood for exchange transfusion is modified whole blood (red blood cells and plasma) crossmatched against the mother and compatible with the infant.

Conjugated bilirubin should not be subtracted from the total.

Figure 2. BAMR values for blood exchange transfusion in infants < 35 weeks GA.



Recommended use of BAMR for initiation of exchange transfusions. BAMR values have been calculated to bilirubin (mg/dL)/albumin (g/dL). Values above the thresholds for select serum albumin values of 1.5, 2, 2.5, and 3 g/dL are presented as bands above which bilirubin is likely to be displaced and may be neurotoxic. (Data from Ahlfors CE. Criteria for exchange transfusion in jaundiced newborns. *Pediatrics* 1994;93:488–94.)

## THERAPY FOR UNCONJUGATED HYPERBILIRUBINAEMIA

1. Phototherapy
2. Intravenous immunoglobulin (IVIG)
3. Blood exchange transfusion

## PHOTOTHERAPY

1. Phototherapy is the initial intervention used to treat and prevent severe hyperbilirubinaemia in asymptomatic infants.
2. Phototherapy should be provided to infants with signs of acute bilirubin encephalopathy (ABE) while preparations are made for exchange transfusion.
3. Phototherapy given as prophylaxis phototherapy, should initiate in ELBW (extremely low birth weight) infants when TSB (total serum bilirubin) is > 5 mg/dl. (Table 2, Figure 3)
4. Intensive phototherapy implies the use of high levels of irradiance in the therapeutic range delivered to as much of the infant's surface area as possible.
5. The AAP recommends the use of intensive phototherapy, especially for infants readmitted for hyperbilirubinaemia, or if the threshold for exchange transfusion is approaching. (Figure 6)
6. Emission Spectra of blue LEDs phototherapy lamps are more effective and recommended.
7. Phototherapy should not be used in neonates with significant conjugated hyperbilirubinaemia or other evidence of cholestasis, and in Congenital erythropoietic porphyria syndrome.



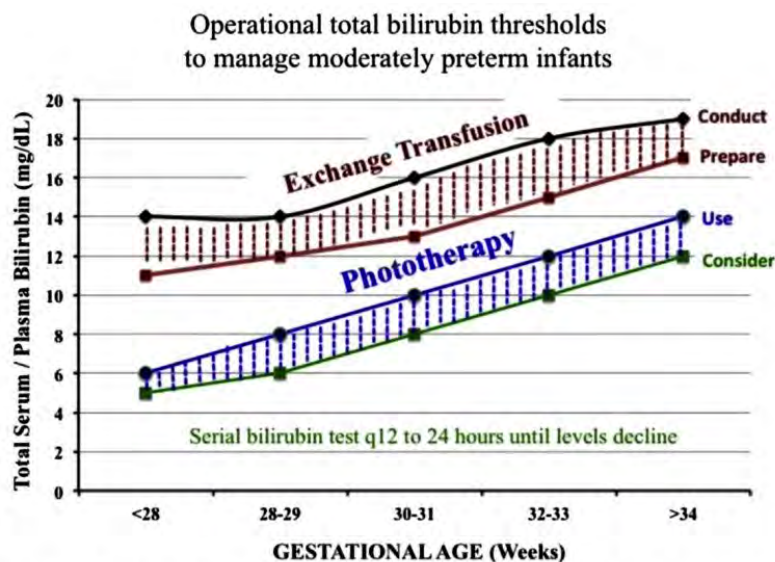
8. TSB should be measured in 2-6 hours after initiating phototherapy. Measurements should be repeated every 6-12 hours once bilirubin levels are stable or descending.
9. Discontinue phototherapy when TB is 1 to 2 mg/dL (17–34 mmol/L) below the initiation level for an infant's postmenstrual age in two separate measurements 6-12 hours apart.
10. TSB should be measured 12-24 hours after discontinuing phototherapy and TSB measurements should be discontinued when TSB is declining and phototherapy is no longer required.

Table 2. Suggested use of Phototherapy and Exchange Transfusion in Premature Infants <35 weeks GA

	Phototherapy	Exchange Transfusion
Gestational Age (week)	Initiate Phototherapy Total Serum Bilirubin (mg/dL)	Total Serum Bilirubin (mg/dL)
<28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18
34 0/7–34 6/7	12–14	17–19

*Source: Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol 2012;32:660–664.*

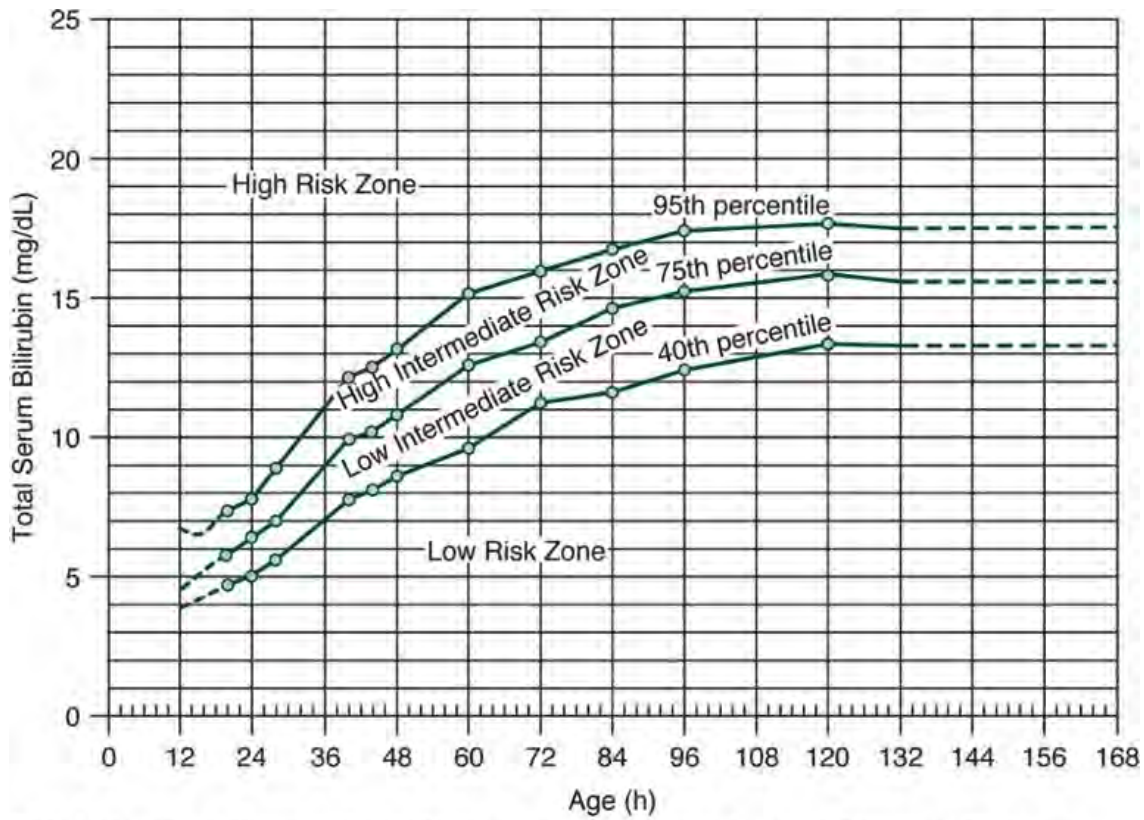
Figure 3. Suggested use of Phototherapy and Exchange Transfusion in Premature Infants <35 weeks GA



Suggested use of phototherapy and exchange transfusion in preterm infants less than 35 weeks' GA. The operational thresholds have been demarcated by recommendations of an expert panel. The shaded bands represent the degree of uncertainty. Recommended thresholds to prepare for exchange transfusion assume that these infants are already being managed by effective phototherapy. Increase in exposure of BSA to phototherapy may inform the decision to conduct an exchange transfusion based on patient response to phototherapy. (Adapted from Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol 2012;32(9):660–4; with permission.)



Figure 4. Hour-specific Bhutani et al nomogram



Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values. The high-risk zone is designated by the 95th percentile track. The intermediate-risk zone is subdivided to upper- and lower-risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track. (Dotted extensions are based on <300 TSB values/epoch). This study is based on heel stick venous bilirubins.

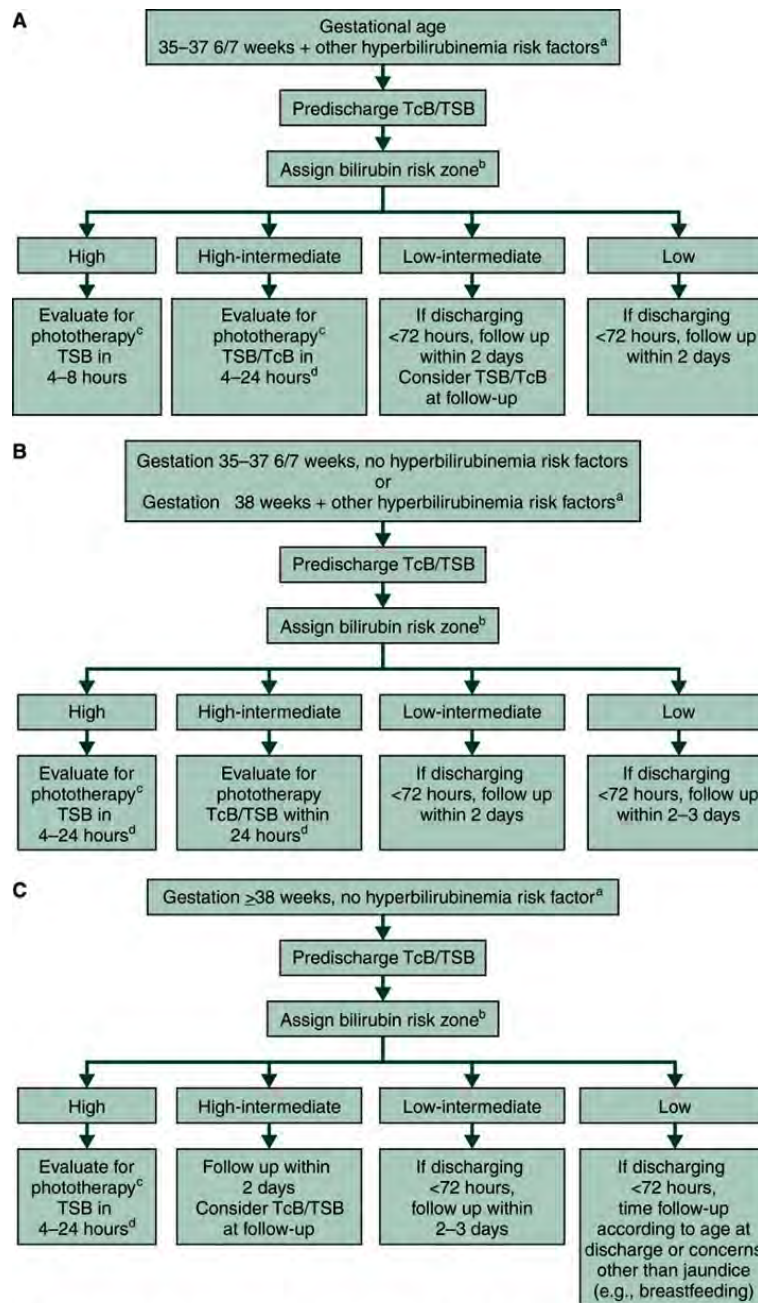
Source: From AMERICAN ACADEMY OF PEDIATRICS, Subcommittee on Hyperbilirubinemia. CLINICAL PRACTICE GUIDELINE. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics* 2004;114:297.

Complications of phototherapy:

1. Retinal degeneration
2. Fluid imbalance (especially in the premature neonate)
3. Bronze baby syndrome



Figure 5. Evaluation of the Jaundiced Infant  $\geq 35$  Weeks of Gestation

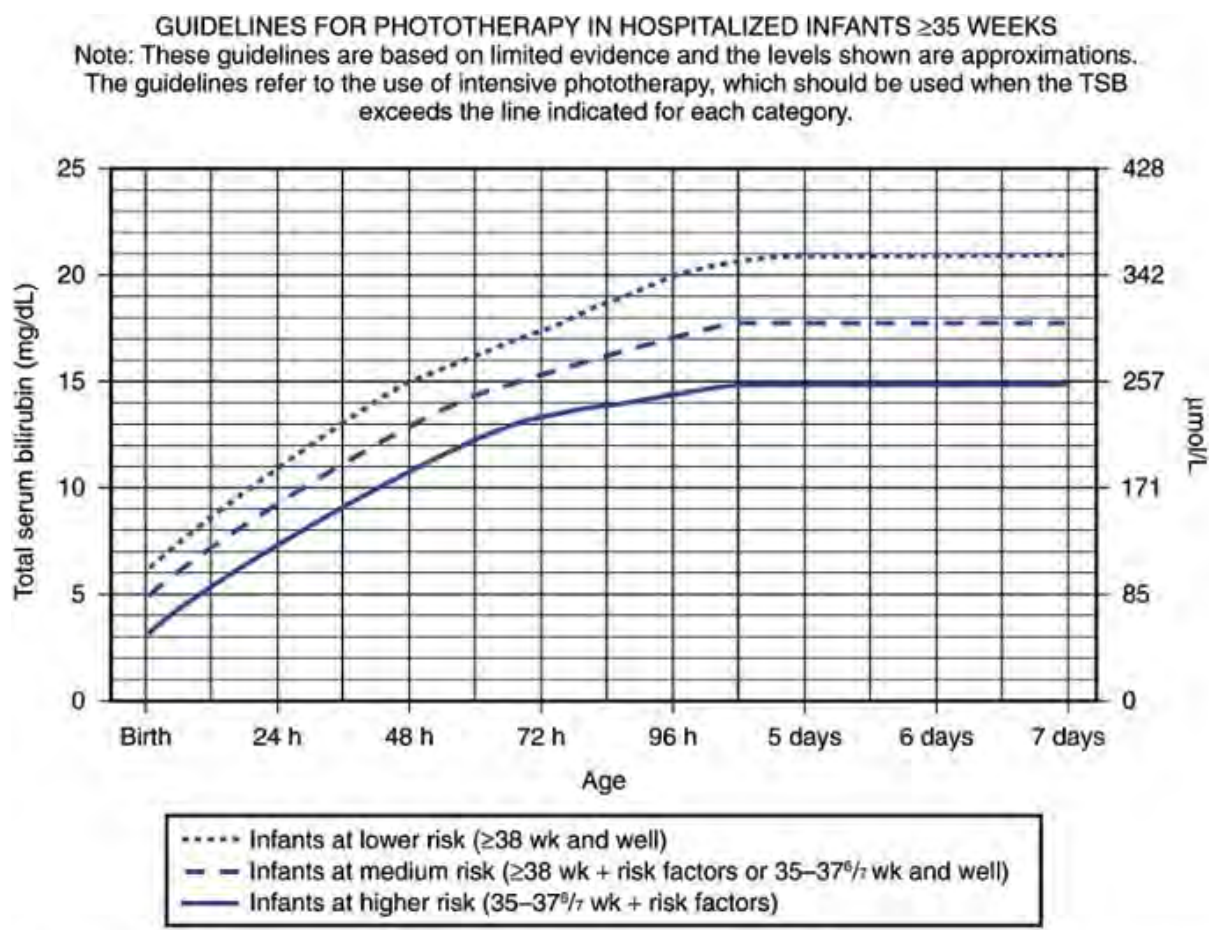


- Provide lactation evaluation and support for all breastfeeding mothers.
- Recommendation for timing of repeat TSB measurement depends on age at measurement and how far the TSB level is above the 95th percentile (Fig 26.1). Higher and earlier initial TSB levels require an earlier repeat TSB measurement.
- Perform standard clinical evaluation at all follow-up visits.
- For evaluation of Jaundice, see 2004 AAP guideline.
- <sup>a</sup> Table 26.1. <sup>b</sup> Fig 26.1. <sup>c</sup> Fig 26.3. <sup>d</sup> In hospital or as outpatient. <sup>e</sup> Follow-up recommendations can be modified according to level of risk for hyperbilirubinemia; depending on the circumstances in infants at low risk, later follow-up can be considered.

Source: From Stark AR, Bhutani VK. Chapter 26: Neonatal Hyperbilirubinemia. In: Eichenwald E, Hansen AR, Martin CR, Stark AR, editors. Cloherty and Stark's Manual of Neonatal Care. Eighth ed. Philadelphia, PA; Wolters Kluwer; 2017.



Figure 6. Guideline for the commencement of phototherapy in infants greater than 35 weeks' gestation.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35–37<sup>6/7</sup> wk, can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wk and at higher TSB levels for those closer to 37<sup>6/7</sup> wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2–3 mg/dL (35–50 μmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

Source: From AMERICAN ACADEMY OF PEDIATRICS, Subcommittee on Hyperbilirubinemia. CLINICAL PRACTICE GUIDELINE. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics* 2004;114:297.



## Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion

### Treatment

- Use intensive phototherapy and/or exchange transfusion as indicated

### Laboratory Tests

- TB and direct bilirubin level
- Blood type (ABO, Rh)
- Direct antiglobulin test (Coombs test)
- Serum albumin
- CBC with differential and peripheral blood smear for RBC morphology
- Reticulocyte count
- ETCOc (end-tidal carbon monoxide, corrected for inhaled CO; G6PD) (if technology is available)
- G6PD screen, if indicated by ethnicity or geographic origin or if poor response to phototherapy
- Urinalysis for reducing substances
- If history or presentation suggests sepsis, perform blood culture, urine culture, and CSF examination for protein, glucose, cell count, and culture

### Interventions

- If TB  $\geq 25$  mg/dL or  $\geq 20$  mg/dL in a sick infant or infant  $<38$  weeks of gestation, obtain a type and crossmatch, and request blood in case exchange transfusion becomes necessary.
- In infants with isoimmune haemolytic disease and a TB rising despite intensive phototherapy or rising to within 2 to 3 mg/dL of exchange level, administer IVIG (500 to 1000 mg/kg) over 2 hours and repeat if necessary.
- If infant's weight loss from birth is greater than 12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake in question, give IV fluids.
- For Infants Receiving Intensive Phototherapy
- Breastfeed or bottle feed (formula or expressed breast milk) every 2 to 3 hours.
- If TB  $\geq 25$  mg/dL, repeat TB within 2 to 3 hours.
- If TB 20 to 25 mg/dL, repeat TB within 3 to 4 hours.
- If TB  $< 20$  mg/dL, repeat TB in 4 to 6 hours.
- If TB continues to fall, repeat TB in 8 to 12 hours.
- If TB is not decreasing, or is moving closer to level for exchange transfusion, or the bilirubin-to-albumin ratio exceeds levels, consider exchange transfusion.
- When TB is below 13 to 14mg/dL, discontinue phototherapy.
- Depending on the cause of the hyperbilirubinaemia, it is an option to measure TB 24 hours after discharge to check for rebound hyperbilirubinaemia.

ADAPTED From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297.





## INTRAVENOUS IMMUNOGLOBULIN (IVIG):

1. IVIG (0.5 g to 1 g/kg) administered over 2 to 4 hours, may be repeated in 12 hours.
2. Should be considered in neonates with DAT-positive immune hyperbilirubinaemia caused by Rh or ABO incompatibility with a TSB rate of production > 0.5 mg/dl/hr despite intense phototherapy or whose TB is within 2 or 3 mg/dL of the threshold recommended for exchange transfusion.

## EXCHANGE TRANSFUSION

This procedure replaces approximately 85% of the circulating RBCs.

The indications are based on a combination of: (Table 2, Figure 3, Figure 7)

1. TB concentrations
2. Postnatal age
3. Gestational age
4. Other risk factors: isoimmune haemolytic disease, G6PD deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, and bilirubin-to-albumin molar ratio.

Exchange transfusion is recommended for any infant who shows signs of ABE (hypertonia, arching, retrocollis, opisthotonos, and high-pitched cry) although these signs are often subtle.

Note: Fresh type O Rh-negative irradiated packed RBCs that are resuspended in AB plasma and cross-matched against maternal plasma and cells are used.

The volume ordered should be twice the infant's estimated blood volume (2 times 80 to 90 mL/kg plus additional volume to account for tubing losses ~30 mL).

A blood warmer is used to maintain temperature at 37°C.

Pretreatment with albumin before exchange transfusion is not routinely recommended.

Individual aliquots should be approximately 10% or less of the infant's blood volume, with a maximum volume of 20 mL for a term baby who weighs more than 3 kg.

If blood older than 5 days must be used, the pH should be checked and sodium bicarbonate added to correct the pH to 7.1.

Intensive phototherapy should be resumed after the transfusion.

Discontinue enteral feeding during exchange transfusion until 6 hours after procedure.

TB should be monitored at 2, 4, and 6 hours after the transfusion and then at least every 12 to 24 hours until TB declines sufficiently to discontinue phototherapy.

CBC must be repeated after exchange transfusion.

In infants with severe hyperbilirubinaemia owing to isoimmunity or other haemolytic conditions, especially G6PD deficiency, exchange transfusion may be the only effective method of adequately reducing TB concentrations.

For readmitted infants, if TB is above the exchange level, intensive phototherapy may be commenced, provided the infant does not display clinical signs of BIND. Serial TBs should be performed every 2 to 3 hours, and if TB remains at or above levels indicated, exchange is recommended after 6 hours of intensive phototherapy.

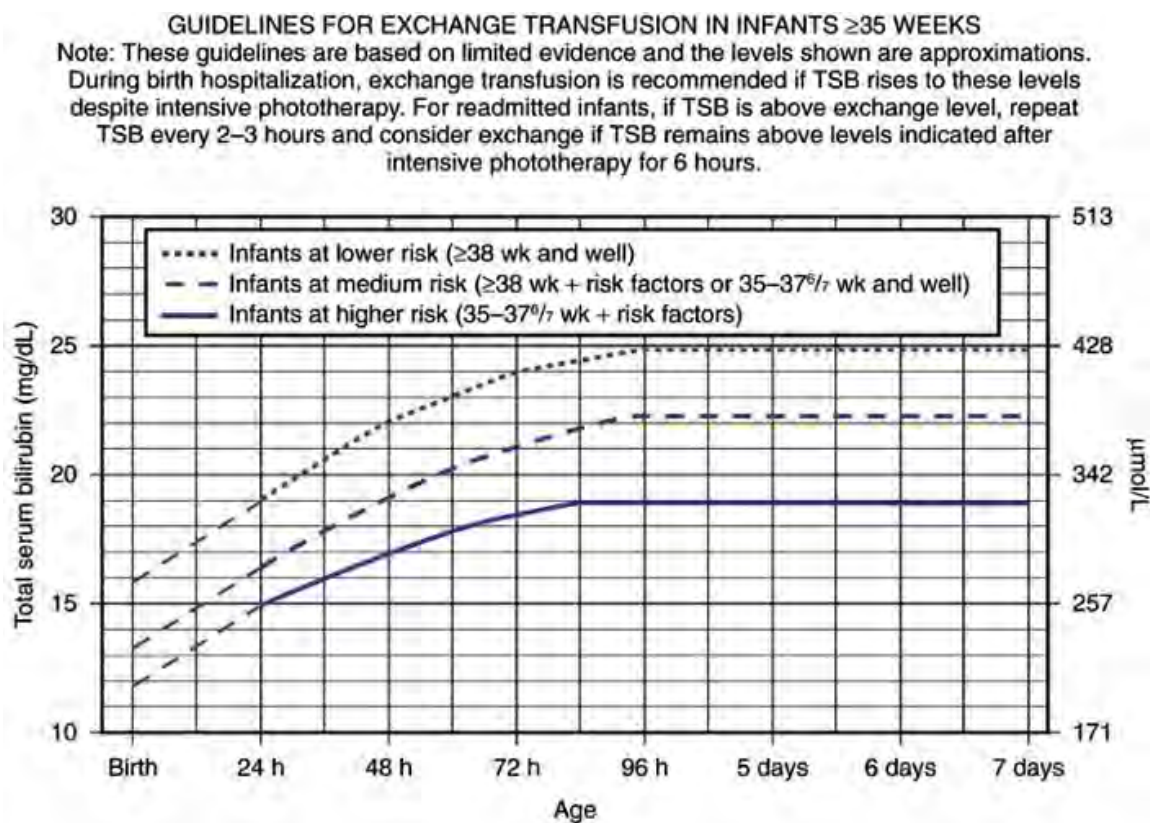
### Potential Complications of Exchange Transfusion

1. Thrombocytopenia, particularly with repeat transfusions
2. Portal vein thrombosis or other thromboembolic complications
3. Umbilical or portal vein perforation



4. Acute necrotising enterocolitis
5. Arrhythmia, cardiac arrest
6. Hypocalcaemia, hypomagnesaemia, hypoglycaemia
7. Respiratory and metabolic acidosis, rebound metabolic alkalosis
8. Graft-versus-host disease
9. Human immunodeficiency virus, hepatitis B and C infection
10. All other potential complications of blood transfusions

Figure 7. Guidelines for exchange transfusion in infants  $\geq 35$  weeks.



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is 25 mg/dL (85 µmol/L) above these lines.
- Risk factors—isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate bilirubin/albumin (B/A) ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35–37<sup>6/7</sup> wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

Source: From AMERICAN ACADEMY OF PEDIATRICS, Subcommittee on Hyperbilirubinemia. CLINICAL PRACTICE GUIDELINE. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics* 2004;114:297.



## FOLLOW-UP

Clinical judgment should be used when scheduling follow-up of infants with risk factors for hyperbilirubinaemia.

In case of isoimmune haemolytic disease, a Hb control is recommended at two weeks after discharge if the Hb on discharge was low and at 4 weeks after discharge if Hb on discharge was normal.

Table 3. Follow-up period.

Infant Discharged	Should Be Seen by
Before age 24 hours	72 hours
Between age 24 and 47.9 hours	96 hours
Between age 48 and 72 hours	120 hours

Consider RAINBOW: Risk of neurotoxicity, Assessment for rate of bilirubin rise, Investigate cause, Number (TB) at which to treat, Breast feeds to continue, Outcome, Well-being at follow-up.

### SEQUELAE:

- Children who had had a positive DAT, a TB of greater than 25mg/dL was associated with a decrease in IQ scores.
- Clinical neuromotor manifestations include: disturbances of visual-motor, auditory, speech, cognition, and language among infants.

## Conjugated Hyperbilirubinaemia

Is always pathologic.

May be caused by:

1. defects in intra-hepatic bile production
2. defects in transmembrane transport of bile
3. mechanical obstruction to flow

Most cholestasis in the NICU is due to inability to tolerate enteral feeding and prolonged exposure to PN.

Diseases that may manifest as conjugated hyperbilirubinaemia in the neonatal period:

1. Obstructive bile duct disorders: Biliary atresia is a frequent cause and must be identified promptly so that intervention can be performed before 2 months of age.
2. Infectious causes
3. Metabolic disorders (galactosaemia, hypothyroidism)
4. Immunologic disorders
5. Endocrine disorders
6. Toxic disorders

### LABORATORY TESTS RECOMMENDED

1. Liver function tests
  - a. TB and direct-reacting bilirubin, total serum protein, and serum protein electrophoresis



- b. SGOT (AST), SGPT (ALT), alkaline phosphatase
  - c. Cholesterol
  - d. Serum and urine bile acid concentrations, if available
2. Haematologic tests
    - a. Complete blood count, smear, and reticulocyte count
    - b. Direct Coombs test and erythrocyte G6PD
    - c. Platelet count
    - d. Prothrombin time and partial thromboplastin time

Tests for infectious disease
  3. Urine tests
    - a. Routine urinalysis, including protein and reducing substances
    - b. Urine culture
    - c. Bilirubin and urobilinogen
    - d. Amino acid screening
  4. Newborn screen for galactosaemia and hypothyroidism
  5. Liver biopsy
  6. Radiologic and ultrasound studies (if indicated)
  7. Additional diagnostic studies for metabolic disorders (if indicated)

## MANAGEMENT

1. Initiate enteral feedings, even at minimal volumes of 10 mL/kg/day.
2. If cholestasis persists as enteral feedings are increased, consider use of ursodesoxycholic acid (ursodiol).
3. Copper and manganese, trace metals that are excreted in bile, are reduced or eliminated from parenteral nutrition.
4. Discontinue intralipid administration and substitute parenteral fish oil.

### Further reading:

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Kaplan M, Wong RJ, Sibley E, Stevenson DK. Chapter 100: Neonatal Jaundice and Liver Diseases. In: Martin RJ, Fanaroff AA, Walsh MC, editors. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 10th ed. Philadelphia, PA; Elsevier Saunders; 2015. p. 1619-68.



# NUTRITIONAL SUPPORT

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## PARENTERAL NUTRITION

1. Nutrition should be started from day 1 of life to promote growth and moderate severity of illness.
2. Early nutrition mediates the influence of severity of illness on ELBW.
3. For each increase of 1 cal/kg/day of total energy intake in the first week of life there is a 2% decrease in NEC, late onset sepsis, BPD and death.
4. Early aggressive TPN/Enteral support are associated with lower rates of death and short term morbidities and improved growth and neuro-developmental outcomes.
5. Early initiation of enteral nutrition is associated with an earlier achievement of full enteral feeding and decrease risk of NEC.

## INDICATIONS OF PN

1. Premature infants < 34 weeks and those with either very low birth weight (VLBW) (<1500 g) or extremely low birth weight (<1000 g).
2. Infants who are unable to tolerate oral or nasogastric feeds.
3. Infants who are expected to take nothing by mouth for more than 3-5 days.
4. Surgical conditions in neonates: Necrotising enterocolitis, Gastroschisis, Omphalocele, Tracheo- oesophageal fistula, Intestinal atresia, Mal-rotation, Short bowel syndrome, and Meconium ileus.
5. Infants with severe malnutrition/failure to thrive.

## GOAL OF PN

1. The initial goal for PN is to provide adequate calories and amino acids to prevent negative energy and nitrogen balance.
2. To promote appropriate weight gain and growth while awaiting the attainment of adequate enteral intake.
3. To obtain body composition similar to age-matched children and maximise long-term growth and neurodevelopment.
4. To prevent postnatal growth failure and to match the in utero human foetal growth rate of approximately 15 g/kg per day by optimising nutritional management of very low birth weight infants.
5. To promote secretion of insulin and decrease the risk of hyperglycaemia.

## DEFINITIONS

1. Total body water (TBW): the total intracellular and extracellular fluids
2. Extracellular fluids (ECF): the total Intravascular and Interstitial fluids
3. Insensible water loss (IWL): the evaporation of water through the skin, respiratory tract and mucous membranes

## GENERAL PRINCIPLES

1. Water accounts for 75%-95% of an infant's body weight.
2. TBW is inversely proportional to gestational age (GA).
3. First week of life: physiologic weight occurs loss due to contraction of ECF.



a. VLBW infants loose – 10%-15% of birthweight

b. Term infants loose – 10% of birthweight

4. ELBW infants at lower GA have the highest Trans-epidermal water loss (TEWL).

- ▶ Have a humidified incubator with porthole sleeves ready on admission for infants < 32 weeks and/or < 1,200 grams to decrease TEWL.

Table 1. Factors affecting IWL

INCREASE	DECREASE
Low maturity	High maturity
Low relative humidity	Increasing postnatal age
Ambient temperature exceeding neutral thermal environment	High environmental relative humidity
Skin defects (omphalocele, gastroschisis)	High ventilator relative humidity
Phototherapy and use of radiant warmer	

IWL:

Intake – Output (mainly urine) -  $\Delta$  in weight = IWL

Urine output: normal 1-3 ml/kg/hr

Urine specific gravity: 1005-1012 is consistent with a balance in TBW

Urine Osmolarity (UO) = (specific gravity – 1000) x 30

Premature: Normal UO 500 mOsm/l (corresponds to a specific gravity 1020-1025)

Full term: Normal UO 800 mOsm/l (corresponds to a specific gravity 1030)

Serum electrolytes and Cr should be routinely monitored to evaluate Renal Function and Fluid balance. (Na<sup>+</sup> / Cr / BUN) especially in premature infants and critically ill newborns.

Table 2. Maintenance fluid requirements during the first week of life

Birth Weight (g)	IWL (ml/kg/d)	Dextrose (g/100ml)	Day 1-2 (ml/kg/day)	Day 3-7 (ml/kg/Day)
<750	100+	5-10	100-200	120-200
750-1,000	60-70	10	80-150	100-150
1,001-1,500	30-65	10	60-100	80-150
>1,500	15-30	10	60-80	100-150



Table 3. Estimated energy requirements for growing premature infants

Energy Expenditure	Kcal/kg/d
Resting metabolic rate	40-60
Activity	0-5
Thermoregulation	0-5
Synthesis/energy cost of growth	15
Energy stored	20-30
Energy excreted	15
Total energy requirement (estimated)	90-120

### RECOMMENDED ENERGY INTAKE FOR PRETERM INFANTS

- ▶ American Academy of Pediatrics: 105-130 kcal/kg/day
- ▶ ESPGHAN (Committee on Nutrition): 110-135 kcal/kg/day

### FORMS OF ADMINISTRATION OF PN

#### PERIPHERAL:

1. For PN with max osmolarity of 900 mOsm/l
2. For PN with maximum concentration of Dextrose of 12.5% (limits increase of energy)
3. For short term nutrition
4. Risk: infiltration, phlebitis, thrombosis

#### CENTRAL:

1. For PN with osmolarity >1000 mOsm/l
2. For prolonged Nutrition > 3 weeks
3. For PN with concentration of Dextrose > 12.5%
4. Risk: infiltration, phlebitis, thrombosis, infection

Umbilical catheters can be used for PN.

- a. The risk of complications increases if umbilical artery catheters are being left in place for more than 5 days.
- b. The risk of complications increases if umbilical venous catheters are being left in place for more than 14 days.

### COMPONENTS OF PN

- ▶ Macronutrients
  1. Amino acids
  2. Carbohydrates
  3. Lipids
- ▶ Micronutrients:



1. Electrolytes: Mg, K, Na,Cl
2. Minerals
3. Vitamins
4. Calcium Gluconate

OSMOLARITY OF A PN DEPENDS MOSTLY ON:

1. DEXTROSE: 5 mOsm/gr
2. AMINO ACIDS: 10 mOsm/gr
3. ELECTROLYTES: 1 mOsm/mEq

To calculate PN mOsm/L: Total of Osmol/total volume in TPN (ml) x 1000 (ml to litre)

NORMAL PLASMA OSMOLARITY: 280 -290 mOsm/L

Calculation of plasma osmolarity:  $2 \times \text{Na} + \text{Glucose (mg/dl)}/18 + \text{BUN (mg/dl)}/2.8$

## DEXTROSE

An early start of parenteral glucose together with amino acids (2–3 g/kg and day) from the very first day on wards contributes to preventing hyperglycaemia in premature infants.

1. In preterm infants glucose infusion should be started with 4–8 mg/kg/min.
2. In critically ill children glucose intake should be limited to 5 mg/kg/min.
3. Glucose intake should usually cover 60–75% of non-protein calories.
4. Normal serum glucose level: 50-120 mg/dl.
5. Infants who require high infusion rates or a dextrose concentration (Tenor) > 12.5% require placement of central venous catheter (UVC, PICC).

## NORMAL GLUCOSE REQUIREMENTS

Glucose Infusion Rate (GIR):

Preterm: 6-8mg/kg/min

Term: 3-5mg/kg/min

Total grams of glucose= GIR (mg) x Weight (kg) x 1.44

Glucose concentration [G] or Tenor (%) in TPN: Total Glucose (g)/Total fluids in TPN x 100

1 gram of glucose = 3,4 kcal

## AMINO ACIDS (aa)

1. Infants with a birth weight <1,500 g are provided with 2 to 3 g/kg/day shortly after birth.
2. Infants > 1,500 g are also initiated on 2 to 3 g/kg/day if indicated, depending on their size, clinical condition, and estimated time to achieve significant enteral volumes.
3. Protein infusion rates are increased to a target of 3.5 to 4 g/kg/day for premature infants and up to 3 g/kg/day for the term neonates.
4. The urea production rate is a sensitive measurement for amino acid utilisation.





5. Up to 50% of ELBW-premature infants receiving long-term parenteral nutrition develop cholestasis.
6. Ursodesoxycholic acid (Ursodiol) and the reduction of protein intake have a positive effect on the development of PN induced cholestasis in newborns.

Recommended Protein intake:

1g of aa = 4 kcal

3 – 4 g/kg/day in VLBW infants and 3 g/kg/day in term infants

This account for obligate protein loss of 1.5 – 2.0 g/kg/day.

The administration of recommended aa will:

1. limit catabolism
2. improve protein balance
3. preserve endogenous protein stores

PARENTERAL AMINO ACID SOLUTIONS AVAILABLE (PRESENTATION ALSO AVAILABLE AS 8,5%)

- ▶ Aminosyn 10%
- ▶ TrophAmine 10%
- ▶ Primene 10%

## LIPIDS

Intravenous lipids

1. Provides a significant source of non-protein energy.
2. Prevents essential fatty acids deficiency (EFAD) (linoleic/linolenic acids).
3. EFAD can be avoided with 0.5 – 1.0 g/kg/day of IV lipids in the first 24 hrs of life.
4. Recent recommendation reports that in infants <1,500 g at birth, 2 g/kg/day of lipids should be provided within the first 24 hours after birth.
5. Should usually be limited to a maximum of 3–4 g/kg per day in infants.
6. Intravenous lipid emulsions should be started no later than on the third day of life.
7. Early administration of intravenous lipids in the first days of life does not increase the incidence of chronic lung disease or death in premature infants.
8. Preterm infants weighing less than 1000 g deserve special attention because their tolerance to intravenous lipids may be limited.
9. Intralipids® are available as 10% and 20%.
10. SMOF (Soy oil, medium-chain triglycerides, olive oil, and fish oil) lipids® 20% are preferable in neonates.
11. 20% solutions are preferred due to lower cholesterol and plasma triglyceride levels.
12. IV lipid solutions have long chain triglycerides (LCT).
13. It helps maintain serum glucose levels.
14. Lipid intake should be limited to 40% - 50% of total calories.



Requirements: 1-4 g/kg/day

1g of lipid = 9 kcal

Care should be taken in:

1. Infants with unconjugated hyperbilirubinaemia to avoid bilirubin toxicity as a result of free fatty acids displacing bilirubin from albumin binding sites.
  - a. As a general rule, do not advance lipids beyond 0.5 g/kg/d until bilirubin is below threshold for phototherapy.
  - b. Monitor Triglycerides: <200 mg/dl and < 140mg/dl with hyperbilirubinaemia.
2. Infants with BPD (due to release of thromboxanes and prostaglandins, and increased pulmonary vascular resistance).
3. Infants with increased sepsis risk.
4. Infants with severe unexplained thrombocytopenia serum triglyceride concentrations should be monitored and a reduction of parenteral lipid dosage be considered.
  - ▶ Lipids in amounts supplying at least the minimal essential fatty acids requirements should always be given to maintain normal platelet function.
5. In patients with marked progressive cholestasis associated with PN, unrelated to acute infection, potential causes should be explored and a decrease or even a transient interruption in intravenous lipid supply should be considered.

Table 4. Electrolytes

ELECTROLYTE	INITIATE	REQUIREMENT	OBSERVATION
Sodio (Na+)	> 3days of life	PT: 2 to 5 mEq/kg/day AT: 2 a 4 mEq/kg/day	May start after the first 2 days under monitoring of serum electrolytes levels.
Potassium (K+)	48 hrs	RNPT y RNT: 1-4 mEq/kg/day	Can be administer as KCL salt or KH <sub>2</sub> PO <sub>4</sub> salt.
Phosphuros	with aa	Dose:20-40 mg/kg/day	
Calcium (Ca <sup>2+</sup> )	at birth	Dose: 1.5 – 4 mEq/kg/day	Adjustment to increase dose in: <ul style="list-style-type: none"><li>• Asphyxia</li><li>• NB of Diabetic mother</li><li>• PT and SGE</li></ul>
Magnesium (Mg)	as required	Dose: 0.25 - 0.5 mEq/kg/day	Measure serum Mg levels before administration.



## INCOMPATIBILITY Ca-P IN PN:

CONSIDER RELATION CALCIUM/PHOSPHORUS = Ca (mEq/l) X [P (MMOL) X 1.8]

Ca/P Relationship < 300 considered safe.

## TRACE ELEMENTS IN PN

1. Supplementation initiation is recommended to coincide with an increase in body weight - 5th - 7th day of life.
2. Should start after 5 - 7 days of receiving PN.
3. Intravenous trace elements: Trazel® or PaediaTrace®.
4. Dose - Term and Preterm infants: 0.2 - 0.6 ml/kg/day.
5. Trace elements should be supplemented in long-term PN (>3weeks).
6. Discontinue:
  - a. Copper and manganese in hepatic cholestasis.
  - b. Selenium, chromium and molybdenum in Acute Renal Disease.
7. Zinc deficiency has to be excluded in infants and children with unclear, poor development (especially linear growth) and/or skin efflorescences (typically on acra, mechanically burdened parts of the body or in the nappy region) or diarrhoea.

Table 5. Requirements of trace elements

Element	(AAP 2009)		(ESPGHAN 2005)
	<1000 gm	1000-1500 gm	
Zinc, µg/kg/day	400	400	450-500
Copper, µg/kg/day	20	20	20
Selenium, µg/kg/day	1.5-4.5	1.5-4.5	2-3
Chromium, µg/kg/day	0.05-0.3	0.05-0.3	0
Manganese, µg/kg/day	1	1	1
Molybdenum, µg/kg/day	0.25	0.25	1
Iodine, µg/kg/day	1	1	1 µg /day
Fluorine, µg/kg/day	?	?	?

## VITAMINS IN PN

1. Vitamin supplementation should be given during parenteral nutrition.
2. Intravenous vitamins available for paediatric use: MVI® paediatrics or Dodemina® paediatrics.
3. Vitamin A is necessary for physiological lung growth (lung epithelial cells).
4. Infants weighing <1,000 g at birth are supplemented with 5,000 IU vitamin A intramuscularly three times per week for the first 4 postnatal weeks, beginning in the first 72 hours.
5. Carnitine plays an important role in the transport of long-chain fatty acids to mitochondria for oxidation, thereby aiding fat metabolism.
6. Carnitine supplementation should be considered on an individual basis in low birthweight infants receiving PN for more than 2-4 weeks. Dose: 8-10 mg/kg/day until enteral nutrition can be established.
7. Primary carnitine deficiency has been associated with cholestasis and steatosis.



8. Folic acid for all infants with BW < 1500 g: 50 mcg until ≥ 1500 g.
9. Patients receiving long-term PN (>3 weeks) should receive iron supplementation at 100–200 µg/kg/d.
10. Iron supplementation should be delayed in very low birth weight infants receiving PN.
11. The dose of iron in premature infants: 200 µg/kg per day.
12. An oral intake of 1000 IU Vitamin D/day is adequate in extremely premature infants.

Table 6. Requirements of IV vitamins

Element	AAP <1000 gm	AAP 1000-1500 g	ESPHAGN
Vit A, IU/k/day	700-1500	700-1500	150-300
Vit D, IU/k/day	40-160	40-160	32
Vit E, IU/K/day	2.8-3.5	2.8-3.5	2.8-3.5mg
Vit K, µg/k/day	10	10	10
Ascorbate, mg/k/day	15-25	10	15-25
Thiamine, µg/k/day	200-350	200-350	Up to 500
Riboflavine, µg/k/day	150-200	150-200	150-200
Pyridoxine, µg/k/day	150-200	150-200	150-200
Nicotinamide, mg/k/day	4-6.8	4-6.8	4-6.8
Pantothenate, mg/k/day	1-2	1.2	1-2
Biotin, µg/k/day	5-8	5-8	5-8
Folate, µg/k/day	56	56	56
Vit B12, µg/k/day	0.3	0.3	0.3

#### SHORT, MEDIUM AND LONG-TERM (PARTIAL) PARENTERAL NUTRITION

1. The utilisation of an adapted glucose/electrolyte solution (usually 10% glucose) with potassium and sodium supplementation in short-term (<48 h) intra- venous intake is recommended in well-nourished toddlers and school children without specific metabolic or nutritional risks.
2. An adapted glucose/electrolyte solution (usually 10% glucose) with the required supplementation of sodium, potassium, amino acids, lipids and vitamins should be administered in medium-term PN (>2–7 days).
3. An additional supplementation of magnesium, phosphate, and trace elements (where enteral nutritional provides 50% of the energy intake or less) should be administered in long-term PN (>7 days).

#### HEPARIN

1. Although some centres use Heparin (1 unit/mL) added to all central venous lines and to all peripheral infusions running at <2 mL/hr in order to maintain catheter patency, the ESPEN does not recommend it.
2. The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines specifically recommends:
  - a. Routine use of heparin has not been shown to be useful in prevention of complications related to peripherally placed percutaneous CVCs in neonates.
  - b. A routine heparin supply to prevent thrombotic occlusion of CVC's or to prolong central venous catheter survival time has not proven benefit in infants and is not recommended.
  - c. Heparin does not improve utilisation of intravenous lipids and should not be given with lipid infusion on a routine basis.

#### WEANING OF PN

1. When the patient is tolerating >50 ml/kg/day of feedings, the TPN should be gradually tapered off.
2. PN may be discontinued when the infant is tolerating ≥100-120 cc/kg of enteral feedings or is receiving ≤25 cc/kg/d of PN.



3. Gradual omission if patient has 75% of total fluids as Enteral Nutrition and complement with glucose at an adequate GIR.

#### MEASURES TO REDUCE SIDE-EFFECTS OF PN

1. Procedures should be standardised wherever possible in order to minimise errors in the provision or preparation of partial (PPN) or total PN (TPN).
2. Exposure of PN solutions to light generates peroxides, which can cause oxidative stress in neonates, potentially leading to lung remodelling and an increased incidence of BPD.
3. Shielding the PN solution from light may help decrease levels of peroxides and thus decrease the incidence of premature neonate complications such as BPD.
4. Minimum enteral nutrition minimises the time until (re)establishing of total enteral nutrition and Length of Hospital Stay (LOS).
5. Non-nutritive sucking during PN has shown to reduce LOS.
6. There is a specific risk of developing osteopenia due to the rapid bone growth in premature and full-term infants.
7. Osteopenia prophylaxis should be started enterally once the (re)establishing of enteral nutrition has been completed without complications.
8. In order to determine appropriate Ca and P intakes, the Ca and P excretion can be assessed in spot urine samples.
9. The optimum duration of Ca and P supply is unclear, but it appears reasonable to provide a Ca and P supply up to the corrected third month of life in premature infants with a birth weight < 1500 g.

#### COMPLICATIONS OF PN

1. Hypertriglyceridaemia and Essential Fatty Acid Deficiency
2. Hyperglycaemia
3. Metabolic Bone Disease
4. PN-Associated Cholestasis
5. Catheter-Related Blood Stream Infections

#### LONG-TERM EFFECTS OF EARLY NUTRITIONAL SUPPORT

1. Higher Bayley Mental Development Index scores and lower likelihood of length growth restriction at 18 months' corrected age.
2. Every increase of 1g/kd/day of aa during the first week of life was associated with an 8.2 points increase on Bayley's MDI at 18 months.
3. Infants who received a minimum of 3g/kg per day of intravenous amino acids in the first 5 days of life were found to have improved growth outcomes (weight, length, and head circumference) at 36 weeks' post-menstrual age.



## LABORATORY TEST MONITORING DURING PN

Table 7. Laboratory tests monitoring.

Test	Initial	When stable
Electrolytes, BUN/creatinine	Daily	2-3x/week
Chemstrip/glucose	q6hr-daily	Daily, more frequently when changing CHO
Calcium, ionized	daily	2-3x/week
Total calcium, phosphorus, magnesium, bilirubin (T/D), ALT, alkaline phosphatase, GGT, albumin	Baseline	weekly
Triglycerides	When lipid infusion reaches 1.5 g fat/kg/d and 3 g fat/kg/d	weekly
CBC/Diff and platelets		weekly

### MONITORING GROWTH

1. Infants receiving PN should have continuous monitoring of growth.
2. This includes: daily weight monitoring, weekly measurements of head circumference, and length.
3. These measurements should be plotted on standard post-natal growth charts.
4. Growth delay or restriction is defined as a weight <10<sup>o</sup> percentile for gestational age.
5. Linear growth is proportional to cerebral growth.
6. Ideal growth velocity: 16-18g/kg/day of weight; 1.1-1.4 cm/week of length; 0.7-0.9 cm/week of head circumference.
7. The use of Fenton's growth curves for preterm infants is the standard rule of measure for determining appropriate height and weight gain until 50 weeks postnatal age. (See Appendix D/E. Fenton's growth chart)
8. The WHO growth chart is recommended for term infants.
9. When an infant is in full-term—corrected gestational age, the Centers for Disease Control and Prevention (CDC) recommends the WHO Child Growth Standards be used for monitoring of growth.

### PREVENTION OF INFECTION

Hospital-acquired infection (HAI) is a major complication of PN. All efforts should be made to avoid HAI.

Aseptic precautions during preparation of PN:

1. Use of laminar flow
2. No compromise on disposables
3. Trained staff
4. No reuse of the PN solutions
5. No interruption of the venous line carrying PN
6. Use of bacterial filter



## QUALITY IMPROVEMENT

Following process and outcome indicators should be audited in neonatal units which use parenteral nutrition:

1. Incidence rate of central catheter-associated blood stream infection (per 1000 catheter days)
2. Incidence rate of central catheter occlusion necessitating catheter removal
3. Incidence rate of parenteral nutrition-associated cholestasis
4. Proportion of eligible neonates who receive parenteral nutrition

Note: For those patients with only 1 lumen, clinicians must consider the compatibility of the medication running via Y site into the same catheter as the PN solution. (See Appendix K. Y-Site Medication Compatibility with 2-in-1 and 3-in-1 PN Solutions)

2-in-1: two macronutrients (Glucose and AA) in PN running in 1 lumen catheter

3-in-1: three macronutrients (Glucose, AA, Lipids) in PN running in 1 lumen catheter

## ENTERAL NUTRITION

### TROPHIC FEEDING

Minimal enteral nutrition (also referred to as “gut priming” or “trophic feedings”): may be described as the nonnutritive use of very small volumes of human milk or formula, for the intended purpose of preservation of gut maturation rather than nutrient delivery.

Benefits associated with minimal enteral nutrition include the following:

1. Improved levels of gut hormones
2. Less feeding intolerance
3. Earlier progression to full enteral feedings
4. Improved weight gain
5. Improved calcium and phosphorus retention
6. Fewer days on PN

Note: For infants < 1,250 g birth weight: 10 to 20 mL/kg/day divided into eight aliquots.

Advance 15-30 mL/kg/day. Feed every 3 or 4 hours depending on individual assessment of the infant.

Trophic feeding should begin as soon after birth, ideally by postnatal days 1 to 2.

Do not measure pre-feed gastric residuals.

Continue trophic feeding for at least 72-120 hours. Then advance feedings accordingly.

Include trophic feeding volumes in the cumulative fluids total, but not in the total fluid intake as they are a “fluid gift”.

Full-strength colostrum/preterm maternal milk or pasteurised donor human milk should be use.

Human milk provides the gold standard for feeding term infants, and fortified human milk will meet the needs of premature infants.



## CONTRAINDICATION

In severe haemo-dynamic instability, suspected or confirmed NEC, serum Mg  $\geq$  4mg/dl, evidence of ileus, or clinical signs of intestinal bowel obstruction or other gastrointestinal pathology.

The following are NOT contraindications to trophic feeding:

- ▶ Umbilical catheters
- ▶ Intrauterine growth restriction
- ▶ Inotropic or nitric oxide support
- ▶ In utero reversal of end-diastolic flow
- ▶ Decreased bowel gas seen on an abdominal x-ray
- ▶ Treatment for Patent Ductus Arteriosus (PDA)

## FORMULAS

### HUMAN MILK

The strongest evidence of the benefit of human milk for premature infants is a reduced incidence of necrotising enterocolitis.

### DONOR HUMAN MILK

The use of pasteurised donor human milk is recommended for preterm infants if the mother's own milk is unavailable.

### HUMAN MILK FORTIFIERS

Human milk does not completely meet the nutritional needs of premature infants.

Current options for human milk fortification include bovine products and a pasteurised human milk-based fortifier.

The use of HMF is recommended for infants <1,500 g birth weight.

HMF may also be considered for infants with birth weights up to 1,800 to 2,000 g and <34 weeks' gestation.

Powdered and liquid, bovine milk-based HMF as well as liquid donor human milk-based HMF are available.

The U.S. Food and Drug Administration recommends that powdered preparations not be used in premature infants given the risk of bacterial contamination.

HMF is added at 2 to 4 kcal/oz prior to the infant reaching 100 mL/kg/day.

### PRETERM FORMULA

Preterm formulas contain more protein than term formulas.

Examples:

Similac Special Care Premature<sup>®</sup> - Abbott - High Protein 24kcal/oz; 24kcal/oz; 30kcal/oz

Enfamil Premature<sup>®</sup> - Mead Johnson - High Protein 24kcal/oz; 24kcal/oz; 30kcal/oz

Gerber Good Start Premature<sup>®</sup> - Nestle - High Protein 24kcal/oz

### POST DISCHARGE FORMULA

Preterm infant discharge formulas have a nutrient content between preterm and standard term formulas.





Indicated for infants born with ELBW or VLBW, infants on exclusive breastfeed milk without fortifiers, and for infants below the 3<sup>o</sup> or 15<sup>o</sup> percentile in the growth curve at discharge.

Continue post discharge formula until 6 -12 months corrected gestational age (CGA) if growth velocity appropriate or until weight-length relation is above the 25<sup>o</sup>-50<sup>o</sup> percentile.

Examples:

Similac Expert Care Neosure<sup>®</sup>- Abbott - 22kcal/oz

Enfamil Enfacare<sup>®</sup>- Mead Johnson - 22kcal/oz

Gerber Good Start Nourish<sup>®</sup>- Nestle - 22kcal/oz

## SPECIALISED FORMULAS

THESE FORMULAS WERE NOT DESIGNED TO MEET THE SPECIAL NUTRITIONAL NEEDS OF PRETERM INFANTS.

Have been designed for a variety of congenital and neonatal disorders, including milk protein allergy, malabsorption syndromes, and several inborn errors of metabolism.

Preterm infants who are fed these formulas require close nutritional assessment and monitoring for potential protein, mineral, and multivitamin supplementation.

Examples:

1. Extensively hydrolysed protein or free amino acids formula
2. Semi-elemental formula
3. Soy protein-based formula
4. AR (anti-reflux) formulas
5. Lactose-free formula.

## FEEDING METHOD

Nasogastric/orogastric feedings

1. Infants <34 weeks' gestation, as most do not yet have the ability to coordinate suck-swallow-breathe patterns.
2. Infants with impaired suck/swallow coordination due to conditions such as encephalopathy, hypotonia, and maxillofacial abnormalities.

Feedings are usually initiated as bolus, divided every 3 to 4 hours.

If difficulties with feeding tolerance occur, the amount of time over which a feeding is given may be lengthened by delivery via a syringe pump for 30 to 120 minutes.

Trans-pyloric feedings

1. Infants intolerant to nasogastric/orogastric feedings
2. Infants at increased risk for aspiration
3. Severe gastric retention or regurgitation
4. Anatomic abnormalities of the GI tract such as microgastria

Transition to breast/cup-feedings

1. Nonnutritive attempts at the breast should be encouraged before 33 to 34 weeks, if tolerated.



2. Early, nonnutritive sucking facilitates milk production and increases the likelihood the infant is still breastfeeding at the time of hospital discharge.
3. Infants who are approximately 33 to 34 weeks' gestation, who have coordinated suck-swallow-breathe patterns and respiratory rates < 60 breaths per minute, are appropriate candidates for introducing breast/cup-feedings.
4. If able, nutritive oral feeding attempts at the breast should precede oral cup feeding attempts.

Note: When advancing enteral feeding volumes, decrease intravenous fluids as appropriate to meet daily fluid requirements.

Consider fortification of breast milk and supplementation of vitamins and minerals when enteral intake is greater than 75 mL/kg/day to meet estimated nutritional requirements.

When the infant's history or condition places them at a higher risk for developing necrotising enterocolitis, consider advancing feeds at a slower rate.

Gastric residuals are normal in the first 2 weeks of life and volume is influenced by body position. It may have protective function and serve as markers of gut maturation.

Feeds should not be withheld every time there is a gastric residual and once NEC has been ruled out by exam.

Unless residual is more than 50% and residual continue at 30-50% of current feeding volume with new green bilious emesis then withhold feeds/NPO, examine and observe for other worsening clinical signs.

In the absence of other symptoms, there is no evidence to support the discontinuation of enteral feeds based only on gastric residuals.

Future studies are needed to further define the optimal rate of advancement, especially in ELBW infants.

## MONITORING GROWTH

Monitor growth patterns closely and adjust nutritional care plan accordingly.

Document weight, length and head circumference regularly on Fenton/WHO growth chart.

- ▶ Adequate weight gain in growing phase: 15–20 g/kg/day
- ▶ Adequate weight gain if weight > 2.0 kg : 25–30 g/day

## IRON

The AAP recommends that growing preterm infants receive 2 to 4 mg/kg/day of iron supplement after 2 weeks of age, and recommends 2 to 3 mg/kg/day for VLBW infants.

Iron supplementation is recommended until the infant is 6-12 months of age.

## IMMUNONUTRIENTS

Providing immuno-nutrients to premature infants may aid in the prevention and treatment of BPD.

Selected immuno-nutrients include vitamin A, vitamin D, inositol, and long-chain polyunsaturated fatty acids (LCPUFAs), such as docosahexaenoic acid (DHA) and arachidonic acid (ARA).

Vitamin A: 3300 IU/day

The AAP recommend 400 IU/day of vitamin D to prevent vitamin D deficiency rickets in preterm infants.

Vitamin E is recommended for preterm infants: 2.2 to 12 IU/kg/day.



## SPECIAL CONSIDERATIONS

### Gastro-oesophageal reflux (GER)

Emesis can be associated during the introduction and advancement of enteral feedings in preterm infants.

These episodes are most commonly related to intestinal dysmotility secondary to prematurity and will respond to modifications of the feeding regimen.

- ▶ Reduce temporarily the feeding volume
- ▶ Lengthen the duration of the feeding

Specialised formulas are used when all other feeding modifications have been tried without improvement.

If symptomatic emesis is associated with respiratory compromise, repeated apnoea, or growth restriction, therapeutic manoeuvres are indicated:

- ▶ Reposition the infant to elevate the head and upper body, in either a prone or right side down position.
- ▶ Shortening the interval between feedings to give a smaller volume during each feeding may sometimes improve signs of GER. Infants fed by gavage may have the duration of the feeding increased.

### Necrotising enterocolitis (NEC)

Nothing by mouth (NPO) for at least 5 to 14 days after the initial diagnosis of NEC. Administer total PN.

If the patient is clinically stable after a minimum of 5 to 14 days of bowel rest, feedings are generally introduced at approximately 10 to 20 mL/kg/day, preferably with maternal milk, PDHM, or a standard formula appropriate for the gestational age of the patient such as preterm formula.

If low-volume feedings (10 to 20 mL/kg/day) are tolerated for 24 to 48 hours, gradual advancement is continued at approximately 10 mL/kg every 12 to 24 hours for the next 2 to 3 days.

Signs of feeding intolerance include emesis, abdominal distension, and increased numbers of apnoea episodes.

If growth targets cannot be achieved using enteral feedings, continued use of supplemental PN may be indicated depending on the patient's overall status and liver function.

### Bronchopulmonary dysplasia (BPD)

Infants with BPD have increased caloric requirements and may require up to 30 kcal/oz feedings.

Infants with BPD have a lower tolerance for excess fluid intake; thus, restriction to 130 mL/kg/day may be required.

## CRITERIA FOR DISCHARGE

1. Infant has overcome active illness.
2. Infant thermoregulates in open environment.
3. Weight target of at least 1800g - 2000g before discharge.
4. A sustained daily weight gain of 15 g/kg/day.
5. Infant can be feed adequately.
6. Parents are capable to continue with the infant's feeding at home.



## CLINICAL CASE

Extremely preterm male neonate, extremely low birthweight, adequate for gestational age, born at 27 weeks GA in his 4th day of life with weight of 945 g and tolerating trophic feeding with colostrum at 16 ml/kg/day. Infant in incubator receiving phototherapy and on nCPAP.

1. Calculate total fluid requirements per day: 120 ml/kg/day

$$120 \text{ ml} \times 0.945 = 113.4 \text{ ml}$$

2. Total volume in medications (IV/Oral): i.e 8 ml

3. Total volume in feeds per day (Trophic feeding): 16 ml x 0.945 kg = 15 ml

$$15 \text{ ml} / 8 \text{ aliquots} = 1.9 \text{ ml colostrum every 3 hours by OGT}$$

4. Total volume in TPN: 113.4 ml - (8 ml meds + 15 ml enteral feeds) = 90.4 ml

5. GIR: 6 mg/kg/min (maintain glucose between 60-120 mg/dl)

6. Calculate total Grams of glucose: 6 mg (GIR) x 0.945 kg x 1.44 = 8.16 grams

Note: 1.44 = 1440 (minutes in 24 hours) / 1000 (change mg to gram)

Dextrose 5% = 5 grams in 100 ml

Dextrose 10% = 10 grams in 100 ml

Dextrose 50% = 50 grams in 100ml

7. Calculate Protein (AA) requirements: 3 g/kg/day

$$3 \text{ g} \times 0.945 \text{ kg} = 2.8 \text{ grams}$$

Aminosyn<sup>®</sup> 10%: 10 grams aa in 100 ml solution

$$2.8 \text{ g} \times 10 = 28 \text{ ml or } 2.8 \text{ g} \times 100 / 10 = 28 \text{ ml}$$

8. Calculate Lipid requirements: 2.5 g/kg/day

$$2.5 \text{ g} \times 0.945 \text{ kg} = 2.3 \text{ grams}$$

SMOF lipids<sup>®</sup>/Intralipid<sup>®</sup>/Liposyn<sup>®</sup> 20%: 20 grams lipids in 100 ml solution

$$2.3 \text{ g} \times 5 = 11.5 \text{ ml or } 2.3 \text{ g} \times 100 / 20 = 11.5 \text{ ml}$$

9. Calculate Electrolyte requirements

- a. NaCl 17.7 % (can use 3% or 20% if available or NSS 0.9%): Presentation of 17.7 % = 3 mEq/ml

(Note: NSS 0.9% = 0.154 mEq/ml. This solution will administer lots more volume as NaCl.)

$$\text{Dose: } 2 \text{ mEq/kg/day} = 2 \text{ mEq} \times 0.945 \text{ kg} = 1.9 \text{ mEq}$$

$$1.9 \text{ mEq} / 3 \text{ mEq} = 0.6 \text{ ml}$$

- b. KCl (1.49 g/5ml): Presentation of 4 mEq/ml (Note: KCl (1.49 g/10ml) = 2 mEq/ml)

$$\text{Dose: } 2 \text{ mEq/kg/day} = 2 \text{ mEq} \times 0.945 \text{ kg} = 1.9 \text{ mEq}$$

$$1.9 \text{ mEq} / 4 \text{ mEq} = 0.4 \text{ ml}$$

10. Calculate Calcium requirements: Calcium Gluconate 10% (1 mEq/1ml)

$$\text{Dose: } 2.5 \text{ mEq/kg/day}$$

$$2.5 \text{ mEq} \times 0.945 \text{ kg} = 2.3 \text{ mEq} = 2.3 \text{ ml}$$



11. Calculate Vitamin requirements: MVI<sup>®</sup> paediatrics or Dodemina<sup>®</sup> paediatrics

Dose: 0.5 - 1.0 ml

For ELBW = 0.5 ml

12. Calculate Trace element requirements: Trazel<sup>®</sup> or PaediaTrace<sup>®</sup>

Dose: 0.2 - 0.6 ml/kg/day

For ELBW = 0.5 ml

13. Carnitine: 8-10 mg/kg/day

Dose: 1.0 ml

14. Calculate PN Osmolarity:

1. Glucose: 8.16 grams x 5 mOsmol/g of glucose = 40.8 mOsmol

2. Amino acids: 2.8 grams x 10 mOsmol/g of aa = 28 mOsmol

3. Electrolytes: 1 mOsmol = 1 mEq

(2 mEq of NaCl + 2 mEq of KCl + 2.5 mEq of Ca Gluconate) x 0.945 kg = 6.14 mOsmol

▶ Total: 40.8 + 28 + 6.14 = 74.9 mOsmol

(74.9 mOsmol/Total vol TPN of 90.4 ml) x 1000 (change ml to litre) = 829 mOsmol/L

▶ Can be administered via a peripheral line

15. Calculate Glucose concentration [G] in PN

Total grams of glucose/ Total vol of TPN x 100 (change to %)

8.16 grams/90.4 ml x 100 = 9%

▶ Can be administered via a peripheral line

16. To calculate the Dextrose % concentration to be used in order to yield 8.16 grams of dextrose

8.16 g/45.6 ml (the volume for dextrose) x 100 = 17.9 % Dextrose (Use 10% and 50% Dw to prepare this 17.9% Dw solution)

17. Calculate PN Caloric intake

Glucose: 8.16 grams x 3.4 kcal per gram = 27.7 Cal

Amino acids: 2.8 grams x 4 kcal per gram = 11.2 Cal

Lipids: 2.3 grams x 9 kcal per gram = 20.7 Cal

Feeds: trophic feeding is non-nutritive but calories may be calculated. 20 kcal/oz of colostrum = 15 ml/30 ml (1 oz) x 20 kcal = 10 Cal

Total: 27.7 + 11.2 + 20.7 + 10 = 69.6 cal/0.945 kg = 73.6 cal/kg/day



NOTE: Total volume in TPN (90.4 ml) - sum of all other additives in TPN (44.8 ml) = 45.6 ml (volume of Dextrose 17.9% to be used to yield 8.16 g of glucose).

<b>MEDICAL ORDER : TPN</b>	
DEXTROSE 10%	36.6 ml
DEXTROSE 50%	9.0 ml
} 17.9% Dext	
AA 10% (3g/kg/d)	28 ml
Lipids 20% (2.5g/kg/d)	11.5 ml
Ca Gluconate 10% (2.5mEq/kg/d)	2.3 ml
NaCl 17.7% (3 mEq/ml) (2mEq/kg/d)	0.6 ml
KCL (4 mEq/ml) (2mEq/kg/d)	0.4 ml
Trace elements	0.5 ml
Vitamins	0.5 ml
Carnitine	1.0 ml
<b>Total</b>	<b>90.4 ml in 24 hours at infusion rate of 3.7 ml/hr</b>

Total fluids: 120 ml/kg/day

Feeds: 16 ml/kg/day

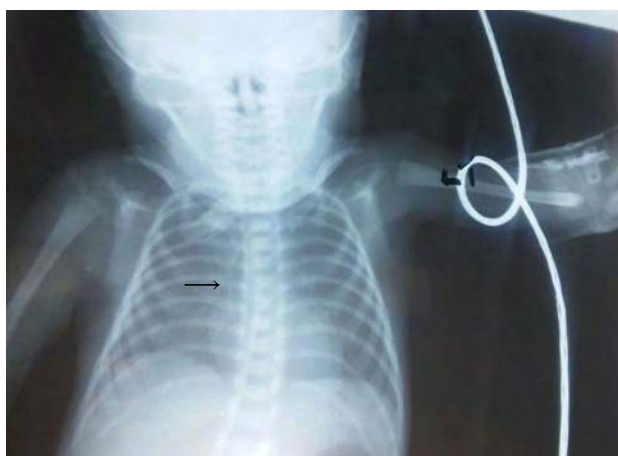
GIR: 6 mg/kg/min

Glucose Concentration [G]: 9%

Osmolarity: 829 mOsmol/L

Calories: 73.6 cal/kg/day

Figure 1. Premature infant with a 2 Fr. Percutaneously Inserted Central Catheter on left arm for TPN.



Source: Constanza E, 2016; KMHM, Belize.



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# HYPOGLYCAEMIA AND HYPERGLYCAEMIA

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## HYPOGLYCAEMIA

Clinical hypoglycaemia is defined as a plasma glucose (PG) concentration low enough to cause symptoms and/or signs of impaired brain function.

Note: During the normal transition period, newborn glucose levels fall to as low as 30mg/dl in the first 1 to 2 hours of life and then increase to >45 mg/dL, stabilising at mean levels of 55 to 60 mg/dL by 3 to 4 hours of age and rising to > 70 mg/dL after 48 hours of age.

Hypoglycaemia beyond the first 48 hours of life, and particularly beyond the first week, increases the concern for an underlying hypoglycaemia disorder. i.e. neonatal hyperinsulinism, genetic disorder.

### RISK GROUP

1. Large for gestational age (LGA) infants (>90th percentile)
2. Small for gestational age (SGA) infants (<10th percentile)
3. Infants of diabetic mothers (IDMs)
4. Late preterm infants (34 to 36 6/7 weeks of gestation)
5. Infants with perinatal stress due to:
  - a. Birth asphyxia/ischaemia; cesarean delivery due to foetal distress
  - b. Maternal preeclampsia/eclampsia or hypertension
  - c. Meconium aspiration syndrome, erythroblastosis foetalis, polycythaemia, hypothermia
6. Infants with a family history of a genetic form of hypoglycaemia
7. Infants with a congenital syndromes i.e. Beckwith-Wiedemann
8. Acutely ill infants: septicemia, asphyxia, respiratory distress, prematurity, and other illnesses

### DEFINITIONS

Transient hypoglycaemia:

- ▶ low glucose values < 50mg/dl that last for a short time, usually < 48 hours

Persistent and recurrent hypoglycaemia:

- ▶ low glucose values < 50mg/dl that usually lasts more than 48 hours, and
- ▶ requires prolonged management with high rates of glucose infusions for several days and possible pharmacologic intervention

### SCREENING

1. Late pre-term infants and SGA:
  - a. Screen before each feeding every 2 to 3 hours for the first 0-24 hours.
  - b. Discontinue screening after 24 hours if PG is more than > 45 mg/dl.
2. IDM and LGA  $\geq$  34 weeks:
  - a. Screen before each feeding for the first 0-12 hours.
  - b. First feeding should be given in the first hour of life.





## CLINICAL SIGNS

Many infants are asymptomatic.

Table 1. Clinical signs of hypoglycaemia.

Irritability	Lethargy
Tremors	Hypotonia
Jitteriness	Cyanosis
Exaggerated Moro reflex	Apnoea
High-pitched cry	Poor feeding

Seizures

## DIFFERENTIAL DIAGNOSIS

1. Sepsis
2. Central nervous system (CNS) disease
3. Toxic exposure
4. Metabolic abnormalities
  - a. Hypocalcaemia
  - b. Hyponatraemia or hypernatraemia
  - c. Hypomagnesaemia
  - d. Pyridoxine deficiency
5. Adrenal insufficiency
6. Heart, renal, and liver failure

Table 2. Causes of hypoglycaemia

Transient Hypoglycaemia	Persistent or Recurrent Hypoglycaemia
Associated with changes in maternal metabolism	Hyperinsulinism
Intrapartum administration of glucose	Congenital hyperinsulinism
Drug treatment	Beckwith-Wiedemann syndrome
Terbutaline, ritodrine, propranolol	Endocrine disorders
Oral hypoglycemic agents	Pituitary insufficiency
Diabetes in pregnancy: infant of diabetic mother (IDM)	Cortisol deficiency
	Congenital glucagon deficiency
	Epinephrine deficiency



## Transient Hypoglycaemia

## Persistent or Recurrent Hypoglycaemia

### Associated with neonatal problems

Idiopathic condition or failure to adapt  
Intrauterine growth restriction  
Small for gestational age  
Inadequate caloric intake  
Delayed onset of feeding  
Polycythaemia

### Inborn errors of metabolism

Carbohydrate metabolism  
Galactosemia  
Hepatic glycogen storage diseases  
Fructose intolerance  
Amino acid metabolism  
Maple syrup urine disease  
Propionic acidemia  
Methylmalonic acidemia  
Hereditary tyrosinemia  
3-hydroxy, 3-methyl glutaric acidemia  
Ethylmalonic-adipic aciduria  
Glutaric acidemia type II  
Fatty acid metabolism  
Defects in carnitine metabolism  
Acyl-coenzyme dehydrogenase defects

### Perinatal stress

Sepsis  
Shock  
Asphyxia  
Hypothermia (increased utilization)  
Respiratory distress  
Postresuscitation

Neurohypoglycemia (hypoglycorrachia) caused by defective glucose transport

## MANAGEMENT

The clinical management of neonatal hypoglycaemia should include:

1. Anticipation of the group at high risk.
2. Correction of hypoglycaemia.
3. Investigation and treatment of the cause of hypoglycaemia.



The Pediatric Endocrine Society recommends:

1. For high-risk infants without a suspected congenital hypoglycaemia disorder:
  1. < 48 hours of life: target PG > 50 mg/dl
  2. > 48 hours of life: target PG > 60mg/dl
2. For neonates who require dextrose infusion, transitioning to normal feedings alone can be attempted once PG concentration is stabilised at >60 mg/dL.
3. For neonates with a suspected congenital hypoglycaemia disorder: maintain a PG concentration >70 mg/dL.

The American Academy of Pediatrics (AAP) recommends measuring blood glucose levels and treatment for the following:

1. Symptomatic infants with blood glucose <40 mg/dL: treat with intravenous (IV) glucose.
  - a. cutoff for treating symptomatic infants is 40 mg/ dL.
  - b. target plasma glucose concentrations in symptomatic infants between 40 and 50 mg/dL.
2. Asymptomatic infants at risk for hypoglycaemia:
  - a. First 4 hours of life
    1. Initial PG screen: < 25 mg/dL (should be done within first hours after birth)
      1. Feed infant
      2. Recheck glycaemia 1 hour later and if: < 25 mg/dL, treat with IV glucose
      3. If the second check 1 hour later: 25 to 40 mg/dL, consider feeding as an alternative to IV glucose
    - b. Four to 24 hours of life
      1. PG < 35 mg/dL: feed infant and recheck glucose in 1 hour
      2. If PG continues <35 mg/dL: treat with IV glucose
      3. Recheck after initial feeding: if 35 to 45 mg/dL, attempt feed
      4. Recommendation: target glucose >45 mg/dL prior to routine feeds.
  - ▶ Cutoff for treating symptomatic infants is 40 mg/ dL.

#### PERSISTENT HYPOGLYCAEMIA

1. Can be treated with a mini-bolus of 2 mL/kg (200 mg/kg) D10W and/or
2. Intravenous infusion of D10W at 5 to 8 mg/kg per minute (80 to 100 mL/kg per day)
3. The goal is to achieve a plasma glucose concentration: 40 to 50 mg/dL.
4. Persistent hypoglycaemia that requires high GIR of 8 to 10 mg/kg/minute suggests increased utilisation due to hyperinsulinism and may require pharmacologic interventions.

Neonates in whom to exclude persistent hypoglycaemia before discharge:

1. Severe hypoglycaemia (i.e. episode of symptomatic hypoglycaemia or need for IV dextrose to treat hypoglycaemia).
2. Inability to consistently maintain preprandial PG concentration >50mg/dL up to 48 hours of age and >60mg/dL after 48 hours of age.



3. Family history of a genetic form of hypoglycaemia.
4. Congenital syndromes.

Note: Often, it is not possible to identify the cause of hypoglycaemia, and the treatment remains limited to correction of the low blood glucose concentrations.

Glucose monitoring in healthy infants born at term gestation is not recommended.

Feeding of glucose water is not recommended.

Early breastfeeding decreases the risk of hypoglycaemia.

Bedside reagent strips measure whole blood glucose, which is 15% lower than plasma levels.

A valid confirmatory laboratory glucose determination is required before diagnosing hypoglycaemia.

Most hypoglycaemia will resolve in 2 to 3 days.

Endocrine evaluation may be necessary to specifically evaluate for hyperinsulinism or other rare causes.

Diagnosing hyperinsulinaemia requires measuring insulin, cortisol, and amino acids at a time when the glucose level is <40 mg/dL.

If the insulin level is normal for the blood glucose level, consider additional testing to evaluate for other causes of persistent hypoglycaemia.

## IV GLUCOSE THERAPY

### Indications

1. Inability to tolerate oral feeding.
  2. Persistent symptoms of hypoglycaemia after feeding.
  3. Oral feedings do not maintain normal glucose levels.
  4. Severe hypoglycaemia.
1. Urgent treatment: 2 mL/kg of dextrose 10% in water (D10W)
    - a. Recheck glucose level 20 to 30 minutes after IV bolus and then hourly until stable, to determine if additional therapy is needed.
    - b. Additional bolus infusions of 2 mL/kg of D10W may be needed.

2. Continuing therapy (not for infants on TPN where GIR should be titrated accordingly)

Indication: infusion of glucose at a rate (GIR) of 6 to 8 mg/kg/minute

$GIR \text{ (mg/kg/min)} = (\text{dextrose \% concentration} \times \text{fluids requirement ml/kg/day}) / 144$

i.e.  $GIR = (\text{Dextrose 10\%} \times 80\text{ml/kg/day}) / 144 = 5.5 \text{ mg/kg/min}$

OR

$GIR \text{ (mg/kg/min)} = (\text{Dextrose \% concentration} \times \text{rate of infusion}) / (6 \times \text{weight in Kg})$

i.e. 4 kg infant receiving fluids (80ml/kg/day) at 13.3 ml/hr using Dextrose 10%

$GIR = (10 \times 13.3) / (6 \times 4) = 5.5 \text{ mg/kg/min}$

Note: Plasma glucose levels are monitored frequently (every 1-2 hours) until they are stable and then less frequently (every 4-6 hours).



If the glucose concentrations do not increase to normal levels, GIR should be increased by 1 to 2 mg/kg/minute every 3 to 4 hours while monitoring the glucose response.

Some infants with hyperinsulinism, IUGR, and persistent hypoglycaemia who are symptomatic, require a GIR of 12 to 15 mg/kg/min (often as D15W or D20W) and are best managed exclusively by parenteral glucose infusion and without oral feeding until their plasma glucose concentrations have stabilised.

Central venous catheter may be necessary to give adequate glucose (D15W to D20W) in an acceptable fluid volume.

IV fluids should be weaned slowly while feedings are advanced.

The infant can be weaned from parenteral glucose infusion after the plasma glucose concentration has been stable at about 50 to 70mg/dL.

Glucose infusions can be decreased every 3 to 4 hours as long as the blood glucose concentration remains stable.

## PHARMACOLOGIC INTERVENTIONS FOR PERSISTENT HYPOGLYCAEMIA

1. Diazoxide is the first-line drug for managing hyperinsulinemic hypoglycaemia.

Dose: 8 to 15 mg/kg/day in divided doses every 8 to 12 hours PO

2. Octreotide is the second-line drug for hyperinsulinemic hypoglycaemia.

Dose: 5 to 20 µg/kg/day divided every 6 to 8 hours SC/IV

3. Hydrocortisone: if it is difficult to maintain glucose values in the normal range despite GIR of 12 to 15 mg/kg/minute.

Dose: 10 mg/kg/day in two divided doses IV,

Do not use hydrocortisone routinely for hypoglycaemia.

4. Glucagon is rarely used.

- ▶ In cases of hyperinsulinism, glucagon can raise PG concentration to normal or above within 10-15 minutes and maintain that concentration for at least 1 hour.

Dose: 0.2 mg/kg IM, SC or IV (maximum 1.0 mg)

## PROGNOSIS

Neonatal hypoglycaemia can cause seizures, permanent neuronal injury, and death.

Other neurologic problems include developmental delay, learning and behaviour problems, hyperactivity and attention difficulties, autistic features, microcephaly, and cortical blindness.

The number of days with moderate hypoglycaemia was strongly related to reduced mental and motor developmental scores at a corrected age of 18 months.

## HYPERGLYCAEMIA

Defined as a whole blood glucose level higher than 125 mg/dL or plasma glucose values higher than 145 mg/dL.

Major clinical problems associated with hyperglycaemia: hyper-osmolarity and osmotic diuresis.

Hyperglycaemia increases blood osmolarity and may cause electrolyte disturbances, osmotic diuresis, and the associated loss of electrolytes in the urine.



Serum osmolarity of more than 300 mOsm/L usually leads to osmotic diuresis (each 18 mg/dL rise in blood glucose concentration increases serum osmolarity 1 mOsm/L). Subsequent dehydration may occur rapidly in small preterm infants with large insensible fluid losses.

## CAUSES

1. Iatrogenic: high GIR
2. Drugs: glucocorticoids, caffeine, theophylline
3. Extremely low birth weight infants (<1,000 g)
4. Lipid infusion: free fatty acids are associated with increased glucose levels.
5. Sepsis
6. Stressed preterm infants
7. Hypoxia
8. Surgical procedures
9. Hyper-osmolar formula
10. Neonatal diabetes mellitus: is usually transient in IUGR infants

## MANAGEMENT

The primary goal is prevention and early detection of hyperglycaemia by:

1. adjusting GIRs
2. frequent monitoring of blood glucose levels
3. monitoring of urine for glycosuria

Measures:

1. Reduce fluid needs and insensible water loss to reduce the glucose intake.
2. Plasma glucose levels below 200mg/dL usually do not require intervention other than lowering the GIR.
3. Plasma glucose levels > 200mg/dL may require NSS 0.9% infusion at the same rate of fluid intake until glucose < 200 mg/dl; consider restarting glucose infusion at a lower GIR.
4. Extremely low birth weight preterm infants (< 1,000 g) should start with a GIR of at least 4 to 6 mg/kg/minute.
5. Begin parenteral nutrition as soon as possible in low birth weight infants. Some amino acids promote insulin secretion.

The routine use of exogenous insulin is not recommended in the NICU.

Exogenous insulin therapy may be considered:

1. When glucose values exceed 250 mg/dL despite efforts to lower the amount of glucose delivered.
2. When prolonged restriction of parenterally administered glucose would substantially decrease the required total caloric intake.

## INSULIN INFUSION

The standard dilution is 15 units regular human insulin (0.15 mL) added to 29.85 mL normal saline for a concentration of 0.5 units/mL.

Prior to starting the infusion, purge the IV tubing with a minimum of 2 times the volume of the connecting tubing using the insulin-containing solution to saturate the plastic binding sites.



### 1. Bolus insulin infusion

Dose: 0.05 to 0.1 units/kg every 4 to 6 hours as needed (PRN)

- a. Infuse over 15 minutes via syringe pump.
- b. Monitor glucose every 30 minutes to 1 hour.
- c. If glucose remains > 200 mg/dL after three doses, consider continuous infusion of insulin.

### 2. Continuous insulin infusion

Rate of infusion is 0.05 to 0.2 units/kg/hour (usual starting dose is 0.05 units/kg/hour).

Infusion rate = (dose in units/kg/hour x weight in kg)/concentration in units/ml

i.e. Dose: 0.05 units/kg/hr; infant's weight: 900 g (0.9 kg); concentration: 0.05 units/ml

Infusion rate = (0.05 units/kg/hr) x (0.9 kg)/0.05 units/ml = 0.9 ml/hr

- a. Check glucose levels every 30 minutes until stable to adjust the infusion rate.
- b. If glucose remains >180 mg/dL, titrate in increments of 0.01 unit/kg/hour.
- c. If hypoglycaemia occurs, discontinue insulin infusion and administer IV bolus of D10W at 2 mL/kg/dose.
- d. Monitor potassium level.
- e. Monitor for rebound hyperglycaemia

### 3. Subcutaneous insulin lispro: (This is rarely used except in neonatal diabetes)

Dose: 0.03 unit/kg PRN for glucose >200 mg/dL.

- a. Do not administer more frequently than every 3 hours to avoid hypoglycaemia.
- b. Rotate administration sites.

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# NECROTISING ENTEROCOLITIS

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Defined as an acute intestinal inflammatory disease in newborn characterised by haemorrhagic necrosis, which may lead to perforation and destruction of the gut.

Necrotising enterocolitis (NEC) is the most common severe neonatal gastrointestinal emergency that predominantly affects premature infants. Greater than 90% of NEC cases occur in premature infants.

The incidence of NEC is inversely proportional to birthweight. The age of onset is inversely proportional to gestation; therefore smaller babies present later.

Genetic predisposition, intestinal immaturities and microbial dysbiosis combine to induce NEC.

## RISK FACTORS

1. Prematurity (the single greatest risk factor)
2. Intrauterine growth restriction
3. Absent or reversed end-diastolic flow on umbilical arterial Doppler antenatally
4. Perinatal asphyxia
5. Low systemic blood flow during neonatal period (including ductus dependent congenital heart disease)
6. Significant patent ductus arteriosus
7. Exchange transfusion: appears within 48 h of transfusion and commonly within 12 h.
8. Formula milk
9. Prolong period of no enteral feeding
10. No antenatal corticosteroids
11. Prolonged empiric antimicrobial use
12. Infections with: Klebsiella, Enterobacter, anaerobes
13. Term infants:
  - a. Congenital heart disease with presumed decreased intestinal perfusion (i.e. hypoplastic left heart syndrome, coarctation of the aorta)
  - b. Polycythaemia
  - c. Intrauterine cocaine exposure
  - d. Intestinal anomalies i.e. gastroschisis

Note: Prolonged periods of nulla per os (NPO) are known to cause atrophy of the intestinal mucosa and result in delayed development of absorptive function, motility, and exocrine hormone secretion, and shift the intestinal inflammatory response to one that favours the pro-inflammatory response.

There has been controversy about whether feedings should be withheld when a baby receives a transfusion, but the evidence for this practice is not very well substantiated.

## DIAGNOSIS:

- a. Clinical Findings b. Laboratory Findings c. Imaging Findings d. Surgical Findings





## CLINICAL PRESENTATION:

Clinical presentation usually comprises a triad of:

1. abdominal distension
2. gastrointestinal bleeding
3. pneumatosis intestinalis

### Bell's Staging Criteria for NEC

Stage I (suspect) includes clinical signs and symptoms, including abdominal signs and non-diagnostic radiographs.

Stage II (definite) includes clinical and laboratory signs and pneumatosis intestinalis and/or portal venous gas on radiographs.

- a. Mildly ill
- b. Moderately ill with systemic toxicity

Stage III (advanced) includes more severe clinical signs and laboratory abnormalities, pneumatosis intestinalis, and/or portal venous gas on radiographs.

- a. Critically ill (i.e. disseminated intravascular coagulation [DIC], shock) and impending intestinal perforation
- b. Critically ill as above but with pneumoperitoneum

Table 1. Clinical manifestations of NEC.

Systemic signs	Abdominal (enteric) signs
respiratory distress, apnoea and/or bradycardia	abdominal distension or tenderness
temperature instability	gastric aspirates (feeding residuals)
poor feeding	vomiting (of bile, blood, or both)
lethargy, irritability	ileus (decreased or absent bowel sounds)
hypotension (shock), decreased peripheral perfusion	hematochezia (grossly bloody stools)
acidosis	abdominal wall erythema or induration
oliguria	persistent localised abdominal mass
bleeding diathesis	ascites

The course of the disease varies among infants. Most frequently, it will appear as

- a. a fulminant, rapidly progressive presentation of signs consistent with intestinal necrosis and sepsis or
- b. a slow, paroxysmal presentation of abdominal distension, ileus, and possible infection.

Note: Guaiac-positive stools are quite common in nasogastric tube-fed preterm neonates (60%-75%) and therefore, are not a useful indicator of NEC.

Intolerance is not a reliable marker for the development of intestinal injury.



## DIFFERENTIAL DIAGNOSIS

1. Sepsis with ileus
2. Bowel obstruction
3. Volvulus
4. Malrotation
5. Cow's milk protein-sensitive enterocolitis
6. Infectious enterocolitis
7. Inborn Error of Metabolism
8. Spontaneous intestinal perforation: associated with early postnatal corticosteroids or indomethacin; abdominal X-ray demonstrates pneumoperitoneum but does not show evidence of pneumatosis intestinalis.
9. Systemic candidiasis: clinical signs can mimic NEC with abdominal distension, metabolic disturbances, hypotension and thrombocytopenia.

## MANAGEMENT

### LABORATORY

1. CBC: anaemia, neutropenia and thrombocytopenia
2. CRP
3. Urea and Creatinine
4. Electrolytes
5. Blood gas: evidence of metabolic acidosis (base deficit worse than -10), raised lactate
6. Coagulation screen
7. Blood culture
8. Analysis of stool for blood

### IMAGING: ABDOMINAL X-RAY

- ▶ Supine antero-posterior view
- ▶ If perforation suspected but not clear on supine view obtain a left lateral view

Serial X-rays (every 6 to 8 hours during the first 2 to 3 days) are used to assess ongoing GI damage in the first 24-48 hours.

Non-specific signs for NEC include:

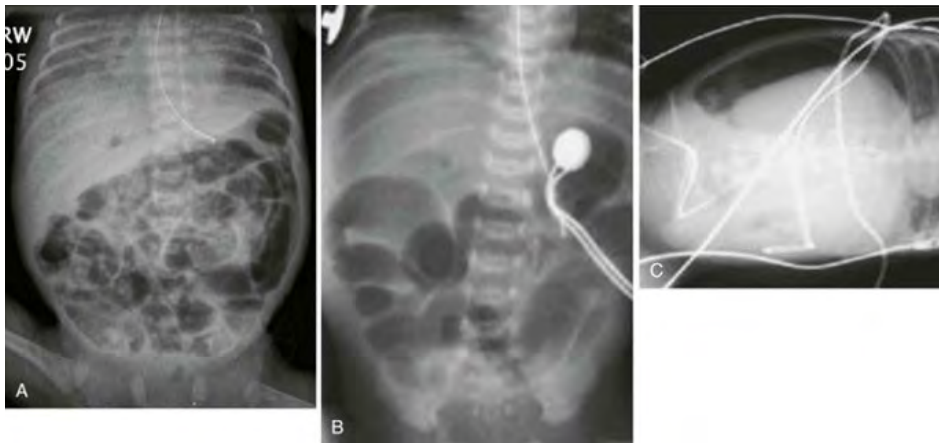
1. Diffuse gaseous distension
2. Asymmetric, disorganised bowel pattern 'featureless' loops
3. Dilated bowel loops
4. Bowel wall thickening
5. Increased peritoneal fluid

Diagnostic signs for NEC include:



1. Persistent loop
2. Pneumatosis intestinalis (virtually pathognomonic): (Figure A)
  - ▶ submucosal bubbly or cystic appearance (may be confused with stool, although stool usually moves on serial x-rays)
  - ▶ subserosal linear or curvilinear appearance portal venous gas (Figure A)
3. Pneumoperitoneum (although may not be due to NEC) (Figures B,C)

Figures A, B, C. Abdominal X-ray with signs of NEC.



During the advanced stages of NEC, the abdomen may appear shiny, distended, and erythematous. (Figure E)



Figure D. (Left). Abdominal X-ray of patient on the right (Figure E) with NEC. Source: Constanza E, 2013; HUC, Caracas.

Abdominal ultrasound: when radiographic signs are non-specific. Can identify even small volumes of free gas, abdominal fluid, and ascites.

## IMMEDIATE TREATMENT

*In all stages*



1. Discontinue feeds and oral medications (NPO).
2. Monitor vital signs: HR, RR, BP and SatO<sub>2</sub>.
3. Monitor weight, total input and output, urine output.
4. Monitor CBC: maintain haematocrit > 35 ml/dl and platelet > 50,000.
5. Monitor electrolytes, BUN, Creatinine, and glucose.
6. ABG: Avoid hypoxaemia and severe respiratory/metabolic acidosis.
7. If respiratory failure and worsening acidosis, intubate and ventilate.
8. Gastric decompression with a large lumen suction catheter (size 8) to low-continuous wall suction or regular intermittent aspiration.
9. Discontinue umbilical arterial line to maximise mesenteric perfusion.
10. Start broad-spectrum antibiotics for NEC beyond Bell stage I.
  - ▶ Triple antibiotics: ampicillin, gentamicin and metronidazole or clindamycin.
11. Start IV fluids/PN: total volume ≤150 mL/kg/day. Provide: 90 to 110 cal/kg/day
12. Start PN: adequate protein (3.5–4.0 g/kg/day) to maintain positive nitrogen balance and to allow the repair of injured tissue. Adequate energy intake necessitates the use of lipids usually at approximately 3 g/kg/day.
13. Central line when stable and bacteraemia/septicaemia excluded.
14. Analgesic: consider morphine infusion

#### Stage 2: Proven NEC (confirmed radiologically)

1. If breathing supported by nasal CPAP, elective intubation to provide bowel decompression.
2. Give IV fluid resuscitation: 10 mL/kg sodium chloride 0.9% for shock and repeat as necessary. Shock is most common cause of hypotension in babies with NEC.
3. Dopamine at low dose: 2-5 mcg/kg/min.
4. If coagulation abnormal, give FFP.
5. If thrombocytopenia and/or anaemia occur, transfuse.
6. Evaluation and discussion with paediatric surgical team.

#### Stage 3 : Advanced NEC (fulminant NEC with or without intestinal perforation)

Treat as for Stage 2 and refer to paediatric surgical team for surgical treatment.

#### Note: *Surgical strategies*

The indications for surgery include bowel perforation, clinical deterioration despite conservative medical treatment, abdominal mass with intestinal obstruction, and development of intestinal stricture.

Relative indications for surgery include fixed dilated intestinal loop, presence of portal gas, thrombocytopenia, and rapid fall in platelet count.

In ELBW infants (<1,000 g) and extremely unstable infants, primary peritoneal drainage (PPD) under local anaesthesia may be an option. In many cases, this temporises laparotomy until the infant is more stable, and in some cases, no further operative procedure is required.



In infants weighing >1000 g who have no associated morbidities and are clinically stable are preferentially treated by primary laparotomy exercising resection with enterostomy, resection with primary anastomosis, proximal jejunostomy or "clip and drop" technique.

Principal surgical objectives of laparotomy in acute NEC are to control sepsis and removal of gangrenous bowel preserving as much bowel length as possible.

In general, an infant with increasing abdominal distension, an abdominal mass, a worsening clinical picture despite medical management, or a persistent fixed loop on serial radiographs may have a perforation and may require operative intervention.

#### SUBSEQUENT MANAGEMENT (In recovery phase)

In Stage 1: if improvement after 48 hr, consider restarting feeds slowly and stopping antibiotics.

In Stage 2: if abdominal examination normal after 7–10 days, consider restarting feeds. Some may need longer period of total gut rest. Stop antibiotics after 7–10 days.

In Stage 3: discuss with surgeon, neonatologist and dietitian before restarting feeds.

Note: When output from the suction catheter diminishes and becomes non-bilious, it can be left to gravity.

Bowel recovery is achieved by resolution of bilious aspirated from the nasogastric tube and passage of stool through the stoma and/or anus.

After completion of medical management, with or without surgical therapy, antibiotics should be discontinued and enteral nutrition started as trophic feeding with slow increases using preferably breast milk or semi-elemental (Nutramigen<sup>®</sup>)/elemental formula (Neocate<sup>®</sup>).

#### COMPLICATIONS

1. Recurrence (in about 10%)
2. Strictures (in about 10% non-surgical cases, and occur 3–8 weeks after the acute episode)
3. Enteric Fistulas
4. Short bowel syndrome and problems related to gut resection as Malabsorption, malnutrition, and dumping syndromes related to loss of terminal ileum and ileocecal valve.
5. Parenteral nutrition-associated liver disease (PNALD), including cholestasis in infants with long-term PN.
6. Neuro-developmental problems

Note: Signs of malabsorption include excessive ostomy output (> 2ml/kg/hr), watery stool, and lack of weight gain.

If the disease process was severe with substantial loss of bowel length, the initial feedings should be with a continuous, low volume of breast milk or an elemental/semi-elemental formula.

Every effort must be made to support and reassure mothers to continue to express breast milk during and following NEC.

#### MONITORING TREATMENT

##### *Antibiotics:*

- ▶ Treatment is generally maintained for 10 to 14 days in cases of definite NEC ( $\geq$ Bell II). There is no evidence to support the use of enteral antibiotics.



- ▶ Routine treatment usually proceeds for 7 to 10 days with NPO and antibiotics in uncomplicated, medical NEC
- ▶ Typical combination therapy is indicated such as ampicillin, gentamicin, and metronidazole. Alternatively, treatments include clindamycin, piperacillin-tazobactam, or meropenem, sometimes in combination with vancomycin.
- ▶ Consider adding anti fungal therapy with fluconazole in selected patients at risk who do not respond to antibacterial therapy.

#### *Nutrition:*

- ▶ Length of withholding enteral nutrition varies between 5 and 14 days for medical NEC and 10 to 14 days for surgical disease.
- ▶ Most clinicians wait at least a week before refeeding, and then take at least 7–10 days (and often much longer) to re-establish full milk feeds. During this period, abdominal distension or large gastric aspirates are common.
- ▶ Infants with short bowel have less mucosal surface area producing lactase and are more likely to develop lactose intolerance. Symptoms are non-specific but include abdominal distension due to increased gas production and more rapid intestinal transit that may cause an increase in stoma output. Infants without a stoma may develop excoriated perineal rashes.
- ▶ Infants with greater lengths of affected or resected bowel will present greater challenges when milk feeds are restarted.
- ▶ Infants with short bowel have more rapid bowel transit time and frequently have impairment of bile acid secretion leading to poor fat digestion and absorption especially of long-chain fatty acids.

Note: The American Society of Parenteral and Enteral Nutrition (ASPEN) guideline suggests

1. that minimal enteral nutrition should be initiated within the first 2 days of life and advanced by 30 mL/kg/d in infants  $\geq 1000$  g
2. the exclusive use of mother's milk rather than bovine-based products or formula in infants at risk for NEC

There are insufficient data to recommend the use of probiotics in infants at risk for NEC.

There is insufficient evidence at this time to recommend glutamine, arginine and/or long-chain polyunsaturated fatty acid supplementation for infants at risk for NEC.

#### *Nutritional status following NEC:*

Preterm infants have very high nutrient requirements and the potential for longer-term neurodevelopmental harm due to inadequate provision of essential or semi-essential nutrients at a vital stage of brain development must not be ignored.

Preterm infants recovering from NEC require higher intakes of a range of minerals, vitamins, electrolytes and metals (especially zinc and iron) as well as higher levels of macronutrients. This is especially important with jejunal or 'high' ileal stomas where electrolyte and micronutrient losses can be very high, and macronutrient absorption is impaired.

B12 deficiency may appear following ileal resection.

#### PREVENTION OF NEC

Preventative strategies include:

1. antenatal corticosteroids
2. early introduction of trophic feeding
3. slower rate of advancement of enteral feedings



4. feeding with breast milk rather than formula
5. avoidance of acid blockade
6. avoidance of hypoxia
7. maintain adequate perfusion and blood pressure
8. minimisation of empiric antibiotic exposure
9. infection control practices may limit the size of disease clusters

Routine use of probiotics in the prevention and treatment of NEC cannot be universally recommended.

## PROGNOSIS

Stage IIB and stage III NEC have a higher incidence of mortality (of over 50%), growth delay (delay in growth of head circumference is of most concern), and poor neuro-developmental outcome.

Metabolic sequelae include failure to thrive, metabolic bone disease, and problems related to central nervous system (CNS) function in the VLBW infant.

Follow-up is indicated for surgical procedures such as bowel lengthening, tapering, and intestinal transplantation for infants with short bowel syndrome.

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## ZIKA

Congenital Zika Syndrome (CZS) represents the spectrum of congenital anomalies that are associated with foetuses exposed to Zika virus in utero. (Table 1)

1. CZS generally manifests with brain defects, craniofacial disproportion, limb contractures, and ocular and hearing abnormalities.
2. Brain anomalies may occur without the presence of congenital microcephaly.
3. Microcephaly (Figure 1) and other neurologic symptoms may also develop after birth, indicating the need for ongoing evaluation in all potentially affected infants.

Table 1. Congenital anomalies associated with CZS include:

Clinical features	Signs and Symptoms
Cranial morphology: foetal brain disruption sequence (FBDS)	FBDS includes: severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, neurologic impairment, and craniofacial disproportion
Abnormal brain radiology findings	Intracranial calcifications Ventriculomegaly Abnormal gyro patterns i.e. lissencephaly Cortical atrophy Hypoplasia of cerebellum, corpus callosum, cerebellar vermis or brainstem
Neurologic sequelae	hypertonicity and hyperreflexia, hypotonia, seizures, sensorineural hearing loss, swallowing dysfunction, vision impairment, motor disabilities, cognitive disabilities, tremors and extrapyramidal symptom
Ocular findings	microphthalmia, coloboma, chorioretinal atrophy or scarring, pigmentary changes, optic nerve hypoplasia, optic disc pallor, hemorrhagic retinopathy and abnormal retinal vasculature, intra-ocular calcifications
Congenital contractures	unilateral or bilateral clubfoot, and arthrogryposis multiplex congenita

### DIFFERENTIAL DIAGNOSIS OF CZS

Includes both infectious i.e TORCH, and genetic aetiologies i.e Aicardi-Goutières syndrome.

Differential causes of microcephaly include other congenital infections, such as cytomegalovirus, toxoplasmosis, varicella-zoster, and rubella infection.

### LABORATORY TESTING IS RECOMMENDED FOR:

1. Infants born to mothers with laboratory evidence of Zika virus infection during pregnancy.
2. Infants who have abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiological link suggesting possible transmission, regardless of maternal Zika virus test results.





Note: Sample should be collected directly from the infant (not umbilical cord) *in the first 2 days after birth*; if performed later, it will be difficult to distinguish between congenital, perinatal and postnatal infection.

Blood sample: 2-5ml; urine sample: 5-15ml; CSF (if clinically indicated and obtained for other purposes): 0.5ml

Samples from suspected cases of Zika are sent to Central Medical Laboratory in Belize city before it's sent to the Caribbean Public Health Agency (CARPHA) for laboratory testing. In addition, samples are sent to the Instituto de Diagnóstico y Referencia (InDRE) in Mexico for molecular confirmation.

#### RECOMMENDED INFANT LABORATORY INCLUDES BOTH:

1. NAT (nucleic acid testing) which includes rRT-PCR (real-time reverse transcription-polymerase chain reaction) method. (Sample: infant's serum and urine)
2. IgM (serologic immunoglobulin M). Sample: infant's serum

Table 2. Laboratory request and interpretation of results according to clinical scenarios.

Infant's testing	Situation 1 Mother (+) for ZV	Situation 2 Mother (+) for ZV	Situation 3 Mother (+) for ZV	Situation 4 Mother (-) or unknown for ZV + Epidemiology (+)	Situation 5 No maternal ZV exposure identified
NAT	+	-	-	Request	
IgM	+/-	+	-	Request	
PRNT	Not necessary	Necessary to confirm infection	Consider to confirm infection		
Diagnosis of CZV infection	Confirmed	Probable	Unlikely		
Infant shows symptoms	+/-	+/-	+	++	-
Comment	Initial evaluation. Follow up with a multi- disciplinary approach.	Initial evaluation. Follow up with a multi- disciplinary approach.	Initial evaluation. Investigate other causes. i.e. TORCH	Request ZV testing and perform initial evaluation.	no testing required; continue with routine paediatric care

NAT, nucleic acid testing; IgM, immunoglobulin M; CZV, congenital Zika virus. NAT: serum, urine, CSF; IgM: serum, CSF; PRNT: serum.

Testing CSF for Zika virus RNA and Zika virus IgM antibodies should be considered, especially if serum and urine testing are negative and another aetiology has not been identified.

Note: A negative NAT result does not exclude infection. Serum PRNT is used to confirm the specificity of the IgM antibodies against Zika virus and rule out a false positive IgM result. PRNT should be performed on a sample collected from a child aged  $\geq 18$  months (when maternal antibodies are expected to wane) whose initial sample was IgM positive if Zika-specific neutralising antibodies were detected by PRNT on either the infant's or mother's sample. If the infant's initial sample is negative by both IgM ELISA and NAT but clinical concerns



remain, PRNT at age 18 months can be considered. If PRNT result at 18 months is positive, congenital Zika infection is presumed, but postnatal infection cannot be excluded.

### *1. Initial evaluation and laboratory testing of infants born to mothers with laboratory evidence of Zika virus infection during pregnancy.*

Note: Laboratory evidence of maternal Zika virus infection includes 1) Zika virus RNA detected by NAT in any clinical specimen i.e. blood, placenta; or 2) positive Zika virus immunoglobulin M (IgM) with confirmatory neutralising antibody titers. Mothers should be tested by NAT within 2 weeks of exposure or symptom onset, or by IgM within 2–12 weeks of exposure or symptom onset. Because of the decline in IgM antibody and viral RNA levels over time, negative maternal testing 12 weeks after exposure does not rule out maternal infection.

Zika virus NAT testing should be offered as part of routine obstetric care to asymptomatic pregnant women with ongoing possible Zika virus exposure .

#### MANAGEMENT OF INFANTS BORN TO MOTHERS WITH LABORATORY EVIDENCE OF ZIKA VIRUS INFECTION DURING PREGNANCY.

##### INITIAL EVALUATION INCLUDES:

1. Comprehensive physical examination
2. Zika virus laboratory testing
3. Cranial Ultrasound by age one month
4. Hearing screening before discharge or within 1st month after birth using automated auditory brainstem response (ABR) method
5. Ophthalmologist evaluation prior to discharge or within 1 month after birth

Note: Laboratory testing for congenital Zika virus infection is not routinely recommended for asymptomatic infants born to mothers with possible Zika virus exposure in pregnancy but without laboratory evidence of possible Zika.

If CT (non contrast) or MRI are not available, transfontanellar ultrasound can be performed if the fontanelle is of adequate size.

Refer to the Belize Council for the Visually Impaired (BCVI) before hospital discharge or before one month of age for extensive eye exam. Further follow-up should be based on ophthalmology recommendations.

Refer to the Inspiration Center for hearing screening using auditory brainstem response (ABR) methodology before one month of age and if initial screening was passed using otoacoustic emission (OAE) method. A diagnostic ABR is no longer recommended at age 4–6 months or a behavioral audiology at age 9 months for infants who passed the initial hearing screen with automated ABR. Early intervention services are also offered.

Recommendation: Neonates should have their head circumference measured in the first 24 hours of life: Term neonates (37-42 weeks), Intergrowth-21 Newborn Size Standards or WHO Child Growth Standards for size at birth should be used. Preterm neonates, Intergrowth-21 Newborn Size Reference for Very Preterm Infants or Fenton Size at Birth Standards for gestational age and sex should be used.

BREASTFEEDING is encouraged regardless of infant Zika virus testing results. Benefits outweigh the theoretical risk of Zika virus transmission.



## MANAGEMENT OF INFANTS WITH FINDINGS SUGGESTIVE OF CONGENITAL ZIKA SYNDROME I.E. MICROCEPHALY HC < -2 SD (SEVERE MICROCEPHALY HC < -3 SD) OR INTRACRANIAL CALCIFICATIONS AT BIRTH:

1. Paediatric neurologist evaluation.
2. Ophthalmologist evaluation prior to discharge or within 1 month after birth.
3. Rule out TORCH. (CZS is considered by many authors as a new TORCH)
4. Rule out genetic and other teratogenic causes.
5. Endocrinologist evaluation for hypothalamic or pituitary dysfunction.
6. Complete Blood Count and Hepatic function tests.
7. Consider other evaluations specific to the infant's clinical presentation i.e. Orthopaedic, speech or occupational therapist, paediatric cardiologist, nutritionist, lactation specialist, pulmonologist or Ear Nose and Throat (ENT) specialist for concerns about aspiration. Subspecialty consultations, can be performed before hospital discharge or as an outpatient.
8. Perform hearing screening using ABR methodology in the first month of life.
9. Provide family and supportive services. i.e. Roving Care Giver Program of the Ministry of Human Development for supportive services.

## *2. Outpatient management and follow-up of infants with microcephaly or other findings consistent with CZS.*

### MANAGEMENT OF INFANTS WITH LABORATORY CONFIRMED OR PROBABLE CONGENITAL ZIKA INFECTION (CZI) AND FINDINGS CONSISTENT OF CZS:

1. Follow-up by Paediatrician/Neonatologist to monitor growth, nutrition, neuro-developmental milestones monthly. Measure head circumference at each encounter (0-59 months) and document in the Belize health information system (BHIS) if there is abnormality (HC -2 SD or -3 SD). Infants should receive routine preventive paediatric health care, including regularly scheduled immunisations.
2. Neurological evaluation at 1 and 2 months of age. Refer to paediatric neurologist if any abnormalities or concerns.
3. Promote early intervention services i.e. physical and occupational therapy.
4. Repeat ophthalmology exam based on ophthalmology criteria.
5. If initial hearing screening was done using ABR methodology within the first month of life, no further testing is necessary. If OAE methodology was use as initial screening then request ABR and refer to ENT specialist if any abnormalities or concerns.
6. Repeat testing for hypothyroidism at age 2 weeks and age 3 months, even if the initial testing results were normal.
7. Provide family and supportive services.

### MANAGEMENT OF INFANTS WITH FINDINGS CONSISTENT WITH CZS BUT WITH A NEGATIVE LABORATORY RESULT:

- Continue to evaluate for other causes of congenital anomalies i.e. TORCH



### 3. Outpatient management and follow-up of infants with laboratory evidence of congenital Zika virus infection but without findings consistent with CZS.

#### MANAGEMENT OF INFANTS WITH LABORATORY CONFIRMED OR PROBABLE CZI BUT WITHOUT FINDINGS CONSISTENT WITH CZS:

1. Follow-up by paediatrician at each well child visit to monitor growth, nutrition, neuro-developmental milestones. Measure head circumference at each encounter (0-59 months) and document in the BHIS if there is abnormality (HC  $-2$  SD or  $-3$  SD). Use a standardised, validated developmental screening tool at 9 months as currently recommended, or earlier for any parental or provider concerns. Infants should receive routine preventive paediatric health care, including regularly scheduled immunisations.
2. Refer to Ophthalmologist within one month of birth.
3. Refer for hearing screening using ABR methodology within the first month of life. If OAE methodology is used as initial screening then request ABR and refer to ENT specialist if any abnormalities or concerns.
4. Provide family and supportive services.

#### MANAGEMENT OF INFANTS WITHOUT FINDINGS CONSISTENT WITH CZS AND WITH A NEGATIVE LABORATORY RESULT:

- Routine care

Note: The management of infants born to mothers with confirmed or possible Zika virus infection during pregnancy includes precise measurement of the occipito-frontal head circumference, comprehensive physical examination noting abnormal neurologic and dysmorphic findings, infant laboratory testing, postnatal cerebral ultrasound, audiology, and ophthalmologic screening.

Five features differentiate CZS from other congenital infections: (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) marked early hypertonia with symptoms of extrapyramidal involvement.

Close follow-up will be required throughout early childhood, monitoring neuro-developmental milestones and growth, and neurologic, visual and audiology assessments.

A multidisciplinary approach is needed to manage infants with CZS.

Figure 1. Microcephaly



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# TORCH

## TORCHES CLAP (updated suggested acronym)

A vertically transmitted (mother to child) infections of the foetus and newborn via the placenta in utero (congenital infections), intrapartum or during the delivery (peripartum infections) or postpartum period, commonly via breast milk feeding (postnatal infections).

Table 1. Suggested Acronym for Microorganisms responsible for Infection of the Foetus.

<b>TO</b>	Toxoplasma gondii
<b>R</b>	Rubella virus
<b>C</b>	Cytomegalovirus (CMV)
<b>HE</b>	Herpes simplex virus (HSV)/Hepatitis virus
<b>S</b>	Syphilis (Treponema pallidum)
<b>C</b>	Chickenpox (Varicella-zoster virus)
<b>L</b>	Lyme disease (Borrelia burgdorferi)
<b>A</b>	AIDS (HIV)
<b>P</b>	Parvovirus (B19)

Note: Diagnosis of each of the possible infectious agents should be considered separately and the appropriate most rapid diagnostic test is requested to implement therapy as quickly as possible.

Congenital cytomegalovirus infection is the most common congenital infection and a leading cause of birth defects and paediatric disabilities.

Congenital Zika virus infection is considered by many authors as a new TORCH.

Pathogen-specific IgM antibodies reflect infant infection status but with variable sensitivity and specificity.

In Belize 3 private laboratories test for TORCH (samples are sent abroad for testing and results are reported in 1 to 2 weeks). Test includes IgG and/or IgM for Toxoplasmosis, Rubella, CMV and HSV1,2.

## Toxoplasmosis

Congenital toxoplasmosis is an infection of the protozoa *Toxoplasma gondii* transmitted from mother with a primary infection during pregnancy to foetus.

Mostly asymptomatic at birth

Classic diagnostic triad:

1. chorioretinitis
2. hydrocephalus
3. intracranial calcifications.

More common manifestations and sequelae include:



1. Anaemia
2. Seizures
3. Jaundice
4. Splenomegaly
5. Hepatomegaly
6. Thrombocytopenia
7. Chorioretinitis
8. Microcephaly
9. Sensorineural hearing loss
10. Intellectual disability (mental retardation)

Table 2. Clinical findings associated with selected TORCH infections

	Toxoplasmosis	Syphilis	Rubella	CMV	HSV	Parvovirus
Hepatosplenomegaly	+	+	+	+	+	+
Cardiac lesions	-	-	++	+	+	+
Skin lesions	+	+	+ 'Blueberry Muffin'	+	+ Vesicles	+
Hydrocephalus	++	-	+	-	+	-
Microcephaly	+	-	-	++	+	-
Intracranial Calcifications	++	-	-	+	-	-
Ocular Disease	+	+	++	+	+	++
Hearing deficits	-	-	++	++	+	-
IUGR/LBW	+	-	+	+	-	-

Cardiac lesions: Patent Ductus arteriosus, pulmonary artery stenosis, myocarditis; Skin Lesions: Petechiae/purpura, maculopapular rash; Ocular disease: Chorioretinitis, glaucoma, cataracts, microphthalmia

#### MANAGEMENT OF INFANTS FOR CONGENITAL TOXOPLASMOSIS

1. Serum IgG, IgM and IgA (CSF if clinically indicated). Positive IgM or IgA antibody at least 10 days after birth is diagnostic. A positive IgG at 12 months of age is also diagnostic of congenital toxoplasmosis.
2. PCR. Blood, CSF, and urine. A positive PCR is diagnostic of infection.
3. Ophthalmologic evaluation at birth and every 3 months until 18 months of age followed by every 6-12 months until 18 years old.



4. Auditory screening for hearing loss with auditory brainstem response by 3 months of age. Full audio logic evaluation by 24 months of age.
5. CBC and liver function tests.
6. Head CT (without contrast) is preferred to visualise intracranial lesions. Cerebral US is an alternative if fontanelle permits.
7. Neurology evaluation and other multidisciplinary consultations according to clinical findings.
8. Treatment: Symptomatic or asymptomatic infants with diagnose: 12 months combined treatment with -
  1. Pyrimethamine 2mg/kg once daily for 2 days, then 1mg/kg once daily for 6 months, then 1mg/kg three times a week (every other day) to complete 1 year of therapy.
  2. Sulfadiazine 50mg/kg every 12 hours for 1 year.
  3. Folic acid 10 mg three times a week until 1 week after completing pyrimethamine (minimise pyrimethamine-associated haematologic toxicity).
  4. Prednisone (0.5mg/kg every 12 hours) may be added if CSF protein exceeds 1g/dl or active chorioretinitis with lesions very close to macula.
9. Repeat testing is recommended 1 month after therapy.
10. Breastfeeding is encouraged.

## Syphilis

Congenital syphilis occur as a result of transmission of the bacterium *Treponema pallidum* across the placenta during pregnancy as a consequence of both primary and non-primary infections, including both reinfection and reactivation.

The risk of transmission to the foetus correlates largely with the duration of maternal infection - the more recent the maternal infection, there more likely transmission to the foetus.

Most common clinical manifestation of early congenital syphilis (<2 years old):

2. Bullous lesions, palmar and plantar rash (Figure 1)
3. Mucous patches
4. Generalised lymphadenopathy
5. Hepatosplenomegaly
6. Rash
7. Watery nasal discharge
8. Jaundice
9. Anaemia
10. Thrombocytopenia
11. Skeletal abnormalities (osteochondritis, periostitis, psuedoparalysis)

Figure 1. Plantar lesions of infant with congenital syphilis.



Source: Constanza E, 2015; HUC, Caracas.

Note: Non-treponemal tests (Venereal disease research laboratory - VDRL and Rapid plasma reagin - RPR) measure antibody directed against an antigen from *T. pallidum* and/or its interaction with host tissues which allows evaluation of recent infection and response to treatment. *Only non-treponemal tests are done in newborn infants.*





Treponemal tests include fluorescent treponemal antibody absorption test (FTA-ABS), the *T. palladium* particle agglutination (TP-PA), and enzyme immunoassay (EIA). These tests are more specific and used to confirm positive non-treponemal tests and should not be used to assess treatment response.

Recommendation: No mother or newborn infant should leave the hospital without maternal serologic status having been documented at least once during pregnancy, and preferable again at delivery. Testing should be performed at the first prenatal visit and, in high-risk populations, should also be repeated at the beginning of third trimester (28 to 32 weeks' gestation if at high risk and at delivery).

#### NEUROSYPHILIS:

CSF abnormalities: increased protein concentration, increased white blood cell (WBC) count, and/or a reactive CSF VDRL.

#### MANAGEMENT OF INFANT FOR CONGENITAL SYPHILIS

Note: The diagnosis and treatment approach to infants being evaluated for congenital syphilis depends on

1. identification of maternal syphilis
2. adequacy of maternal therapy
3. maternal serologic response to therapy
4. comparison of maternal and infant serologic titers
5. findings on the infant's physical examination

Infant born to a mother with a reactive non-treponemal test confirmed by a treponemal test:

1. Complete physical examination for findings suggestive of congenital syphilis.
2. Infant serum RPR or VDRL.
  - a. The infant's titer should begin to fall by 3 months and become nonreactive by 6 months if the antibody is passively acquired.
  - b. If the baby was infected, the titer will not fall and may rise.
  - c. The tests may be negative at birth if the infection was acquired late in pregnancy thus the tests should be repeated later to confirm the diagnosis.
3. If available, pathologic examination of the placenta or umbilical cord using specific fluorescent antitreponemal antibody staining, and dark field microscopic examination of body fluids/lesions.
4. Red Book 2015 recommends standard precautions for all patients, including infants with suspected or proven congenital syphilis. i.e. wearing of gloves.
5. Breastfeeding is encourage. Postnatal transmission from mother to child is exceedingly rare, and there are no data that indicate breast milk itself as being associated with mother to child transmission.

CDC recommends classifying infants evaluated for congenital syphilis into one of the following four scenarios.

#### *Scenario one: Proven or highly probable disease*

Abnormal physical examination consistent with congenital syphilis



Non-treponemal titer fourfold higher than the mother's titer i.e. mother has 1:2 or 1:4 and neonate has 1:8 or 1:16 (The absence of a 4x or greater titer does not exclude congenital syphilis).

*Management:*

1. CSF analysis for VDRL, cell count and protein concentration.
2. Complete blood count (CBC) and liver function test.
3. Other tests as clinically indicated: Long-bone X-ray, ophthalmologic examination and auditory brainstem response.
4. Treatment:

Aqueous crystalline penicillin G 100,000 to 150,000 units/kg/day IV, administered as 50,000 units/kg/dose every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days.

Alternative: Penicillin G procaine 50,000 units/kg/dose IM in a single dose daily for 10 days

*Scenario two: Possible congenital syphilis*

Normal physical examination and serum non-treponemal titer equal to or less than 4 fold the maternal titer and one of the following:

1. Maternal treatment not given, inadequately treated, or has no documentation of having received treatment.
2. Mother was treated with erythromycin or any other non penicillin G regimen.
3. Maternal treatment administered <4 weeks before delivery.

*Management:*

1. CSF (VDRL, cell count and protein)
2. CBC
3. Long-bone X-ray
4. Treatment:

Aqueous crystalline penicillin G 100,000 to 150,000 units/kg/day IV, administered as 50,000 units/kg/dose every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days.

Alternative:

Penicillin G procaine 50,000 units/kg/dose IM in a single dose daily for 10 days.

Penicillin G Benzathine 50,000 units/kg/dose IM in a single dose.

Note: Penicillin benzathine can be given if the complete evaluation is normal (CBC, CSF, and long-bone X-ray) and follow-up is certain. If any part of the evaluation is abnormal or not interpretable, then a full 10 day course of penicillin G should be given.

The use of Penicillin benzathine is questionable for the prevention of neurosyphilis.

*Scenario three: Congenital syphilis less likely*

Normal physical examination and serum non-treponemal titer the same as or less than fourfold the maternal titer and both of the following:

1. Mother was treated during pregnancy with a penicillin regimen appropriate for the stage of infection and >4 weeks before delivery.
2. No evidence of maternal reinfection or relapse.



### Management:

1. Infants require no further evaluation.
2. Treatment:

Penicillin G Benzathine 50,000 units/kg/dose IM in a single dose. (Optional)

Alternative approach: do not treat infant but provide a close follow-up every 2-3 months for 6 months for infants whose mother's non-treponemal titers decrease at least fourfold after proper therapy for early syphilis or remained stable for low titer, latent syphilis (RPR <1:4).

### Scenario four: Congenital syphilis unlikely

Normal physical examination and a serum non-treponemal titer equal or less than fourfold the maternal titer and both of the following:

1. Adequate maternal treatment before progeny.
2. Maternal non-treponemal titer remained low and stable before and during pregnancy and at delivery (VDRL < 1:2 or RPR < 1:4).

### Management

1. No evaluation is recommended.
2. Treatment:

No treatment is required.

Some experts recommend a single dose of penicillin G benzathine 50,000 units/kg IM, particularly if follow-up is uncertain.

### FOLLOW-UP OF INFANTS TREATED FOR CONGENITAL SYPHILIS

1. All neonates with reactive non-treponemal tests (who required treatment or not).
2. Non-treponemal titer every 2 to 3 months until test becomes nonreactive. (Titers should decline by age 3 months and be nonreactive by age 6 months.)
3. If nonreactive by age 6 months, no further evaluation or treatment needed.
4. Treated neonates with persistent non-treponemal test titers by 6-12 months should be re-evaluated with CSF analysis and retreated with a 10 day course of Penicillin G regimen.
5. Neonates whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture every 6 months until results are normal.
6. A reactive CSF VDRL test or abnormal CSF that persist and cannot be attributed to other illness requires retreatment for possible neurosyphilis. Consultation with paediatric infectious disease specialist and paediatric neurologist.
7. Hearing screening test (sensorineural deafness).

### Rubella

Congenital rubella is an infection caused by a human-specific RNA virus transmitted from mother with a primary infection during pregnancy to foetus. The severity of this disease and the risk of transmission occurs mostly in the first trimester with 80%-100%, 10%-20% in second trimester and increases again 60% in third trimester.

Most common clinical manifestation of Congenital Rubella Syndrome (CRS):

1. Sensorineural deafness
2. Cataracts



3. Cardiac defects:
  - a. Patent ductus arterioles
  - b. Pulmonary artery stenosis
  - c. Coarctation of aorta

Other ocular findings:

1. Microphthalmia
2. Corneal opacity
3. Glaucoma

Others: 'Blueberry muffin rash', hepatosplenomegaly, thrombocytopenia, IUGR

#### MANAGEMENT OF INFANT WITH CRS:

1. History of acute maternal infection during pregnancy.
2. Isolation precautions should be instituted if CRS is suspected.
3. Serum or cord blood Rubella-specific IgM (usually positive at birth to 3 months).
4. Serum Rubella-specific IgG appears over the first 7 to 11 months (Avidity testing of IgG can help diagnose recent infection).
5. Isolation of the virus by PCR or culture (blood, CSF, urine, pharyngeal swabs).
6. Follow-up with paediatrician to identify delayed-onset abnormalities or progressive disorders.
7. Hearing screening test and follow-up with ENT specialist if any abnormalities.
8. Ophthalmologic evaluation and follow-up.
9. Paediatric cardiologist evaluation and follow-up.
10. Paediatric neurologist evaluation and follow-up.
11. Treatment: no specific treatment available. Prevention with immunisation.
12. Breastfeeding is not encouraged since vaccine-strain virus may be shed in breast milk and transmitted to breastfed infants, some of whom may develop chronic viraemia.
13. Cases should be reported to health authorities.

Note: Standard practice of obstetric care should include determination of maternal immunity by measuring rubella-specific IgG. If a woman exposed to rubella is known to be seropositive, she is immune, and the foetus is considered not to be at risk of infection.

All infants with CRS are considered contagious until at least 1 year of age, unless 2 cultures of clinical specimens obtained 1 month apart are negative for rubella virus after 3 months of age.

The onset of some of the abnormalities of CRS may be delayed months to years.

## Cytomegalovirus

CMV is the most common perinatal viral infection.

In utero transmission of Cytomegalovirus (CMV) can occur during primary maternal infection, reactivation, or reinfection of seropositive mother with a higher incidence during a primary maternal infection.



Maternal tests:

1. CMV specific IgG and IgM negative - no infection.
2. CMV specific IgG positive and IgM negative - past infection.
3. CMV specific IgG positive and IgM positive - present infection; IgG avidity test low - acute maternal CMV infection; high CMV viral load in maternal blood - acute maternal CMV infection.

Congenital symptomatic CMV disease present with *acute fulminant infection* with 30% mortality.

CLINICAL SIGNS (Figure 2)

1. petechiae or purpura (79%)
2. hepatosplenomegaly (74%)
3. jaundice (63%)
4. pneumonitis
5. "blueberry muffin spots"
6. elevated hepatic transaminases
7. conjugated hyperbilirubinemia
8. anemia
9. thrombocytopenia



Figure 2. Newborn with TORCH. Mother IgM+ for CMV.

Source: Constanza E, 2014; HUC, Caracas.

Other clinical manifestations of congenital CMV: (90% are mostly asymptomatic)

1. Prematurity
2. Small for gestational age
3. IUGR
4. Microcephaly
5. Lethargy/hypotonia
6. Poor sucking/feeding
7. Seizures
8. Sensorineural hearing loss
9. Haemolysis
10. Increased cerebrospinal fluid protein
11. Chorioretinitis

Note: The diagnosis of congenital CMV infection should be considered in

1. Any newborn with signs of congenital infection.
2. History of maternal seroconversion or a mononucleosis-like illness during pregnancy.
3. Any infant who fails a newborn hearing screening examination.

MANAGEMENT OF INFANT WITH CONGENITAL CMV:

1. Virus isolation in tissue culture (urine and/or saliva) at birth or in the first 2 weeks of life.



2. CMV DNA by PCR assay.
3. CMV IgG and IgM.
4. CBC and hepatic function tests.
5. Hearing screening test.
6. Ophthalmologic evaluation.
7. Transfontanelar ultrasound or cerebral CT (non contrast).
8. Isolation precautions should be instituted if symptomatic congenital CMV is suspected.
9. Some experts recommend to start treatment as soon as possible: (treatment and prophylaxis)

Ganciclovir: 6 mg/kg IV over 1 hr every 12 hours for 6 weeks or

Valganciclovir: 16 mg/kg oral every 12 hours for 6 months

If diagnosis is delayed, treatment can start up to the first month of life.

- Some experts recommend to request viral load (VL) before treating. VL < 5000 does not require treatment; treat only if the infant is symptomatic with VL > 1000.

#### FOLLOW UP

1. Annual follow-up for ophthalmologic evaluation.
2. Annual follow-up for hearing screening.
3. Follow-up with paediatrician to monitor neurodevelopmental milestones and sequelae.
4. Complications in infants include sensorineural hearing loss (35%), neurologic deficits (66%), and death (4%).

Note: BREASTFEEDING is encourage in term newborns although nearly 40% of all infants who have been breastfed for at least 1 month by CMV seropositive mothers become infected postnatally. Benefits outweigh the risk. AVOID BREASTFEEDING IN PRETERM NEONATES if mother is positive and baby is asymptomatic.

## Hepatitis B

The transmission of Hepatitis B virus (HBV) from infected mothers to their newborns is thought to result primarily from exposure to maternal blood at the time of delivery.

Note: Trans-placental transfer accounts for < 4% of all cases. The highest rate of viral transmission (90%) occurs from mothers who are both *HBsAg* (*Hepatitis B surface antigen*) and *HBeAg* (*Hepatitis B e-antigen*) positive compared to only 5% to 20% who are born to *HBsAg* positive but *HBeAg* negative. The risk of neonatal infection is greatest when maternal infection occurs during the third trimester.

An infant who has acquired HBV perinatally has a 90% risk of becoming a chronic carrier and a subsequent 15% to 20% chance of dying of chronic liver conditions in adulthood.

Postnatal intervention with hepatitis B immunoglobulin and birth-dose vaccination provides the susceptible infant an 85% to 95% chance of being protected.

Infants infected with HBV rarely show signs of disease at birth or in the neonatal period.

Recommendation: All pregnant women should be screened for *HBsAg* at the first prenatal visit, and at delivery if any other maternal risk factor for Hepatitis B infection is present.



WHO recommends that all infants receive the first dose (birth dose) of hepatitis B (HepB-BD) vaccine as MONOVALENT HEPATITIS B VACCINE as soon as possible after birth, preferably within 24 hours, to prevent mother-to-child (perinatal) HBV transmission.

#### MANAGEMENT OF INFANT WITH VERTICAL EXPOSURE TO HBV:

1. Know mother's serological status.
2. Newborns > 2000 g and < 2000 g of HBsAg positive mothers regardless of mother's HBeAg status:
  - a. Test infant at birth for HBsAg on peripheral blood.
  - b. Administer Hepatitis B vaccine within 12 hours or in the first 24 hours of birth: 0.5ml IM.
  - c. Administer Hepatitis B immunoglobulin (HBIG) within 12 hours of birth: 0.5ml IM (different site of vaccine). (HBIG is not acquired in Belize.)
  - d. If highly suspected due to suggestive clinical signs: CBC, hepatic function test.
3. See appendix H. Schedule for Immunisation of Preterm Infants
  - a. Complete the standard 3-dose Hepatitis B vaccine series for newborns > 2000 g.
  - b. Preterm infants < 2000 g require a subsequent 3-dose Hepatitis B vaccine series starting at 1 month of age for a total of 4.
4. The following are not contraindications to Hep B vaccination: prematurity, low birth weight, small for gestational age, HIV infection of mother or infant, and jaundice.
5. Follow-up testing of HBsAg and anti-HBs at 9-18 months (after completing Hepatitis B vaccine series).
6. Standard precautions for all infants i.e. wearing of gloves.
7. Breastfeeding is recommended with accompanying prophylaxis.

#### Note: BREASTFEEDING

There has been *no* documented increase in the risk of HBV transmission by breastfeeding mothers who are HBsAg positive despite HBsAg being detected in breast milk.

The risk of postnatal infection via breastfeeding is certain to be negligible in infants who have received HBIG and hepatitis vaccine.

Breastfeeding is still encouraged in settings where the infant receives Hepatitis B vaccine and HBIG is unavailable. The virus is not transmitted by breastfeeding.

Recommendation: Acquisition of HBIG for use in vertically exposed HBV infants should be considered by health authorities.



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# NEONATAL SEPSIS

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Is a Systemic Inflammatory Response Syndrome (SIRS) in the presence of or as a result of suspected or proven infection in the first 28 days of life. SIRS:  $\geq 2$  Fever/Hypothermia, Tachycardia, Tachypnea/hyperventilation, Leukocytosis/Leukopenia.

Neonatal sepsis is the third leading cause of neonatal mortality after intrapartum causes; prematurity is the leading cause of neonatal mortality.

## CLASSIFICATION ACCORDING TO ONSET OF CLINICAL MANIFESTATIONS:

### Early onset sepsis (EOS)

1. It presents within the first 72 hours of life although the most commonly used cutoff is less than 7 days.
2. In severe cases, the neonate may be symptomatic at birth.
3. Infants with EOS usually present with respiratory distress and pneumonia.
4. The source of infection is generally the maternal genital tract.

### Late onset sepsis (LOS)

1. It usually presents after 72 hours of age.
2. The source of infection in LOS is either nosocomial (hospital-acquired) or community-acquired.
3. Neonates usually present with septicaemia, pneumonia or meningitis.

## RISK FACTORS:

### EOS:

1. Maternal Group B streptococcal (GBS) colonisation
2. Chorioamnionitis/Fever
3. Premature rupture of membranes (>18 hrs)
4. Prematurity and low birth weight
5. Maternal urinary tract infection
6. Multiple pregnancies

### LOS

1. Breakage of natural barriers (skin and mucosa)
2. Prematurity and low birth weight
3. Delayed enteral feeding
4. Prolonged indwelling use of central line catheter, mechanical ventilation and parenteral nutrition
5. Invasive procedures (ie. endotracheal intubation)
6. Complications of prematurity i.e. Necrotising enterocolitis, PDA, BPD
7. Prolonged use of antibiotics
8. H2 receptor blocker or proton pump inhibitor use (should limit use)

Note: Prematurity increases the risk for both EOS and LOS due to decreased passage of maternal immunoglobulin and specific antibodies, and immature function of immune system.



Premature rupture of membranes (PROM) is when the amniotic sac ruptures more than 1 hour before the onset of labor.

Table 1. Organisms Associated With Early Onset And Late Onset Neonatal Sepsis

EOS	LOS
<i>Group B Streptococcus</i>	<i>Coagulase-negative Staphylococcus (CoNS)</i>
<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>
<i>Listeria monocytogenes</i>	Enterococci
Enterococci	Multidrug-resistant gram-negative rods ( <i>E coli</i> , <i>Klebsiella</i> , <i>Pseudomonas</i> , <i>Enterobacter</i> , <i>Citrobacter</i> , <i>Serratia</i> )
Other streptococci: <i>Streptococcus pyogenes</i> , <i>viridans</i> , <i>Candida pneumoniae</i>	
Nontypable <i>Haemophilus influenzae</i>	

In low-income settings EOS is predominantly caused by gram-negative organisms compared to GBS in developed settings.

Hospitals, especially nurseries and intensive care units, are high-risk environments for acquiring LOS infections.

#### CLINICAL SIGNS

Clinical signs are Non-specific. The earliest signs of sepsis are often subtle and nonspecific affecting many systems. Major clinical signs are in bold.

1. Hypothermia or fever (former is more common in preterm low birth weight infants)
2. Lethargy, poor cry, refusal to suck
3. Poor perfusion, pallor, prolonged capillary refill time
4. Brady/tachycardia
5. Apnoea, respiratory distress and gasping respiration
6. Hypotonia, absent neonatal reflexes
7. Hypo/hyperglycaemia
8. Metabolic acidosis

Other diagnoses to be considered in the immediate newborn period in the infant with signs of sepsis include:

1. transient tachypnea of the newborn
2. meconium aspiration syndrome
3. intracranial haemorrhage
4. congenital viral disease
5. congenital cyanotic heart disease
6. patent ductus arteriosus



7. bowel obstruction
8. necrotising enterocolitis (NEC)
9. inborn errors of metabolism

## MANAGEMENT OF NEONATAL SEPSIS

### Rule out sepsis - The Process

1. Identify the antenatal risk factors for sepsis.
2. Perform a careful physical examination and make an estimate of the probability of sepsis based on those signs & history.
3. Order the appropriate laboratory test and cultures.
4. Decide who needs antibiotics based on the above data.

Note: Identification of risk factors, physical exam and sepsis panel laboratory testing are of much value in ruling out sepsis.

### Laboratory work-up include

1. CBC with differential
  - a. Immature to total neutrophil ratio (I/T) > 0.2
  - b. Absolute Neutrophil Count (ANC) < 7500/mm<sup>3</sup>
  - c. Absolute Band Count (ABC) > 2000/mm<sup>3</sup>
  - d. Neutropenia: ANC < 8,000/mm<sup>3</sup> in a late preterm or term infant  
ANC < 2,200/mm<sup>3</sup> in a preterm infant
  - e. Thrombocytopenia: < 150,000/mm<sup>3</sup>
2. C-reactive protein (CRP): > 1 mg/dl (> 10 mg/L)
3. Procalcitonin (PCT): > 10 ng/ml (detectable 12 hours earlier than CRP and has a high negative predictive value for EOS)
4. Blood culture
5. Others according to clinical manifestation:
  - a. Glycaemia, Chest X-ray, ABG (metabolic acidosis), PT/PTT
  - b. LP for CSF cell count, protein and glucose concentration
  - c. CSF gram stain and culture
  - d. Swab of any suspicious lesion

### Note:

The WBC and ANC are most predictive of infection when these values were low (WBC <5,000 and ANC <1,000). The combination of low ANC and elevated I/T ratio is the most predictive combination of WBC indices for EOS.

Serial CRP determinations at the time of blood culture, 12 to 24 hours and 48 hours later, have been used to manage infants at risk for LOS. Some centres use serial CRP measurements to determine length of antibiotic treatment for infants with culture-negative clinical sepsis.

Neonates have a physiologic PCT rise to 10 ng/ml in the first 72 hours of life before it normalises to < 0.1 ng/ml.



Infants with respiratory symptoms should have a chest radiograph as well as other indicated evaluation such as arterial blood gas measurement.

Selective use of LP only when there is strong clinical suspicion for sepsis and/or specifically for meningitis and should be done before the administration of antibiotics if the infant is clinically stable. The LP may be deferred until after the institution of antibiotic therapy if the infant is clinically unstable, or if later culture results or clinical course demonstrates that sepsis was present.

Perform LPs only on (i) infants with positive blood cultures and (ii) symptomatic infants with a high risk for EOS whose condition is stable enough to tolerate LP and (iii) infants with negative blood cultures who are treated empirically for the clinical diagnosis of sepsis.

Urine cultures should be obtained by catheterisation or ultrasound-guided supra-pubic aspiration (SPA) in VLBW infants.

Remove indwelling catheters for all infections except CoNS (unless access is a major issue). Line removal should be a considered decision.

Diagnostic testing is recommended at 6-12 hours following birth since counts obtained immediately after birth are frequently normal.

Hemoculture remains as the gold standard.

Whenever possible 1 ml of blood sample should be cultured since up to 1/4 of infants with sepsis have low colony count bacteraemia.

Recommendation: Emphasis must be made by health authorities to have available CRP testing, and preliminary haemoculture results by 48 hours to avoid unnecessary exposure to antibiotics.

Figure 1. Proposed algorithm for neonatal sepsis management



Triple I - Intrauterine inflammation, infection or both is the terminology proposed by the expert panel to replace 'chorioamnionitis'.



## Antimicrobial Therapy

### *Empiric therapy:*

- EOS: Ampicillin + Aminoglycoside + \*(3rd Generation Cephalosporin)
- LOS: Vancomycin + Aminoglycoside + \* (3rd Generation Cephalosporin)

\*Suspected Gram negative meningitis

Note: LOS: Cloxacillin may be considered instead of Vancomycin (depending on susceptibility/resistance of CoNS).

Reserve use as last instance or if culture dictate: 4th Generation Cephalosporin or Meropenem + Vancomycin.

When culture results are available: Change to narrowest spectrum antibiotic, or stop antibiotics if negative cultures, CRP not raised and no clinical signs of infection.

Fluconazole prophylaxis: indicated in very preterm infants < 32 weeks GA with PNA > 7 days, infants with birthweight < 1200 g, infants with indwelling central line catheter, infants who receive steroid therapy and post-gut surgery.

Fluconazole prophylaxis: 6mg/kg/dose every 72 hours IV/oral for 4-6 weeks.

### *Duration of antibiotic therapy in neonatal sepsis based on clinical presentation:*

1. EOS without meningitis: treat for 7-10 days
2. LOS without meningitis: treat for 10-14 days
3. Meningitis with EOS or LOS: treat for 14-21 days
4. Gram negative rod meningitis: treat for 21 days

### Note:

Babies with clinical signs of EOS (Early Onset Sepsis) should receive empiric antibiotic therapy.

Ampicillin and an aminoglycoside remain the empiric therapy.

Asymptomatic late preterm infants and term infants, with risk factors for sepsis (including chorioamnionitis/triple I) can be closely observed without empiric therapy and discharged by 48 hours.

Universal GBS screening is recommended in women at 35 to 37 weeks of gestation through a rectovaginal swab followed by intrapartum antibiotic prophylaxis (IAP) in those with positive cultures.

GBS bacteriuria or previous delivery of an infant with invasive GBS always requires IAP.

Adequate GBS prophylaxis: Penicillin G, Ampicillin, or Cefazolin given  $\geq$  to 4 hours prior to delivery.

Because of the high negative predictive accuracy of screening laboratory studies, diagnostic testing may be of value in deciding which infants need antibiotics and when antibiotics can be safely discontinued.

Whenever possible, antibiotics should be stopped by 48 hours if the cultures are negative and the infant remains asymptomatic.

Antibiotics should be continued for 7-10 days in any critically ill infant.

Third generation cephalosporins should be used judiciously.

Do not use Ceftriaxone in neonates since it competes with bilirubin in albumin binding sites.



In many low-resource settings, the WHO now recommends that possible serious bacterial infections (PSBI) in neonates be treated with intramuscular gentamicin with oral amoxicillin at first-level care facilities by a trained health worker.

Most antimicrobial resistance (AMR) occur in low- and middle-income countries (LMIC) where data on etiologic organisms is scarce and indiscriminate use of antimicrobials is high.

Table 2. Evidence of strategies for prevention of Neonatal Sepsis

Evidence of strategies for prevention of neonatal sepsis	
Prevention Strategy	Notes
Lactoferrin	Small studies show reduction of both fungal and bacterial infection; large studies needed.
Intravenous immunoglobulin	No proven efficacy for prevention of neonatal sepsis.
Antistaphylococcal monoclonal antibodies	Monoclonal antibodies against capsular polysaccharide and clumping Factor A have shown no effect in prevention of sepsis. Antilipoteichoic acid antibodies may have an effect but further randomized controlled studies are required.
Probiotics	No proven efficacy for neonatal sepsis. Useful as prevention of necrotizing enterocolitis.
GM-CSF/G-CSF	No proven efficacy of neonatal sepsis.
Glutamine	No proven efficacy of neonatal sepsis.
Fluconazole	Efficacious in prevention of <i>Candida</i> sepsis in VLBW infants.

**Abbreviations:** G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; VLBW, very low birth weight.

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### PERINATAL ASPHYXIA AND HYPOXIC ISCHAEMIC ENCEPHALOPATHY (HIE)

Perinatal asphyxia refers to a condition during the first and second stage of labor in which an interrupted supply of oxygen through the placenta and umbilical cord to the foetus leads to foetal acidosis, hypoxaemia, and hypercarbia.

Asphyxia can also occur in the postpartum period, usually secondary to pulmonary, cardiovascular, or neurologic abnormalities.

HIE describes an abnormal neurologic behaviour in the neonatal period following perinatal hypoxia-ischaemia.

#### RISK FACTORS OF PERINATAL ASPHYXIA LEADING TO FOETAL DISTRESS:

1. Impairment of maternal oxygenation.
2. Decreased blood flow from mother to placenta.
3. Decreased blood flow from placenta to foetus.
4. Impaired gas exchange across the placenta or at the foetal tissue level.
5. Increased foetal O<sub>2</sub> requirement.

#### CAUSES OF FOETAL HYPOXIC-ISCHAEMIC INSULT

1. Maternal
  - a. Cardiac arrest
  - b. Asphyxiation
  - c. Severe anaphylactoid reaction
  - d. Status epilepticus
  - e. Hypovolemic shock
2. Utero-placental
  - a. Placental abruption
  - b. Cord prolapse
  - c. Uterine rupture
  - d. Hyper-stimulation with oxytocic agents
3. Fetal
  - a. Feto-maternal haemorrhage
  - b. Twin-to-twin transfusion syndrome
  - c. Severe iso-immune haemolytic disease
  - d. Cardiac arrhythmia and severe cardiac/circulatory insufficiency
  - e. Anaemia



## NEONATAL CAUSES OF POSTNATAL HIE

1. Cyanotic congenital heart disease
2. Persistent pulmonary hypertension of the newborn (PPHN)
3. Cardiomyopathy, other forms of neonatal cardiogenic and/or septic shock
4. Meconium aspiration syndrome
5. Neonatal pneumonia
6. Pneumothorax

## PATHOPHYSIOLOGY

Effect of hypothermia on the hypoxic- ischaemic cascade of events.

1. Acute phase: minutes-hours - Free radicals and mitochondrial damage
2. Subacute phase: hours - days - Apoptosis and Inflammation
3. Chronic phase: weeks - months - Angiogenesis and remodelling

## DIAGNOSIS

The following must be present for the designation of perinatal asphyxia or HIE:

1. Presence or history of risk factors.
2. Severe metabolic or mixed acidosis ( $\text{pH} \leq 7.0$  or base deficit  $\geq 16$  mmol/L) in the first umbilical artery blood sample or first blood ABG.

AND/OR

Persistence of an Apgar score  $\leq 3$  at  $\geq 10$  minutes (required advance CPR).

3. Neonatal neurologic abnormalities (decreased level of alertness, seizures, hypotonia).
4. Multiple organ involvement (kidney, lungs, liver, heart, intestines). (This criteria is not mandatory to establish HIE since these infants will often present multi-organ dysfunction.)

## CLINICAL PRESENTATION OF HIE: (Table 1)

1. Abnormal consciousness: mild, moderate, or severe. Severe abnormal consciousness points out severe hypoxic-ischaemic encephalopathy. Lethargic or stuporous level of alertness points out moderate HIE.
2. Seizures within 12 to 24 hours of birth (indicate moderate or severe encephalopathy).
3. Burst suppression or suppressed background pattern on EEG or amplitude-integrated electroencephalogram (aEEG).
4. Abnormal or absent brainstem reflexes.
5. Weak or absent suck and swallow with poor feeding.
6. Apnoea or abnormal respiratory patterns.
7. Severe cases: hypotonia, weakness, and abnormal posture with lack of flexor tone.

Note: EEG remains the gold standard for diagnosing neonatal seizures, particularly in HIE.

In general, the more severe or prolonged the hypoxia-ischaemia, the more seizure activity the infant will have.





Table 1. Modified Sarnat for severity of Hypoxic Ischaemic Encephalopathy.

	MILD	MODERATE	SEVERE
Level of consciousness (LOC)	Hyperalert or irritable	Lethargic or poorly responsive	Minimal or no responsiveness
Spontaneous Activity	Slightly decreased	Decreased	Absent
Posture	Mild distal flexion	Distal flexion, complete extension	Decerebrate
Tone	Hypertonic	Hypotonic	Flaccid
Primitive Reflexes			
Suck	N/A	Weak or bites	Absent
Moro	Low threshold to elicit	Weak or incomplete	Absent
Autonomic System			
Pupils	N/A	Constricted	Dilated and fixed/ sluggish; asymmetric
Respiration	N/A	Periodic breathing	Intubated and ventilated

Severity = 3 or more present in a category; LOC breaks ties. N/A: not altered.

#### MULTI-ORGAN DYSFUNCTION

1. Cardiac: transient myocardial ischemia
2. Kidney: acute tubular necrosis (ATN) with oliguria and a rise in serum creatinine (Cr)
3. Haematologic: disseminated intravascular coagulation (DIC), poor production of clotting factors due to liver dysfunction, and thrombocytopenia
4. Liver Dysfunction: elevation of hepatocellular enzymes, hypoglycaemia, slowed metabolism, or elimination of medications
5. Gastro-intestinal: necrotising enterocolitis

#### LABORATORY EVALUATION OF ASPHYXIA

1. CBC
2. PT/PTT
3. ABG and lactic acid
4. Glucose
5. Electrolytes Na, K, Cl
6. Calcium and magnesium
7. Serum creatine kinase myocardial bound - CK/CKMB (optional - low specificity; results does not alter management)
8. Blood Urea Nitrogen (BUN) and serum Creatinine
9. AST/ALT
10. Albumin



11. LDH (optional - low specificity; results does not alter management)
12. If oliguria or Syndrome of inappropriate antidiuretic hormone secretion (SIADH) - urine electrolyte and Cr to calculate Fractional excretion of Na<sup>+</sup> (FENa)

## IMAGING

1. Cerebral Ultrasound (CUS): oedema, intracranial haemorrhage (a contraindication to therapeutic hypothermia)
2. CT: indicated to establish the severity of brain injury after insult, only in case of non-availability of CUS or MRI. CT is not urgent for establishing treatment with therapeutic hypothermia.
3. MRI- Conventional T1- and T2-weighted sequences: Gold standard for the detection of brain injury at least after 7 to 10 days. At 14 days or older: shows full extent of the injury. MRI in the first days of life may be a useful prognostic tool for clinicians and convenient for important decision making in management.
4. Evoked Potentials: Brainstem auditory evoked potentials (BAEPs) or brainstem evoked response and visual evoked potentials (VEPs) are technically easier to perform than somatosensory evoked potentials (SEPs).

## MANAGEMENT

OBJECTIVE: to achieve an integral management of the following

1. multi-organic dysfunction
  2. co-morbidities
  3. systemic and metabolic effects of hypothermia
1. Prevention of foetal asphyxia is far preferable rather than managing the newborn who has suffered a hypoxic-ischaemic insult.
  2. The VII consensus SIBEN recommends initial resuscitation with ambient air to the asphyxiated infants who require PPV. Titration of O<sub>2</sub> should be done according to clinical response of SatO<sub>2</sub> by pulse oximetry. Oxygen administered should be warmed, humidified and mixed, and FIO<sub>2</sub> monitored with a blender.
  3. Infants with diagnosis of HIE should be immediately transferred to a referring centre.
  4. Temperature: Passive cooling by turning off warming lights is an effective way to initiate therapeutic hypothermia (TH) as soon as possible after the HI insult once infant is stabilised and close monitoring is guaranteed.
  5. Passive hypothermia during transfer seems safe and efficient once close monitoring occurs.
  6. Hyperthermia should always be avoided.
  7. Ventilation: maintain normal ranges of O<sub>2</sub> and CO<sub>2</sub>. Avoid hypercapnia and hypocapnia (CO<sub>2</sub> < 25 mmHg). ABG and serum lactate should be monitored at baseline and then at 4, 8, 12, 24, 48, and 72 hours of TH treatment and as clinically indicated.
  8. Perfusion: maintain normal ranges of mean arterial pressure (MAP) ≥ 40 mmHg.
 

Dopamine IV: 5 to 15µg/kg/minute
  9. Maintain physiologic metabolic state: correct Hypocalcaemia, hyponatraemia, hypoglycaemia and hypomagnesaemia.
 

To avoid fluid overload, as well as hypoglycaemia, concentrated glucose infusions delivered through a central line may be needed.

Glucose levels should be monitored closely and rapid glucose boluses avoided.
  10. Gastro intestinal. Feeding should be withheld until BP is stable, active bowel sounds are audible, and stools are negative for blood. Parenteral nutrition should start as soon as possible.



11. Liver and renal function test should be monitored at baseline, and then at 24, 48, and 72 hours of treatment, and as clinically indicated.
12. Infection: if present, antibiotics should be started after complete blood count (CBC) and blood culture drawn per routine.
13. Haematology: Monitor coagulation profile.
  - a. Partial thromboplastin time (PTT) and prothrombin time (PT), fibrinogen, and platelets.
  - b. Platelet count which should be kept  $>100,000/\mu\text{L}$  especially with TH.
  - c. Supportive treatment with platelets, vitamin K, or clotting factors.
  - d. Hypothermia has no effect on coagulation, but thrombocyte counts are lower during hypothermia.
14. Fluid management: overload and hypovolaemia should be avoided.
  - a. Two processes predispose to fluid overload in asphyxiated newborns:
    - (a) Acute Tubular Necrosis can result from the "diving reflex" and result in oliguria followed by polyuria.
    - (b) Syndrome of inappropriate antidiuretic hormone secretion (SIADH): hyponatraemia and serum hypo-osmolarity, low urine output, elevated urine specific gravity, urine osmolarity, and urine  $\text{Na}^+$ .
  - b. Oliguria: maintain adequate fluid balance with daily measurement of serum and urinary creatinine, serum and urinary electrolytes, serum and urine osmolarity, and urine specific gravity.
  - c. Oliguria or anuria: consider using low-dose dopamine infusion ( $\leq 2.5 \mu\text{g}/\text{kg}/\text{minute}$ ). If there is no or low urine output, a 10 to 20 mL/kg NSS bolus followed by furosemide may be helpful.
  - d. Daily assessment of the infant's weight.
  - e. Fluid restriction: Fluid intake should be titrated against measurements of the infant's serum and urinary electrolytes.
15. Neurology evaluation should be requested as soon as possible.

## 16. CONTROL OF SEIZURES

- a. Seizures generally start within 12 hours of birth, and seizures in HIE are often subclinical.
- b. If possible, an aEEG should be used to monitor seizures.
- c. Prophylactic use of phenobarbital for seizures is not recommended.

### PHARMACOLOGIC TREATMENT

#### First line treatment:

##### 1. Phenobarbital

- Loading dose: 20 mg/kg intravenous (IV) in 10 minutes
- If seizures continue, additional loading doses of 5 to 10 mg/kg IV in ten minutes may be given
- Maintenance dose: 3 to 5 mg/kg/day orally (PO) or IV every 12 hours should be started 12 to 24 hours after the loading dose.

#### Second line treatment:

##### 1. Levetiracetam (Keppra<sup>®</sup>) (preferred option)

- Loading dose: 20-40 mg/kg IV/PO



- Maintenance dose: 5-10 mg/kg/day every 12 hours; should be started 24 hours after loading dose. Maximum 60 mg/kg.
2. Phenytoin (usually added when seizures are not controlled by phenobarbital).
- Loading dose: 15 to 20 mg/kg IV
  - Maintenance dose: 4 to 8 mg/kg/day every 8 hours

Third line treatment:

1. Benzodiazepines
  - a. Diazepam: 0.25-0.5 mg/kg/dose IV; infusion: 0.7-2.7 mg/h
  - b. Lorazepam: 0.05 to 0.1 mg/kg/dose IV
  - c. Midazolam: 0.15 mg/kg/dose IV; infusion: 0.06-0.4 mg/kg/hr
2. Lidocaine
  - Loading dose: of 2mg/kg IV over 10 minutes
  - Maintenance dose: 6mg/kg/h IV
    - To be given after 24 hours followed by decreasing infusion rates every 12 hours of 6,4, and 2mg/kg/hr
    - keep serum lidocaine level below 9mg/L
    - to be discontinued within 48 hours to avoid cardiotoxicity

Long-term anticonvulsant management:

- Anticonvulsants can be weaned when the clinical exam ( $\geq 72$  hours seizure-free) and EEG indicate that the newborn is no longer having seizures. If a newborn is receiving more than one anticonvulsant, weaning should be in the reverse order of initiation, with phenobarbital being weaned last.

17. NEURO-PROTECTIVE STRATEGIES: Therapeutic Hypothermia (TH)

Note: Hypothermia is the only treatment currently shown to reduce death or disability after hypoxia-ischaemia in new-borns with moderate to severe encephalopathy in the first 6 hours after birth.

Body and head cooling have been shown to be safe and effective and are recommended for treating newborns with moderate to severe HIE.

Controlled passive whole body cooling by turning off the radiant warmer and external heating devices is effective in places where servo cooling is not possible once infant is stabilised and close monitoring is guaranteed.

In order not to delay the neuro-protection provided by cooling, it is recommended to begin this therapeutic intervention at the referring hospital before the transfer, by turning off the external sources of heat and keeping the infant cooled during transport.

Hypothermia without rigorous supervision and control can be dangerous and non-neuro-protective.

The ideal cooling system would rapidly induce hypothermia to the core target temperature. Servo-regulated cooling improves temperature regulation during transport. CritiCool™ Tecotherm™ Coolcap™

Arterial access and central venous access should be obtained prior to initiation of therapeutic hypothermia.

aEEG or, preferably, full EEG monitoring should be initiated on admission and continued through at least the first 24 hours, and the 12-hour rewarming period.



Cranial US should be obtained as soon as possible after therapeutic hypothermia is initiated to assess for intracranial haemorrhage.

Maintain sedation during treatment with low dose morphine or fentanyl. Midazolam is not recommended.

Cooling should be started before 6 hours of age.

The target core temperature goal during cooling is 33.5°C (33° to 34°C) with acceptable range: 32.5° to 34.5°C.

Core temperature should be monitored continuously and documented every 15 minutes until 1 hour after goal temperature of 33.5°C is achieved and then hourly.

Core temperature is often measured with an oesophageal temperature probe. Rectal temperature may be considered.

During rewarming procedure, core temperature should be monitored continuously and documented every hour.

At the end of 72 hours of induced hypothermia, the newborn is rewarmed at a rate of 0.5°C every 2 hours until patient reaches 36.5°C. This should take approximately 10 to 12 hours.

#### Inclusion criteria

1. Postmenstrual age (PMA)  $\geq$  35 weeks, BW  $\geq$  2,000 g.
  2. Evidence of foetal distress or neonatal distress as evidenced by one of the following:
    - a. History of acute perinatal event (e.g., placental abruption, cord prolapse, severe FHR abnormality).
    - b. pH  $\leq$  7.0 or base deficit  $\geq$  16 mmol/L in cord gas or postnatal blood gas obtained within first hour of life
- AND/OR
- b. Apgar score of  $\leq$  5 at 10-minutes.
    - c. Assisted ventilation initiated at birth and continued for at least 10 minutes.
  3. Evidence of moderate to severe neonatal encephalopathy by exam and/or aEEG.

#### Exclusion criteria

1. Presence of lethal chromosomal abnormality (i.e. trisomy 13 or 18).
  2. Presence of severe congenital anomalies (i.e. complex cyanotic congenital heart disease, major CNS anomaly).
  3. Symptomatic systemic congenital viral infection (i.e. hepatosplenomegaly, microcephaly).
  4. Symptomatic systemic congenital bacterial infection (i.e. meningitis, DIC).
  5. Significant bleeding diathesis.
  6. Major intracranial haemorrhage.
18. New agents such as erythropoietin, melatonin, xenon, and stem cells as neuro-protective agents are undergoing preliminary evaluation in Phase I/II trials.

#### OUTCOME IN PERINATAL ASPHYXIA

1. The overall mortality rate is approximately 20%.
2. Mortality and long-term morbidity are highest for seizures that begin within 12 hours of birth.
3. The frequency of neurodevelopmental sequelae in surviving newborns is approximately 30%.
4. The presence of seizures increases a newborn's risk of cerebral palsy (CP) 50- to 70-fold.



5. The risk of CP in survivors of perinatal asphyxia is 5% to 10% compared to 0.2% in the general population.
6. Most CP is not related to perinatal asphyxia, and most perinatal asphyxia does not cause CP.

#### PROGNOSTIC AND PREDICTIVE VALUE OF STUDIES:

1. Baby with a severe encephalopathy at 6 hours of life (enrolling to therapeutic hypothermia) indicates that the infant has a risk of death or disability of about 60%.
2. A severe altered aEEG background at 48 hours in infants receiving therapeutic hypothermia has a positive predictive capacity of death or moderate/severe disability of 97% (82-100%).
3. For infants with severe HIE not treated with TH and those treated with TH, the positive predictive capacity of death or moderate/severe disability of an altered cerebral MRI in the first week of life is 84-86% respectively, and at 8 - 30 days of life 88 - 73% respectively.

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# NEONATAL SEIZURES

An epileptic seizure is a change in neurologic function (motor, sensory, experiential, or autonomic) that is associated with an abnormal synchronous discharge of cortical neurons.

## CLASSIFICATION

Table 1. Types of neonatal seizures.

Type	Frequency	Clinical signs	EEG findings
Subtle	50%	Eyelid fluttering, eye deviation, staring, blinking, cycling, boxing, mouthing, chewing, lip smacking, smiling, apnoea	Variable correlation. Most likely if ocular signs present
Clonic	25-50%	Repetitive jerking. Unifocal or multifocal	Correlation high, especially if unifocal
Myoclonic	15-20%	Jerking in the flexor muscle groups	Strong association unless benign sleep myoclonus
Tonic	5%	Stiffening & posturing of limbs/ trunk. Deviation of head or eyes	Variable correlation

1. Clonic seizures: characterised by focal rhythmic jerking of one or more extremities which is not suppressible.
2. Tonic seizures: sustained extension of an extremity that cannot be overcome by an examiner.
3. Myoclonic seizures: characteristically involve a rapid jerk of an extremity.
4. Subtle seizures: movements such as nystagmus, tongue thrusting, and bicycling.

Seizures accompanied solely by autonomic changes (such as change in heart rate, oxygenation, and respiration) are rare, but are more common in preterm than term neonates.

## AETIOLOGIES OF NEONATAL SEIZURES:

### 1. Hypoxic Ischaemic Encephalopathy

- The most common cause of neonatal seizures, accounting for 50% to 75% of cases
- Usually seen within the first 12 to 24 hours
- In the absence of clinical seizures, prophylactic treatment with phenobarbital is not recommended.

#### ▶ Perinatal Asphyxia

### 2. Focal Infarction

- the second most common cause of neonatal seizures, accounting for up to 20% of cases

#### a. Arterial

#### b. Venous

### 3. Intracranial Haemorrhage

- accounts for 10% to 15% of neonatal seizures



- preterm infants: usually germinal matrix, intra-ventricular, and parenchymal haemorrhages
  - a. Intra-ventricular
  - b. Periventricular
  - c. Parenchymal
  - d. Subdural
  - e. Subarachnoid
4. CNS infection - accounts for about 5% of neonatal seizures
- a. TORCH
  - b. Postnatal infection
5. Cerebral malformations and structural lesions
- seizures appear from the first day of life
  - cerebral dysgenesis accounts for 5% of cases
  - a. Periventricular leukomalacia
  - b. Cerebral dysgenesis
6. Acute metabolic disorders - accounts for approximately 5% of neonatal seizures
- a. Hypoglycaemia
  - b. Hypocalcaemia
  - c. Hypomagnesaemia
  - d. Hyponatraemia
7. Inborn errors of metabolism (IEM)
- 1% of cases of seizures in the newborn
  - typically caused by an enzyme defect in the metabolic pathways of carbohydrates, proteins, or fat
  - seizures appear after 2 to 3 days
  - a. Pyridoxine dependency
  - b. Pyridoxal phosphate dependency
  - c. Folinic acid responsive seizures
  - d. Serine deficiency
  - e. Glucose transporter 1 deficiency
  - f. Biotinidase deficiency
  - g. Creatine deficiency (GAMT)
  - h. Untreated phenylketonuria
8. Epilepsy syndromes - accounts for about 1% of cases
- a. Benign familial syndromes - occur in otherwise well infants on day 2 or 3 of life





- b. Severe neonatal epileptic encephalopathies - (Ohtahara, Early myoclonic epilepsy (EME), early infantile epileptic encephalopathy (EIEE))

## 9. Withdrawal and Intoxication

- newborns born to mothers who engaged in prenatal substance use or abuse

## DIFFERENTIAL DIAGNOSIS

1. Jitteriness: tremulous, jerky, stimulus- provoked and ceasing with passive flexion.
2. Benign sleep myoclonus: focal or generalised, myoclonic limb jerks that do not involve face, occurring when the child is going to or waking up from sleep; EEG normal; resolves by 4–6 months of age.

## MANAGEMENT

1. Resuscitation and stabilisation must be the priority.
2. Obtain a full perinatal history.
3. Comprehensive physical examination.
4. Essential investigations: (according to clinical suspicion)
  - a. Rule out metabolic and electrolyte imbalances.
  - b. Rule out infection (If present, treat with appropriate antibiotic).
  - c. Rule out intracranial haemorrhage.
  - d. Rule out IEM.
  - e. Rule out congenital CNS malformation.
  - f. Laboratories/other studies:
    - Complete blood count
    - Blood glucose
    - Electrolytes: Sodium, potassium, chloride
    - Serum urea and creatinine, calcium, magnesium, and phosphorus
    - ammonia
    - lactate
    - Blood gas
    - Blood culture
    - acute phase reactants: CRP, erythrocyte sedimentation rate (ESR)
    - Lumbar puncture and CSF culture
    - Cranial ultrasound
    - Metabolic screen: suspect if persistent metabolic acidosis on blood gas; serum and urine organic acid and amino acid determination, and guanidinoacetate in urine
    - Urine for toxicology
    - Virology specimens
5. Commence cerebral function monitoring - Electroencephalogram (EEG).



- a. Continuous EEG monitoring is considered the gold standard in detecting neonatal seizures.
- b. Many neonatal intensive care units rely on both routine EEG and amplitude-integrated electroencephalogram (aiEEG) to evaluate cerebral function in neonates.
- c. aiEEG is a bedside technique increasingly being used by neonatologists for neuro-monitoring.
- d. All electrical seizures should be treated if they are repeated, or when they occur in a context of encephalopathy of any origin, even in the absence of clinically apparent seizures.
- e. All clinical seizures in the neonatal period should be confirmed by EEG.

Monitoring: minimum duration of 24 hours in high-risk infants to screen for seizures, and continued until 24 hours free from seizures.

## PHARMACOLOGIC THERAPY

Treat underlying cause first before considering anti-epileptic drug therapy.

Some newborns may not need treatment with anticonvulsant medication; those with seizures due to reversible and appropriately treated metabolic and electrolyte imbalances.

1. Severe hypoglycaemia: IV administration of 2mL/kg of a 10% dextrose solution followed by an infusion of approximately 8 to 10mg/kg/minute.
2. Hypocalcaemia-induced seizures: IV infusion of 200mg/kg of calcium gluconate 10%.
3. Hypomagnesaemia may accompany hypocalcaemia: 0.2mg/kg of magnesium sulfate IM.
4. Pyridoxine dependency: 50 to 500mg of pyridoxine during a seizure (with coincident EEG monitoring).

Daily dose of pyridoxine: 50 to 100mg IV

Anti-epileptic drug (AED) therapy (*See Appendix P. Neonatal Seizure Management Algorithm*)

Start anticonvulsant drugs when seizure is:

1. prolonged: >2–3 min
2. frequent: >2–3/hr

First line treatment:

1. Phenobarbital - (therapeutic levels: 10 to 40mg/mL)
  - Loading dose: 20 mg/kg intravenous (IV) in 10 minutes
  - If seizures continue, additional loading doses of 5 to 10 mg/kg IV in ten minutes may be given.
  - Maintenance dose: 3 to 5 mg/kg/day orally (PO) or IV every 12 hours; should be started 12 to 24 hours after the loading dose.

Second line treatment:

1. Levetiracetam (Keppra<sup>®</sup>) (preferred option)
  - Loading dose: 20-40 mg/kg IV
  - Maintenance dose: 5-10 mg/kg/day every 12 hours; should be started 24 hours after loading dose. Maximum 60mg/kg.
2. Phenytoin
  - Loading dose: 15 to 20 mg/kg IV
  - Maintenance dose: 4 to 8 mg/kg/day every 8 hours



### Third line treatment:

1. Benzodiazepines
  - a. Diazepam: 0.25-0.5 mg/kg/dose IV; infusion: 0.7-2.7 mg/h
  - b. Lorazepam: 0.05 to 0.1 mg/kg/dose IV
  - c. Midazolam: 0.15 mg/kg/dose IV; infusion: 0.06-0.4 mg/kg/hr
2. Lidocaine
  - Loading dose: of 2mg/kg IV over 10 minutes
  - Maintenance dose: 6mg/kg/h IV
    - To be given after 24 hours followed by decreasing infusion rates every 12 hours of 6,4, and 2mg/kg/hr
    - keep serum lidocaine level below 9mg/L
    - to be discontinued within 48 hours to avoid cardiotoxicity

### LONG-TERM ANTICONVULSANT MANAGEMENT:

Anticonvulsants can be weaned when the clinical exam and EEG indicate that the newborn is no longer having seizures for > 72 hours. If a newborn is receiving more than one anticonvulsant, weaning should be in the reverse order of initiation, with phenobarbital being weaned last.

### FOLLOW-UP

1. Follow-up will depend on cause of seizures and response to treatment.
2. Consider: specialist follow-up for babies discharged on anticonvulsant drugs or as per local unit guideline.
3. Consultation and follow-up with paediatric neurologist.

### PROGNOSIS:

Useful clinical indicators for a good outcome include:

1. normal neonatal neurologic exam
2. normal or mildly abnormal neonatal EEG background activity
3. normal neuroimaging or abnormalities limited to extra-parenchymal injury

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### DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) results from a developmental defect during the formation of the diaphragm that allows for the herniation of abdominal contents into the thoracic cavity.

Note: CDH occurs mostly on the left side (85%), with the defect in the diaphragm being posterior (foramen of Bochdalek).

50% are associated with other malformations (cardiac, neural tube, intestinal, skeletal, and renal defects), chromosomal disorders, and syndromes.

Severity of CDH is related mostly to the degree of lung hypoplasia, which depends on the size of the defect, the presence of the liver in the chest, and how early in gestation the abdominal contents were displaced.

#### PATHOPHYSIOLOGY

CDH → pulmonary hypoplasia → pulmonary insufficiency and persistent pulmonary hypertension of the newborn (PPHN) → right to left shunting.

#### DIAGNOSIS

##### *Prenatal diagnosis*

1. CDH can be diagnosed at the routine 16th week prenatal ultrasound.
2. Presence of polyhydramnios.
3. Assessment of severity: Lung-to-head ratio (LHR): < 1 has 0% survival rate and >1.4 has a 100% survival rate.

##### *Postnatal diagnosis*

1. Clinical:
  - a. Inspection: presence of severe respiratory distress, cyanosis, scaphoid abdomen, and failure to improve with ventilation.
  - b. Auscultation: absence of breath sounds on the affected side with displacement of heart sounds to the contralateral side, and occasionally bowel sounds can be heard over the thorax.
  - c. 5% are minimally symptomatic or asymptomatic at birth.
2. Diagnostic
  - a. Confirmed by thoraco-abdominal radiograph
  - b. Chest radiograph: bowel loops in the affected chest cavity with shifting of the heart to the contralateral side. (Figures 1, 2)

#### DIFFERENTIAL DIAGNOSIS

Diaphragmatic eventration, congenital cystic adenomatoid malformation (CCAM), pulmonary sequestration, bronchogenic cyst.



Figure 1. Left CDH.

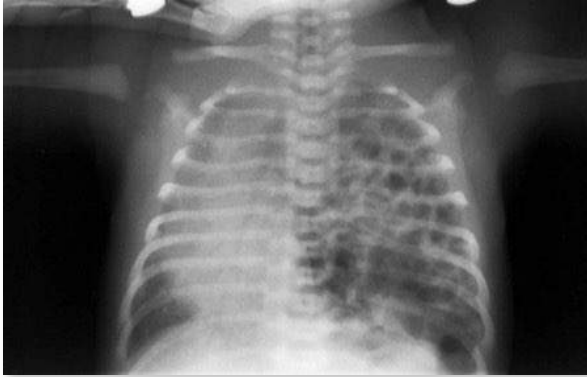


Figure 2. Left CDH with right pneumothorax.  
Source: Constanza E, 2013; HUC, Caracas.



## MANAGEMENT

Note: Severe cases that have been diagnosed before birth may be best managed with delivery by the ex-utero intrapartum treatment (EXIT) procedure.

Bag-and-mask ventilation is contraindicated.

Nasal CPAP is contraindicated.

Aggressive ventilatory strategies should be avoided.

Surgical repair is contraindicated until infant is stable for at least 24 hours:

- $FiO_2 < 0.50$  with  $SpO_2 \geq 92\%$
- $MAP < 16$  cm H<sub>2</sub>O
- $PaCO_2 < 55$  mm Hg

### Pre-operative Care

1. Immediately intubated infant and place an orogastric tube to evacuate the stomach.
2. Monitor vital signs.
3. Central lines
  - ▶ Placement of arterial catheter, ideally a right radial arterial catheter, and a percutaneous central venous access may be considered as first choice to umbilical lines. (Samples obtained from sites other than the right arm will be affected by right to left shunting.)
4. Ventilatory support
  - a. Use preferably pressure support: assist-control, time-cycled, pressure-limited ventilation.
  - b. Ventilator settings:
    - (a) PEEP: 4 - 6 cm H<sub>2</sub>O
    - (b) PIP: < 25 cm H<sub>2</sub>O (low PIP to minimise lung injury)
    - (c)  $FiO_2$ : goal < 0.50



- (d) MAP: < 12 cm H<sub>2</sub>O
  - (e) RR: 40-60 x'
  - (f) Ti: 0.30 seconds
- c. Acceptable ABG (as long as there is evidence of adequate tissue perfusion and oxygenation):
    - (a) pre-ductal saturations ≥ 85% (regardless of post-ductal saturation)
    - (b) PaCO<sub>2</sub>: 45 - 65 mmHg
    - (c) pH of ≥ 7.25
  - d. Permissive hypercapnia is the preferred respiratory approach.
  - e. Avoidance of hypoxia and acidosis will aid in minimising pulmonary hypertension.
  - f. High-frequency oscillatory ventilation (HFOV) is an alternative respiratory support if severe respiratory or metabolic acidosis persist despite PIP ≥ 30 cmH<sub>2</sub>O, or hypoxaemia persist despite FIO<sub>2</sub> of 1.
  - g. HFOV is used by some as the primary mode of ventilation.
  - h. The role of exogenous surfactant remains controversial.
5. Sedation
    - a. Heavy sedation should be avoided as spontaneous respiratory effort enables the use of the pressure support mode of ventilation which have been found to induce the least barotrauma.
    - b. Use intermittent low dose sedation. Fentanyl 1-2 mcg/kg and midazolam 0.1 mg/kg.
    - c. Do not use midazolam for infants < 35 weeks.
    - d. Avoid neuromuscular blockade.
  6. Cardiopulmonary support
    - a. Use dopamine infusion to treat hypotension or right ventricular dysfunction.
    - b. Use low dose epinephrine to treat right ventricular dysfunction.
    - c. Administer 5- 10 ml/kg boluses of normal saline to treat hypotension.
    - d. If ductus is restrictive use prostaglandin 1 infusion to improve ductal potency and prevent over distension of the right side of the heart.
    - e. Administer pulmonary vasodilators i.e. Sildenafil for PPHN.
    - f. Losses that exceed 10ml/kg every 12 hours via nasogastric tube should be replaced.
  7. TPN should be initiated preferably on the second day of life.
  8. Empiric antibiotic therapy with ampicillin and gentamicin should be considered.
  9. Control CBC, electrolytes, BUN and creatinine should be obtained.
  10. If dysmorphic features or other anomalies are present, consider obtaining a sample of blood for chromosomal analysis (if possible) before red blood cell transfusion.
  11. Head, heart and abdominal ultrasound should be done to rule out other malformation.
  12. Extracorporeal membrane oxygenation (ECMO) as rescue therapy is indicated in persistent oxygenation index (OI) greater than 40, persistent hypoxaemia (pre-ductal PaO<sub>2</sub> < 50 mmHg), hypotension (MAP < 35mm Hg) or failure of ventilatory management to support oxygenation, ventilation, or tissue perfusion.



### *Surgical Strategies*

1. Delayed surgical repair strategy until physiologic stabilisation and improvement of PPHN.
2. Severity and location of hernia is evaluated intra-operatively.
3. Surgical repair is through either the abdomen or the chest, with reduction of intestine into the abdominal cavity.
  - a. Primary repair: for small CDH and adequate muscle tissue.
  - b. Patch repair: for large CDH. (Synthetic biocompatible material is used)
  - c. Muscle flap repair: use of the Internal oblique or Latissimus dorsi muscle.
  - d. Thoracoscopic approach: for selective cases.

### *Post-operative Care*

1. Ventilation: Immediate post operative period
  - a. Controlled ventilation mode while still under the effects of anaesthesia and neuromuscular blockade.
  - b. As soon as an infant recovers spontaneous respiration, synchronised assisted ventilation mode should be set.
  - c. If a chest tube has been placed during surgery, it is placed to water seal or to a very low level of suction - 5 cmH<sub>2</sub>O.
  - d. Over time, the pneumothorax is gradually replaced with fluid and progressive expansion of the hypoplastic lung occurs.
  - e. The mediastinal structures do not immediately return to the midline after reduction of the intra-thoracic intestines.
  - f. Chylothorax occurs in up to 20% of newborns following repair and may be an indication for chest tube if not previously placed during surgery.
2. Nutrition
  - a. Total parenteral nutrition should continue.
  - b. Enteral trophic feedings are delayed until bowel function has clearly been established with minimal nasogastric drainage, presence of bowel sounds, and passage of stool.
  - c. Trans-pyloric tube is placed if GER occurs. Continuous feeds are initiated at 1 ml/kg/h and advanced as tolerated.

3. Monitor urine output and fluids closely.

4. Monitor CBC, glucose, calcium, electrolytes, renal and hepatic function.

Weaning from mechanical ventilation may occur over days or weeks until adequate gas exchange occurs with FIO<sub>2</sub> < 0.4 and PIP < 16 with PEEP 3-4 cm H<sub>2</sub>O.

Following extubation, high caloric intake will be required. Aim 180 kcal/kg/d.

### COMPLICATIONS

1. Gastro-oesophageal reflux disease (GERD), sometimes in combination with failure to thrive.
2. Chronic lung disease. (Indication for Palivizumab - Synagis vaccine.)
3. Mortality from CDH is largely related to presence of pneumothorax, and associated defects, especially pulmonary hypoplasia and congenital heart disease.
4. Recurrence of the hernia.



5. Factors associated with better prognosis include herniation of bowel into chest after second trimester, absence of liver herniation, and absence of coexisting anomalies, especially cardiac.

#### FOLLOW UP

Requires a multidisciplinary team approach in the postoperative management and follow-up of all survivors.

Monitor nutritional, developmental and neurological status.

#### Further reading:

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# OESOPHAGEAL ATRESIA AND TRACHEO-OESOPHAGEAL FISTULA (OA/TOF)

OA/TOF is a congenital anomaly with blind ending oesophagus which may be associated with a fistula between the abnormal oesophagus and the trachea.

Note: 85% of infants with OA also have TOF.

Approximately 7% of affected infants have a chromosomal abnormality such as trisomy 13, 18, or 21.

70% of cases are related to the VACTERL association (vertebral, anorectal, cardiac, tracheal, oesophageal, renal/genitourinary, and limb structures), and CHARGE syndrome (coloboma, heart defects, atresia choanae, retarded development, genital hypoplasia, ear defects/deafness).

OA/TOF includes five well-recognised variants.

The most common variant is the combination of a proximal oesophageal atresia and a distal tracheo-oesophageal fistula in about 85% of affected patients. (Figure 1. A)

The next two most common variants are isolated OA and isolated TOF, both of which occur in approximately 10% and 5% of patients respectively. (Figures 1 B,C)

H-type fistula, the rarest variants, include the proximal fistula/distal atresia, and the double fistula, both occurring in no more than 2% and 1% of patients respectively. (Figures 1 D,E)

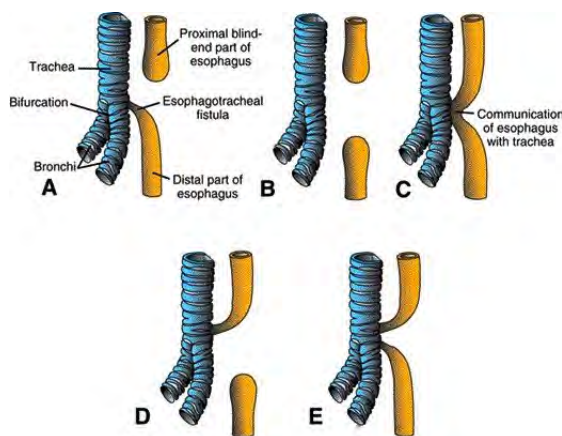


Figure 1. Five Variants of OA/TOF

A:85% B:10% C:5% D:2% E:<1%

## DIAGNOSIS

### Prenatal

- ▶ History of maternal polyhydramnios and a small or absent stomach.

### Postnatal

- ▶ OA itself is diagnosed by the inability to pass a catheter from the mouth or nose into the stomach.
- ▶ Presentation depends on the presence or absence as well as location of a TOF.
- ▶ The presence of gas within the gastrointestinal tract distinguishes TOF from isolated OA.

## CLINICAL MANIFESTATION

1. Excessive salivation and vomiting soon after feedings.
2. Respiratory distress due to the following:
  - a. Airway obstruction by excess secretions.



- b. Aspiration of saliva and milk.
- c. Compromised pulmonary capacity due to diaphragmatic elevation secondary to abdominal distension.
- d. Reflux of gastric contents up the distal oesophagus into the lungs through the fistula.

If there is no fistula, or if it connects the trachea to the oesophagus proximal to the atresia, no GI gas will be seen on x-ray examination, and the abdomen will be scaphoid. (Figure 2)

Figure 2. X-ray of a pure OA.



In patients with a distal fistula, the stomach may dilate with air, leading to the reflux of gastric secretions back into the lungs, resulting in significant and progressive respiratory distress caused by reactive bronchoconstriction and chemical pneumonitis. (Figure 3)

Figure 3. X-ray of OA with distal TOF.



TOF without OA (H-type fistula) is extremely rare and usually presents after the neonatal period.

- ▶ The diagnosis of TOF without OA is suggested by a history of frequent pneumonias or respiratory distress temporally related to feedings.

## MANAGEMENT

### Pre-operative Care

Objective: to minimise the risk of aspiration, to avoid gaseous distension of the GI tract with positive pressure crossing from the trachea into the oesophagus, and to define associated anomalies.

1. Keep nil-per-Os (NPO).
2. Insert a multiple end-hole suction 10 Fr. catheter (Reprogle (Figure 4) or Vygon) in the proximal oesophageal pouch and put to continuous suction using low pressure.
  - ▶ If Reprogle tube is unavailable, place a 10 Fr NG tube into pouch, aspirating every 15 min.
3. Place infant in semi-fowler position (head at 30° angle).
4. Obtain IV access.
5. Start maintenance of IV fluids.
6. Proton pump inhibitor for acid blockade is indicated.
7. Broad-spectrum antibiotics may be considered. (Ampicillin and gentamicin)
8. Mechanical ventilation (MV) of these babies should be avoided until the fistula is controlled.
  - ▶ If the infant needs to be intubated, position the endotracheal tube just above the level of the carina to bypass the fistula.
  - ▶ If required, use relatively high rate and low pressure to minimise GI distention.
9. Heavy sedation should be avoided.
10. Take blood sample for CBC, coagulation profile, blood glucose, BUN, creatinine, electrolytes, crossmatch, blood culture and arterial blood gas.
11. A thorough evaluation for other VACTERL - associated defects is necessary.
12. Request cardiology evaluation for echocardiogram in all patients.
13. Request renal ultrasound in patients with inadequate urine output.
14. Consult and discuss with paediatric surgery.

Figure 4. Reprogle tube



Note: In premature infants mechanical ventilation and nutritional management may be difficult because of the TOF. These patients need careful nursing care to prevent aspiration. Infants with pure EA would need gastrostomy with G-tube feedings to allow growth until repair is possible.

### Surgical Strategies

Surgical therapy usually involves *immediate* placement of a gastrostomy tube (GT) for feeding, and/or gastric decompression in patients that need ventilation and have an excessive amount of air passing into the stomach via the fistula.

Strategies include:

1. Immediate primary repair
2. Delayed primary repair



3. Staged repair
  4. Oesophageal replacement via thoracotomy.
- ▶ Thoracoscopic repair of OA/TOF has been shown to be equally effective to the open approach but is more challenging.

*Immediate primary repair* is appropriate for the majority of infants with OA/TOF and is done shortly after birth.

1. Closure of fistula between trachea and oesophagus is performed.
2. Anastomosis between proximal and distal portion of oesophagus is followed.

A chest tube is positioned intra-operatively to drain possible oesophageal leakage.

Prematurity or the presence of associated defects may delay primary repair.

*Approach to long-gap OA:*

(Long-gap OA: 2.5-3 cm distance between the proximal and distal oesophageal pouch.)

1. Fistula ligation is performed. Once ligated, a GT is placed for feeds.
2. Decompression of proximal pouch is performed and growth of oesophagus allowed over a 2-3 months period.
3. Thoracotomy and repair performed.

*Oesophageal replacement* is reserved for those cases of long-gap atresia unsuitable for immediate or delayed primary repair, and when attempted primary repair has failed irretrievably because of leakage or stricture.

### *Post-operative Care*

1. Care of patients with primary oesophageal repairs must be meticulous and conservative.
2. Maintain infant in semi-fowler position.
3. Continue broad-spectrum antibiotics.
4. Continue with proton pump inhibitor for acid blockade.
5. Removal of the endotracheal tube should occur only after respiratory mechanics have been optimised with low risk of extubation failure.
6. If a oro-gastric tube is placed intra-operatively, it may be left in place until a contrast oesophagram is done.
7. After 5 to 7 days, if the patient is clinically stable without signs of sepsis, a contrast oesophagram is carefully performed with a water-soluble agent followed by barium.
  - ▶ If no leak is demonstrated, oral feedings may be initiated and the chest tube removed.
  - ▶ An oro-gastric tube should never be inserted blindly past a fresh oesophageal anastomosis.
8. If the anticipated surgical delay is brief, careful upper pouch suctioning and parenteral nutrition may be used until the delayed primary repair can be carried out. i.e. Long gap oesophageal atresia
9. If a lengthy or indeterminate delay is expected, a staged approach may be required; this allows later oesophageal repair to be undertaken electively.

### POSTOPERATIVE COMPLICATIONS

1. Anastomotic leak. Usually closes in 1-2 weeks. Infant is kept NPO with parenteral nutrition.
2. Anastomotic strictures (the most common complications of surgical treatment)



- An anastomotic stricture should be suspected whenever dysphagia or respiratory symptoms occur in a patient who had previously tolerated oral feedings. A contrast oesophagram is indicated.
- 3. Recurrent TOF. Usually presents with respiratory distress and feeding difficulties.
- 4. Dysphagia
- 5. Gastro-oesophageal reflux disease (40% of patients)
- 6. Tracheomalacia
- 7. Recurrent aspiration
- 8. Injured recurrent laryngeal nerve

## PROGNOSIS

Table 1. Determinants of Survival in Cases of Tracheo-oesophageal malformation.

Group	Characteristics	Survival
I	Birth weight >1500 g without CHD	97%
II	Birth weight <1500 g or CHD	59%
III	Birth weight <1500 g and CHD	22%

CHD: Congenital Heart Disease

## LONG TERM EFFECTS:

1. Poor growth
2. Recurrent respiratory infections and wheezing
3. Chest wall deformities
4. Scoliosis

## FOLLOW-UP

Close follow-up with a multidisciplinary approach.

## Further reading:

Hansen AR, Manfredi MA, Hamilton TE. Chapter 6, Part 6.1: Oesophageal Atresia and Tracheoesophageal Fistula. In: Hansen AR, Puder M, editors. *Manual of Neonatal Surgical Intensive Care*. Third ed. Shelton, Connecticut; PMPH-USA; 2016. p. 175-83.

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# GASTROSCHISIS

Described as an abdominal wall defect, to the right of a normally inserted umbilical cord, without membranous covering of the extruded organs.

- ▶ Gastroschisis is not commonly associated with chromosomal or non-GI tract anomalies.
- ▶ Intestinal atresias occur in 5% to 25% of patients with gastroschisis.

## RISK FACTORS

1. Young maternal age
2. Primigravidity
3. Low body mass index
4. Low socioeconomic status
5. Exposure to external agents i.e. vaso-constricting decongestants, non-steroidal anti-inflammatory agents, cocaine, and possibly pesticides/herbicides

## PRENATAL DIAGNOSIS

1. Ultrasonography in the second trimester of pregnancy.
2. Elevated alfa-fetoprotein.
3. Higher incidence of oligohydramnios, fatal growth restriction and meconium-stained amniotic fluid.
4. Polyhydramnios if intestinal atresia is present.

## FORM OF DELIVERY

Uncomplicated gastroschisis: normal vaginal or cesarean section.

Large lesions or those in which the liver is exposed: cesarean section.

## POSTNATAL PRESENTATION (Figure 1)

1. Eviscerated intestinal loops, without a covering sac, protruding through an abdominal wall defect located just right of the umbilical cord.
2. Umbilical cord is intact.
3. Intestinal loops may be thickened, foreshortened, and covered with a fibrous peel.

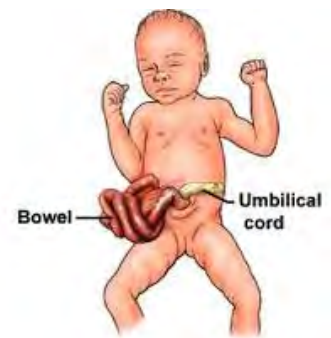


Figure 1. Clinical presentation

## MANAGEMENT

### Pre-Operative Care

Note: The eviscerated intestine should be completely covered in the delivery room to prevent water and heat loss through evaporation, conduction, and convection.

Temporary coverage can be provided by wrapping the torso with transparent plastic film or by placing the baby in a transparent surgical "bowel bag" and closed by the drawstring under the axillae.

If bowel bag is not available, saline soaked dressing may be used.

1. Moisten gauze with warm sterile saline.
2. Place an 8 Fr feeding tube into the gauze wrap to provide sterile access for subsequent hydration if surgical correction cannot be performed immediately, and then cover with plastic wrap.



3. Moisten the dressing every 4 hours by drawing 20-30 ml of warmed sterile saline into a syringe and slowly injecting it into the 8 Fr feeding tube inserted under the plastic wrap.
4. Take adequate measures to prevent hypothermia and ensure that the infant doesn't get too wet.

1. Urgent closure or coverage of the defect is priority.
2. Position of infant:
  - a. lateral decubitus position: better tolerated than supine.
  - b. supine position: for small defects.
3. Nil-by-mouth (NPO).
4. Place a nasogastric tube to low continuous suction at 20-40 mmHg.
5. Insert IV line in the upper extremity.
  - ▶ *Umbilical arterial and venous catheters, and lower extremity peripheral intravenous central catheters are not recommended.*
6. Start IV fluids at higher maintenance. (Increased insensible water loss)
7. Parenteral nutrition (PN) should be provided if enteral feedings are to be delayed. i.e. Staged closure
  - ▶ Administered PN preferably through a peripherally inserted central venous catheter.
8. Laboratories: CBC, blood culture, electrolytes, BUN, creatinine, blood group and crossmatch.
9. Start broad spectrum antibiotics (generally ampicillin and gentamicin). Addition of Metronidazole may be considered.
10. Monitor vital signs.
11. Monitor fluid balance and urine output.
12. Monitor acid-base status.
13. Consult with paediatric surgery.
  - ▶ Surgical management is advisable as soon as baby is stabilised.

### *Surgical Strategies*

Surgical strategies depend on the extend of the lesion and infant 's stability.

1. Primary closure.
2. Staged closure.

In 80% of cases a primary closure is preferred unless there is a compartment syndrome, or respiratory compromise then staged closure is preferred.

Many centers are now proceeding in doing a "plastic" closure whereby several centimetres of umbilical cord are placed over the defect after the abdominal contents are reduced into the abdomen and then covered with an occlusive dressing.

Staged closure: placement of a temporary prosthetic "silo". (Figure 2)

1. Allows for more gradual reduction of the eviscerated intestine into the abdominal cavity.
2. Allows delayed primary closure at a later time.

If intestinal atresia is present, the atretic segment can be addressed at the time of repair with a resection and primary anastomosis or by creation of a stoma.





Figure 2. Silastic “silo” for delayed primary closure of abdominal wall defects.

If intestinal perforation or necrosis is present, an enterostomy may be necessary at the time of the initial repair.

Abdominal wall cellulitis related to the open wound and presence of the prosthetic material limits the use of a silo to a period of approximately 2 weeks.

When reduction of the silo contents is complete, the patient is returned to the operating room for final closure.

### *Post-Operative Care*

1. Maintain hemo-dynamic stability.
2. Monitor blood pressure, SatO<sub>2</sub>, RR, HR and temperature.
3. Respiratory support:
  - ▶ Spontaneous ventilation during staged closure is preferable to positive-pressure ventilation.

Note: Infants should be maintained on a ventilator to allow for neuromuscular paralysis in only the most severe cases of abdomino-visceral disproportion requiring aggressive closure.

When postoperative mechanical ventilation is required, increased levels of positive end-expiratory pressure (PEEP) may be necessary to maintain functional residual capacity and optimise lung compliance.

4. Maintain adequate fluid balance and urine output.
5. Maintain gastric decompression with OGT.
6. Replace OGT losses mL-for-mL with sodium chloride 0.9% .
7. Generally broad-spectrum antibiotics are given until the silo is removed or 72 hours after final closure, whether it is primary or staged repair.
8. Nutrition:
  - a. Parenteral nutrition is administered during staged closure.
  - b. PN should be provided until full enteral feedings are achieved.
  - c. The average length of time to achieve full enteral feeds is 2-3 weeks.
  - d. Enteral feedings should be initiated only after clinical resolution of the ileus is apparent—cessation of bilious gastric aspirates, presence of bowel sounds, and passage of meconium.
  - e. Advancement of enteral feedings, preferably with human milk, should be conservative.
  - f. Introduction of exclusive human milk feedings after gastric repair has been shown to decrease the time to achieve full enteral feeds and time to discharge.
9. Prokinetic agents are not recommended. (have not been found beneficial)





10. Pain control: use IV narcotics i.e. morphine or fentanyl.

#### COMPLICATIONS

1. Gastroschisis has an overall survival rate of > 90%.
2. Most patients experience good long-term health and growth.
3. Prematurity, degree of peel formation, and associated atresias account for most of the morbidity in gastroschisis.
4. Most of the deaths attributed to gastroschisis are related to peri-operative complications, such as sepsis, necrotising enterocolitis, and abdominal visceral ischemia, or to late hepatic failure caused by parenteral nutrition-related cholestatic disease.

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# ANO-RECTAL MALFORMATION

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## IMPERFORATE ANUS

1. Anus is not present and bowel opens in the wrong position in the perineum via a fistula.
2. More common in males.
3. 50-60% are associated with the other abnormalities including the VACTERL association, chromosomal abnormalities and duodenal atresia.

V: vertebral anomalies

A: imperforate anus

C: cardiac anomalies i.e. Tetralogy of Fallot, ventricular septal defect, patent ductus arteriosus

TE: tracheoesophageal fistula

R: renal and genitito-urinary anomalies

L: radial limb abnormalities

## SIGNS AND SYMPTOMS

It can take up to 24 hours to observe expulsion of meconium through a perineal fistula.

Females:

1. 95% have fistula.
2. Perineal fistula can be seen as meconium in the perineum. (Figures A,B)
3. Vestibular fistula can be seen in the posterior aspect of the introitus but outside the hymen.
4. Cloaca presents as small external genitalia with a single opening connecting the rectum, vagina, and urethra.
5. Recto-vaginal fistula is extremely uncommon.

Males:

1. 80 % to 90% have fistula.
2. Perineal fistula can be seen as meconium in the perineum. (Figure C)
3. Recto-urethral fistula may present with meconium in the urine.
4. Recto-vesical fistula connects to the bladder (Rare).
5. No fistula - the risk of Down syndrome is increased.

During physical examination observe presence of :

1. Dysmorphic features
2. Cardiac anomalies
3. Limb anomalies
4. Abdominal distension
5. Absence of anus
6. Abnormal position of bowel opening



Figures A and B. Female infant with imperforate anus and perineal fistula. Source: Constanza E, 2017; NMSP, Belize.



Figure C. Male infant with imperforate anus and perineal fistula.



## MANAGEMENT

1. Nil-by-mouth
2. Insert a size 8 Fr orogastric tube (OGT) and leave on free drainage.
  - ▶ Successful passage of an OGT excludes diagnosis of oesophageal atresia.
3. Empty stomach by aspirating OGT every 4 hours with a 5 mL syringe.
4. Access an IV site and start maintenance IV fluids.
5. Replace OGT losses mL-for-mL using sodium chloride 0.9%.
6. Obtain blood for CBC, BUN, creatinine, glucose and blood cultures. Request blood group and crossmatch.
7. Broad spectrum antibiotics may be considered.
8. Request a thoraco-abdominal X-ray and look for:
  - a. position of OGT
  - b. vertebral anomalies
  - c. abnormal cardiac outline
  - d. dilated bowel/associated bowel atresia
  - e. vertebral anomalies
9. Request abdominal ultrasound to rule out the presence of hydronephrosis or any other obstructive process.
10. Refer to paediatric surgery for evaluation and decision on whether to proceed with a colostomy or a definitive repair.
  - a. The most conservative option is to place a colostomy and perform the repair at a later date.
  - b. Primary repair of these infants without a colostomy is now being performed at some institutions.
11. Consult with other specialities if necessary. i.e. paediatric cardiologist for suspected cardiac anomaly.



## Surgical Strategies

Depend on the presence of a fistula (perineal in males, vestibular and perineal in females) and the position of the rectum. Strategies include:

1. Repositioning of anus: in cases where a fistula is present, it is placed within the anal sphincter.
2. Anorectoplasty (anorectal reconstruction): in cases where no fistula is present with low rectum.
  - ▶ One surgery with possible perineal and abdominal approach is sufficient for repositioning of anus and for anorectoplasty as long as infant is clinically stable.
3. Colostomy followed by anorectoplasty 3 - 6 months later with colostomy closure 2 - 3 months after anorectoplasty is performed: in cases where no fistula is present with high rectum.

### Colostomy

1. Provides immediate relief of bowel obstruction related to imperforate anus.
2. Allows time to plan the definitive repair.
3. Permits other urgent medical and surgical issues to be addressed.

After colostomy, broad-spectrum antibiotics are continued for 2 to 3 days.

Once the colostomy is productive, feeding may be initiated.

A temporary colostomy may be necessary in neonates with an imperforate anus without a perineal fistula.

Colostomy is unnecessary if a perineal fistula can be dilated. (perineal in males/perineal and vestibular in females)

After repair of an anorectal malformation, dilations are begun 2-3 weeks after surgery using Hegar dilators (Figure D) and continued for 6 to 12 months postoperatively.

If a colostomy is present, it can be closed once the desired anal size is reached, typically a 14 Hegar dilator in a 6-month-old child.

Figure D. Hegar dilators



### COMPLICATIONS

Hydronephrosis, urosepsis, and metabolic acidosis from poor renal function are the main sources of mortality and morbidity in newborns with anorectal malformation.

### FOLLOW-UP

Lifelong follow-up is necessary.

Constipation is the most common sequela in patients with anorectal malformations.



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### RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP), previously known as retrolental fibroplasia, is a multifactorial vasoproliferative retinal disorder that increases in incidence with decreasing gestational age.

- ▶ ROP is a major cause of childhood blindness.
- ▶ Globally 60,000 children are estimated to be blind from ROP. Latin America is the region with the highest incidence of ROP, occurring mostly in newborns < 34 weeks gestational age or with birthweight < 2,000 g.
- ▶ The major morbidities of very preterm infants such as intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), and ROP have been called the “*oxygen radical diseases of prematurity*” to emphasise a common role for oxidative stress in their pathogenesis.

#### RISK FACTORS

1. Low gestational age (GA)
  2. Low birth weight (LBW)
  3. Prolonged oxygen exposure and mechanical ventilation
  4. Systemic infection
  5. Blood transfusion
  6. Intraventricular haemorrhage
  7. Poor postnatal weight gain
- ▶ The NICUs with the highest rates of severe ROP have been reported to have the poorest nurse to infant ratios of 1:8 and 1:17.

#### ONSET OF ROP

Consists of two stages:

##### 1. First stage

Involves an initial insult or insults, such as hyperoxia, hypoxia, or hypotension, at a critical point in retinal vascularisation that results in vasoconstriction and decreased blood flow to the developing retina, with a subsequent arrest in vascular development.

##### 2. Second stage

Neo-vascularisation occurs.

#### PROPHYLAXIS

1. Primary prevention of ROP: involves quality improvement of antenatal and perinatal care, delivery room management, and neonatal care.
2. Secondary prevention of ROP: involves the establishment of an efficient ROP programme for early detection (screening), treatment, and follow-up.

Note: Neonatal care should include

1. Air/oxygen blenders, heater humidifiers, oxygen analysers, and oxygen saturation monitors.



2. Avoidance of both hyperoxaemia and hypoxaemia.
3. Avoidance of frequent and wide fluctuations in oxygen saturation.
4. Target arterial oxygen saturation between 88% and 94%.
5. Target arterial oxygen saturation between 93% and 95% for infants > 34-36 weeks post menstrual age who have residual lung disease.

## DIAGNOSIS

ROP is diagnosed by retinal examination with indirect ophthalmoscopy using preferably a 28 diopter lens or by wide-field digital imaging system by an ophthalmologist experienced in diagnosis of ROP.

## ROP PROGRAMME

Criteria for ROP programmes

Guidelines for ROP examination and treatment in Latin American Countries suggest:

1. Birth weight:  $\leq 1,750$  g or gestational age  $\leq 32$  weeks.
2. Birthweight:  $> 1,750$  g at the discretion of the neonatologist.

SIBEN recommends:

1. Birthweight  $\leq 1,800$  g
  2. Birthweight between 1,800 - 2,000 g with risk factors such as mechanical ventilation, supplementary oxygen, infection, intracranial haemorrhage, periventricular leukomalacia, and hypoxia.
  3. Birthweight  $> 2,000$  g at the discretion of the neonatologist and according to associated risk factors.
- ▶ Criteria adopted in Latin American countries vary (i.e.  $< 1,900$  g in Ecuador;  $< 2,000$  g in Peru), and given the fact that GA data are often unreliable, birthweight criteria tend to be relied on more than gestational age.
  - ▶ It is necessary for NICUs that may want to set their own criteria, carry on a longitudinal study of at least one year in which details of the BW, GA and eye findings of consecutive babies are recorded.

## OBJECTIVE OF ROP PROGRAMMES

To reduce the incidence and severity of ROP, and detect and treat cases optimally so that the overall burden of childhood blindness, low vision, and other visual sequelae from ROP is minimised.

- a. ROP programmes require collaboration among neonatologists, ophthalmologists, nurses, and allied health personnel, together with parents.
- b. Most units appoint a nurse ROP coordinator (usually unit nurse in charge) to oversee the programme.

Responsibilities of the neonatal care team physicians and nurses should be explicitly assigned and include:

1. Developing minimal acceptable standards for oxygen monitoring.
2. Identifying and recording of babies needing examination (who and how).
3. ROP coordinator assigned prepares list of infants to be examined. Checks with the neonatal team.
4. Information given to parents by neonatologists with respect to ROP.
5. Care during examinations in intensive and intermediate care.



6. Ensuring discharged and treated babies attend follow-up.
7. Care during laser/cryo treatment.
8. Follow-up of premature babies by paediatricians.
9. Data to be collected for monitoring and evaluating programmes.

Responsibilities of examining or treating ophthalmologists include:

1. Being adequately trained to perform diagnostic examinations in premature babies and treatment.
2. Ensuring timely examinations and treatment.
3. Adhering to the norms or policy of the NICU at all time.
4. Providing information for parents.
5. Developing criteria for examining babies in collaboration with neonatologists.
6. Determining frequency of follow-up examinations.
7. Indications and consent for treatment.
8. Method of treatment and follow up.
9. Referral to low vision services for children with visual impairment from ROP.

The following information should be available for each newborn meeting the criteria for examination in the unit:

1. Date of birth
2. Sex
3. Birth weight
4. Gestational age
5. Multiple/singleton birth
6. Days on oxygen and ventilation
7. Admission diagnosis
8. Date of first eye examination
9. Date of last eye examination
10. Stage of ROP
11. Treatment given (laser, cryo, vitreoretinal surgery), and outcome of treatment.
12. Follow-up appointments or dropped out of program.

TIMING AND FREQUENCY OF EXAMINATIONS:

1. When a reliable estimate of gestational age is not available, the first examination should be 4-6 weeks after birth.
2. For babies with a reliable estimated gestational age of < 28 weeks, examinations should begin at 4 weeks after birth.
3. For babies > 28 weeks, examination should be at completing 31 weeks post menstrual age, and always before discharge.





- ▶ It is the responsibility of the neonatologist to defer eye examination at the interval suggested by the ophthalmologist if the infant is too unstable to undergo procedure; the reason for the deferral should be documented in the infant's chart.
- ▶ A NICU nurse must be available to assist the ophthalmologist with the examination, and a neonatologist available in case the baby develops cardiovascular or respiratory complications.
- ▶ Babies in NICU should be examined in the NICU at the appropriate postnatal age, regardless of whether the baby is in an incubator or being ventilated.

#### RETINAL EXAMINATION:

1. The examination should be performed by an ophthalmologist experienced in diagnosis of ROP at a regular day and time each week for screening. The Belize Council for the Visually Impaired (BCVI) ophthalmologist visits the NICU at the Karl Heusner Memorial Hospital (KMH) on Friday mornings for ROP screening.
2. Experienced assigned nurse cares for infant during examination. Infant should be swaddled, heart rate monitored and pulse oximeter attached; a pacifier may be considered.
3. Location of screening: ideally quiet darkened room in NICU equipped with air/oxygen suction, and resuscitation trolley.
4. Equipment: sterile eyelid speculum and scleral indentors.
5. All mydriatic eyedrops should be instilled by designated NICU nurse at least 30 minutes or 1 hour prior to examination.
6. Eye drop medications used: 2.5% cyclopentolate and 1% phenylephrine × 2 at 5-minute intervals or Cyclopentolate 0.5 % combined with phenylephrine 2.5% or tropicamide 0.5%.
7. Side effects of mydriatic eye drops: hypertension, feeding intolerance, and reactive airway disease in infants with chronic lung disease.
8. Instillation of topical anaesthetic, i.e. 0.5%–1% proparacaine is strongly recommended if a lid speculum is being used.
9. Results of each examination and the management decision should be clearly documented in agreed place in notes.

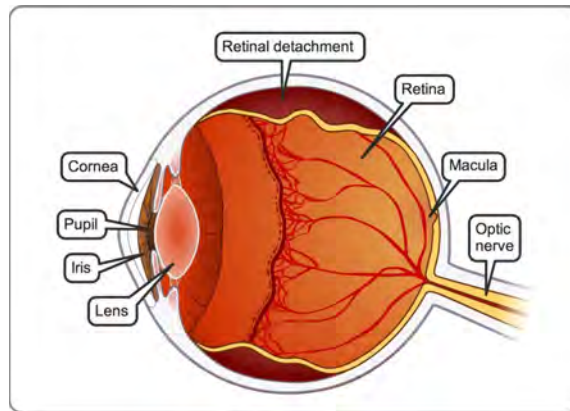
#### INTERNATIONAL CLASSIFICATION OF RETINOPATHY OF PREMATURITY

ROP is recorded according to the following criteria:

1. Severity by stages: 1-5 and aggressive posterior ROP (AP-ROP).
  - a. Demarcation line: thin white line, lying within the plane of the retina and separating avascular from vascular retinal regions.
  - b. Ridge: the line of stage 1 has increased in volume to extend out of the plane of the retina.
  - c. Ridge with extra retinal fibrovascular proliferation.
  - d. Retinal detachment - subtotal: 4A - Extrafoveal and 4B - Foveal (Figure 1)
  - e. Retinal detachment - total
- ▶ Aggressive Posterior ROP (AP-ROP)
  - Commences with posterior pole vessel dilation and tortuosity in all four quadrants and appears as a flat network of vessels at the junction between vascularised and non-vascularised retina. Typically located in zone I or posterior zone II.



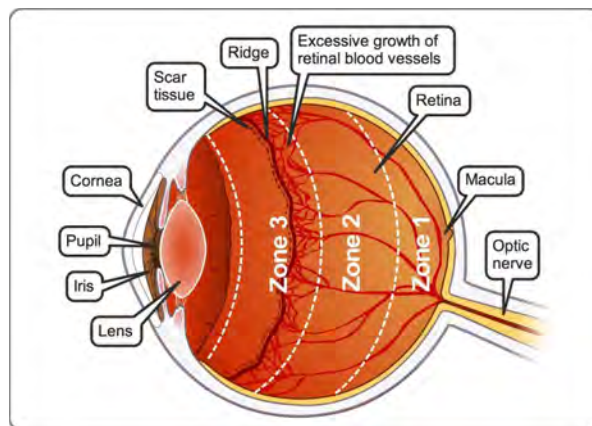
Figure 1. Location of ROP with retinal detachment.



2. Location by zone I- III: (Figure 2)

- ▶ Retinal blood vessels grow out from the optic disc in zone I towards the periphery (zone III). ROP in zone I affects the most immature baby and is very likely to become severe with a poor outcome. ROP located in zone III almost never causes visual disability.

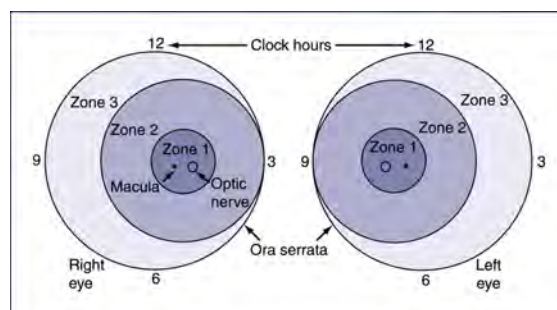
Figure 2. Location of ROP by Zone.



3. Extent by clock hour involvement.

- ▶ ROP extent around the retinal circumference is recorded in 'clock hours' 1-12. (Figure 3)

Figure 3. Location of ROP by clock hour and zone.



4. Presence of 'pre-plus' and 'plus' disease: are critical indicators that ROP is, or will become, severe.
  - a. Plus disease is an indicator of ROP activity: venous dilatation and arteriolar tortuosity of the posterior pole retinal vessels, iris vessel engorgement, pupil rigidity and vitreous haze.
  - b. Plus involves vessels in two or more quadrants.
  - c. Pre-plus describes abnormalities that are insufficient for the diagnosis of plus.

## TREATMENT

1. Most ROP are mild and have no major visually disabling sequelae.
2. Severe ROP is defined as pre-threshold ROP, types 1 and 2.

### Indications for ROP treatment:

1. Type 1 Pre-threshold ROP:
  - a. Zone I, any stage of ROP with plus disease
  - b. Zone I, Stage 3 ROP with or without plus disease
  - c. Zone II, Stages 2 or 3 with plus disease
  - ▶ Type 1 ROP which is particularly active such as aggressive posterior ROP (AP-ROP) should be treated as soon as possible, within 24 -48 hours since it rapidly progresses to retinal detachment, but if less aggressive but still requiring treatment the eyes should be treated within 72 hours.
2. Type 2 Pre-threshold ROP:
  - a. Zone I, Stages 1 or 2 ROP without plus disease
  - b. Zone II, Stage 3 ROP without plus disease
  - ▶ Type 2 pre-threshold ROP is an indication that ROP may progress to Type 1 and therefore should be observed closely with re-assessment in 48-72 hours.
  - ▶ 'Plus' disease is a feature of Type 1 ROP with one rare exception (Zone I, stage 3 without 'plus'). The presence of 'plus' is the major driver for treatment and is the critical difference between Type 1 that requires treatment and Type 2 ROP that does not.

Note: In general, ROP requiring treatment occurs around 36-38 weeks postconceptional age, a time when many of the babies are nearing discharge.

All treatment should be within 48 hours of decision to treat even if that entails transfer elsewhere.

Type 1 ROP can progress very rapidly to a worse situation.

Any zone III disease has an excellent prognosis for complete recovery.

Eyes with partial retinal detachments (stage 4a and stage 4b): Vitreoretinal surgery may be indicated.

Stage 5: Complex vitreoretinal surgery is not recommended at present, as the functional results are generally extremely poor even in anatomically successful results.

Standard treatment for ROP consists of ablation of the peripheral avascular retina by either laser therapy or cryotherapy.

1. Laser photocoagulation therapy for ROP is the preferred initial treatment in most centres.
2. Cryotherapy is equally effective but generally causes more inflammation and discomfort. It is used infrequently.

The use of intravitreal injection of anti-VEGF drugs in severe acute phase ROP has not been proven beneficial and the ocular and systemic side effects are not yet known.



BCVI has been carrying out ROP screening in the NICU at KMH since January 2016 and outpatient follow-up at their headquarter. However, urgent need to instil prompt and adequate treatment for babies who require immediate surgical management needs to be addressed.

BCVI in 2016, examined 42 babies at risk of ROP in the NICU of which 3 were referred for follow up as outpatients.

#### SUBSEQUENT EXAMINATIONS:

1. It is the responsibility of the ophthalmologist to decide when the next examination should take place.
2. If the retina is immature and there is no ROP, the next examination should be at 2 - 3 weeks.
3. If there is ROP in zone 3, the next examination should be at 2 weeks.
4. If there is ROP zone 1 or 2 the next examination should be at 1 week, or at 3-4 days depending on the stage of disease and the appearance of the posterior pole vessels.
5. Examinations should continue until the retina is fully vascularised (vascularisation has entered Zone 3) or the ROP has regressed.
6. If infant has postmenstrual age < 37 weeks, a further examination should still be considered even if vessels are into zone 3.

#### POSTOPERATIVE CARE:

1. Post operative medication includes: antibiotic or antibiotic/steroid ointment or eyedrops twice daily for 3-5 days.
2. After treatment the baby should be re-examined in 5-7 days.
3. Re-treatment of the peripheral retina should be considered if signs of progression are present.

#### FOLLOW UP

1. Most very preterm infants in need of ophthalmology follow-up will also require paediatric follow-up clinics.
2. At transfer or discharge parents should have a copy of the examination findings and date of next examination or follow-up, and understand the need for these.
3. Designated NICU nurse ROP coordinator should maintain a diary system to ensure timely follow up (if infant is still in NICU).
4. ROP prevention is a team responsibility, and parents must be seen as equal partners in that team.
5. Parents should be made aware that mild ROP is common and usually resolves spontaneously without adverse consequences.
6. Premature babies who do not develop ROP will need ophthalmological follow up during the first year of life.
7. Infants with significant ROP have an increased risk of refractive errors such as myopia, anisometropia and astigmatism, strabismus, amblyopia, late retinal detachment, and glaucoma.
8. All premature infants who meet screening criteria regardless of the diagnosis of ROP are at risk for long-term vision problems, from either ocular or neurologic abnormalities.



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## HEARING LOSS

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The goal of early hearing detection and intervention (EHDI) is to maximise linguistic competence and literacy development for children who are deaf or hard of hearing.

1. Undetected, hearing loss negatively affects communication development, academic achievement, literacy, and social and emotional development.
2. Early intervention improves the outcome for babies with a congenital hearing deficit.
3. Approximately 50% of congenital hearing loss is hereditary.
4. Cytomegalovirus remains the most common medical cause of nonhereditary sensorineural hearing loss, both early and delayed-onset hearing loss in infants and children.
  - ▶ Screening for CMV with urine or saliva in all babies who fail their newborn hearing screen has been implemented by some hospitals to facilitate diagnosis.
5. Types of permanent hearing loss that can be identified with newborn screening include
  - a. Sensorineural
  - b. Neural
  - c. Conductive
6. Hearing loss can be classified as transient or permanent, bilateral or unilateral, and as mild, moderate, severe, or profound.
7. Targeted hearing loss is defined as congenital permanent bilateral, unilateral sensory, or permanent conductive hearing loss, and neural hearing loss (i.e. auditory neuropathy/dyssynchrony) in infants admitted to the NICU.
8. Neonatal intensive care infants have higher false-positive rates and higher fail rates than well-baby nursery infants.

Note: The 1-3-6 recommendation:

Hearing screening of all infants should be done no later than 1 month of age.

Those who do not pass screening should have a comprehensive audiological evaluation at no later than 3 months of age.

Infants with confirmed hearing loss should receive appropriate early intervention at no later than 6 months of age from health care and education professionals with expertise in hearing loss and deafness in infants and young children.

In Belize, early hearing screening at birth is not practiced at any level of birthing healthcare facility. It is recommended to initiate an early hearing screening programme targeting all babies with at least one risk factor - COST EFFECTIVENESS AND BETTER HEALTH. For the meanwhile, it is encouraged to refer infants, especially those at risk, to the Inspiration Center in Belize City for screening and early intervention services.

### RISK INDICATORS ASSOCIATED WITH PERMANENT CONGENITAL, DELAYED-ONSET, OR PROGRESSIVE HEARING LOSS IN CHILDHOOD.

1. Caregiver concern regarding hearing, speech, language, or developmental delay.
2. Family history of permanent childhood hearing loss.
3. Neonatal intensive care of more than 5 days or any of the following regardless of length of stay: extracorporeal membrane oxygenation (ECMO), assisted ventilation, exposure to ototoxic medications (gentamicin and tobramycin) or loop diuretics (furosemide), and hyperbilirubinaemia requiring exchange transfusion.



4. In utero infections, such as CMV, herpes, rubella, syphilis, toxoplasmosis, and Zika.
5. Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies.
6. Physical findings, such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss.
7. Syndromes associated with hearing loss or progressive or late-onset hearing loss, such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange - Nielson.
8. Neurodegenerative disorders, such as Hunter syndrome, or sensory motor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth syndrome.
9. Culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis.
10. Head trauma, especially basal skull/temporal bone fracture that requires hospitalisation.
11. Chemotherapy.

## HEARING SCREENING METHODS

Otoacoustic emissions (OAE) and automated auditory brainstem response (A-ABR) technology are recommended for newborn hearing screening and are considered efficient and highly reliable (high sensitivity and specificity).

1. OAEs reflect the status of the peripheral auditory system extending to the cochlear outer hair cells.
2. Automated ABR measurements reflect the status of the peripheral auditory system, the eighth nerve, and the brainstem auditory pathway.

Note: Both OAE and ABR detect sensorineural and conductive hearing loss.

1. OEA detects sensorineural and conductive hearing loss but cannot be used to screen for neural (eighth nerve or auditory brain- stem pathway) hearing loss.
2. ABR detects sensorineural, conductive, and neural hearing loss.

*Babies at risk for Auditory Neuropathy Spectrum Disorder (ANSD) such as NICU infants admitted for more than 5 days are to have ABR included as part of their screening so that neural hearing loss will not be missed.*

*All other babies (well babies and babies in the NICU for less than 5 days with no risk indicators for late onset or progressive hearing loss) can be screened with OAE.*

*In Belize only OAE testing is currently done at the Inspiration Center for all infants in general.*

The AAP recommends the ABR over the OAE in high-risk infants including NICU patients and graduates.

A threshold of  $\geq 35$  dB has been established as a cutoff for an abnormal screen, which prompts further testing.

## SCREENING PROTOCOLS

All babies are eligible for screening.

Separate protocols are recommended for NICU and well-infant nurseries.

1. For those infants born in a birthing facility or at home, it is recommended that hearing screening be performed within the first 2 weeks of the infant's life.
2. Screening Protocols in the Well-Infant Nursery.



- a. Infants born without any complications can be screened for hearing loss as early as 6 hours of age or close to discharge as possible.
- b. Many centres will wait for the infant to be at least 24 hours old before hearing screening is attempted.
- c. Use of either technology in the well-infant nursery will detect peripheral (conductive and sensory) hearing loss of 40 dB or greater.
- d. Some programs use a combination of screening technologies (OAE testing for the initial screening followed by automated ABR for re-screening).
- e. With this approach, infants who do not pass an OAE screening but subsequently pass an automated ABR test are considered a screening “pass”.

### 3. Screening Protocols in the NICU

If an infant is in the NICU, hearing screening is performed prior to the infant’s discharge from the hospital or when the infant is in stable condition and in an open crib. NICU infants may be screened earlier or more than once, depending on their medical condition.

Neonates at risk of having neural hearing loss (auditory neuropathy/auditory dyssynchrony) in the target population should be identified in the NICU.

### RESCREENING

1. For infants who do not pass automated ABR testing in the NICU, referral should be made directly to an audiologist, within 3 weeks of their initial test, for re-screening and, when indicated, comprehensive evaluation including a diagnostic ABR.
2. Infants with mild or unilateral hearing loss should also be monitored closely with repeat audiology evaluations and provided with early intervention services because they are at increased risk for both progressive hearing loss and delayed and abnormal development of language and communication skills.
3. For re-screening, a complete screening on both ears is recommended, even if only 1 ear failed the initial screening.
4. Infants who pass the neonatal screening but have a risk factor should have at least 1 diagnostic audiology assessment by 24 to 30 months of age.

### FAILED HEARING SCREENING

Comprehensive audiological evaluation of newborn and young infants who fail newborn hearing screening should be performed by audiologists experienced in paediatric hearing assessment.

The initial audiological test battery to confirm a hearing loss in infants must include physiologic measures and, when developmentally appropriate, behavioural methods.

Confirmation of an infant’s hearing status requires a test battery of audiological test procedures to assess the integrity of the auditory system in each ear, to estimate hearing sensitivity across the speech frequency range, to determine the type of hearing loss, to establish a baseline for further monitoring, and to provide information needed to initiate amplification-device fitting.

The audiological assessment should include:

1. Child and family history.
2. A frequency-specific assessment of the ABR
3. Click-evoked ABR testing
4. Distortion product or transient evoked OAEs.
5. Tympanometry using a 1000-Hz probe tone.





6. Clinician observation of the infant's auditory behaviour as a cross-check in conjunction with electrophysiologic measures.

## CONFIRMED HEARING LOSS

Every infant with confirmed hearing loss should:

1. Be evaluated by an otolaryngologist who has knowledge of paediatric hearing loss.
2. Have at least 1 examination to assess visual acuity by an ophthalmologist who is experienced in evaluating infants.
3. Be referred for radiologic imaging with computed tomography (CT) or magnetic resonance imaging (MRI) when needed.
4. Be referred for genetics consultation.
5. Be provided early intervention services by professionals who have expertise in hearing loss, including educators of the deaf, speech-language pathologists, and audiologists.
6. Be provided supportive family education, and counselling.
7. Should be followed-up by their paediatricians or primary health care professionals.

## EARLY INTERVENTION SERVICES

The term "intervention services" is used to describe any type of habilitative, rehabilitative, or educational program provided to children with hearing loss.

The initiation of early intervention services should begin as soon as possible after diagnosis of hearing loss but at no later than 6 months of age.

Children with high-frequency losses and normal hearing in the low frequencies may only be seen by a speech-language pathologist, and those with significant bilateral sensorineural hearing losses might be seen by an educator of the deaf and receive additional services.

## HEARING DEVICES

1. Hearing aids are compact and worn either in-the-ear (ITE) or behind-the-ear (BTE), and can be fitted on an infant in the first month of life.
2. Frequency modulated (FM) systems were developed for individuals with hearing loss to hear better in noisy environments.
3. Candidacy criteria for paediatric cochlear implantation currently is 18 months or older for children with severe to profound bilateral sensorineural hearing loss and 12 to 18 months for children with profound hearing loss.

## PROGNOSIS

The prognosis depends largely on the extent of hearing loss, the time of diagnosis and treatment, as well as the presence of syndromes or other congenital anomalies.

The earlier habilitation starts, the better the child's chance of achieving age-appropriate language and communication skills.

Fitting of hearing aids by the age of 6 months has been associated with improved speech outcomes.

Infants who do not pass the speech-language portion of a standardised global screening with a validated tool during well-child visits at 9, 18, and 24 to 30 months or for whom there is a concern regarding hearing or language should be referred for speech-language evaluation and audiology assessment since:

1. Mild hearing loss is missed with newborn screening tools.
2. Some children experience delayed-onset or progressive hearing loss such as that associated with cytomegalovirus.



3. Some children experience late-onset hearing loss secondary to trauma or chemotherapy.

Infants with otitis media with effusion (OME) may have transient hearing loss and associated language delays.

Family involvement is also critical to success.

Early identification, together with early intervention, optimal fitting of amplification, specialised language intervention services provided by speech-language pathologists and teachers of the deaf, and an actively involved family, result in higher level language outcomes at age 5 years.

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## COMMON MEDICATIONS USED IN NEONATOLOGY

### ANTIBIOTICS

#### AMPICILLIN

Classification: Semisynthetic penicillinase-sensitive penicillin with bactericidal activity.

Indications: Combined with either an aminoglycoside or cephalosporin for the prevention and treatment of infections with group B streptococci, *Listeria monocytogenes*, enterococci, and susceptible *Escherichia coli* spp.

Dosage/administration: For susceptible infection and prophylaxis minimum dose may be indicated, and for GBS bacteraemia and meningitis maximum dose may be indicated.

Indication	Dosage (IV/IM)	Comment
Mild to moderate infections (non-CNS)	$\leq 2,000$ g and $\leq 7$ days: 50–100 mg/kg/dose q12h $\leq 2,000$ g and $> 7$ days: 50 mg/kg/dose q8h $> 2,000$ g and $\leq 7$ days: 100 mg/kg/dose q12h $> 2,000$ g and $> 7$ days: 50 mg/kg/dose q6–8h	
Meningitis—Group B <i>Streptococcus</i> (GBS)	All weights: $\leq 7$ days: 50–100 mg/kg/dose q8h $> 7$ days: 50–75 mg/kg/dose q6h	When treating meningitis, use only the IV route.
CNS, central nervous system.		

Adverse reactions: Diarrhoea, hypersensitivity reaction (rubella-like rash and fever, although rare in neonatal population), nephritis (typically preceded by eosinophilia), elevated transaminases, penicillin encephalopathy (CNS excitation and seizure activity associated with large or rapidly administered doses), haemolytic anaemia, and pseudomembranous colitis.

#### AMIKACIN

Classification: Aminoglycoside, antibiotic.

Indications: Active against gram-negative aerobic bacteria, ineffective against anaerobes, streptococci and staphylococci; reserve for organisms resistant to gentamicin and tobramycin.

Dosage/administration: For newborns  $> 2000$  g and  $> 7$  days: 17.5 mg/kg/dose every 24 hours is now indicated.

Weight	Postnatal Age	Dosage (IV/IM)
$< 1,000$ g	$\leq 14$ days	15 mg/kg/dose q48h
$< 1,000$ g	$> 14$ days	15 mg/kg/dose q24–48h
1,000–2,000 g	$\leq 7$ days	15 mg/kg/dose q48h
1,000–2,000 g	$> 7$ days	15 mg/kg/dose q24–48h
$> 2,000$ g	$\leq 7$ days	15 mg/kg/dose q24h
$> 2,000$ g	$> 7$ days	15 mg/kg/dose q12–24h

Adverse reactions: Vestibular and irreversible auditory ototoxicity (associated with high trough levels) and renal toxicity (occurs in the proximal tubule, associated with high trough levels, usually reversible). Treat extravasation with hyaluronidase around periphery of affected area.



## AMOXICILLIN

Classification: Penicillin antibiotic.

Indication: Prophylaxis against urinary tract infections in patients with hydronephrosis and vesicoureteral reflux.

Dosage/administration: 30 mg/kg/day in divided doses q 12 hours PO.

Adverse reactions: Diarrhoea, hypersensitivity reaction (rubella-like rash and fever, although rare in neonatal population), elevated transaminases, penicillin encephalopathy (CNS excitation and seizure activity associated with large doses), haemolytic anaemia, and pseudomembranous colitis.

## GENTAMICIN

Classification: Aminoglycoside, antibiotic.

Indications: Active against gram-negative aerobic bacteria, synergistic activity against *Staphylococcus aureus* and *Enterococcus*, ineffective against anaerobes and streptococci (except enterococcus).

Dosage/administration: Interval dosage of q 36 hours now replaces q 24-48h, and q 24 hours replaces q 12-24h.

Weight	Postnatal Age	Dosage (IV/IM)
<1,000 g	≤14 days	5 mg/kg/dose q48h
<1,000 g	>14 days	4–5 mg/kg/dose q24–48h
1,000–2,000 g	≤7 days	5 mg/kg/dose q48h
1,000–2,000 g	>7 days	4–5 mg/kg/dose q24–48h
>2,000 g	≤7 days	4 mg/kg/dose q24h
>2,000 g	>7 days	4 mg/kg/dose q12–24h

Adverse reactions: Vestibular and irreversible auditory ototoxicity (associated with high trough levels) and renal toxicity (occurs in the proximal tubule, associated with high trough levels, usually reversible). Treat extravasation with hyaluronidase around periphery of affected area.

## CEFOTAXIME

Classification: Third-generation cephalosporin.

Indications: Reserved for suspected or documented gram-negative meningitis or sepsis. Combine with ampicillin or vancomycin for empiric therapy.

Dosage/administration:

Weight	Postnatal Age	Dosage (IV/IM)
<1,000 g	≤14 days	50 mg/kg/dose q12h
<1,000 g	>14 days	50 mg/kg/dose q8–12h
1,000–2,000 g	≤7 days	50 mg/kg/dose q12h
1,000–2,000 g	>7 days	50 mg/kg/dose q8–12h
>2,000 g	≤7 days	50 mg/kg/dose q12h
>2,000 g	>7 days	50 mg/kg/dose q6–8h

Adverse reactions: Leukopenia, granulocytopenia, pseudomembranous colitis, serum–sickness-like reaction, and transient elevation of BUN, creatinine, eosinophils, liver enzymes, and rash.



## CEFTAZIDIME

Classification: Third-generation cephalosporin.

Indications: Broad-spectrum cephalosporin with antipseudomonal activity. Treatment of gram-negative meningitis.

Dosage/administration:

Weight	Postnatal Age	Dosage (IV/IM)
<1,000 g	≤14 days	50 mg/kg/dose q12h
<1,000 g	>14 days	50 mg/kg/dose q8–12h
1,000–2,000 g	≤7 days	50 mg/kg/dose q12h
1,000–2,000 g	>7 days	50 mg/kg/dose q8–12h
>2,000 g	≤7 days	50 mg/kg/dose q12h
>2,000 g	>7 days	50 mg/kg/dose q8h

Adverse reactions: Transient leukopenia and bone marrow suppression, rash, false-positive direct Coombs test, candidiasis, haemolytic anaemia, pseudomembranous colitis, and transient elevation of eosinophils, platelets, renal, and LFTs.

## CEFEPIME

Classification: Fourth-generation cephalosporin.

Indications: Broad-spectrum cephalosporin with antipseudomonal activity. Treatment of gram-negative meningitis.

Dosage/administration:

Weight	Postnatal Age	Dosage (IV/IM)
<1,000 g	≤14 days	30–50 mg/kg/dose q12h
<1,000 g	>14 days	50 mg/kg/dose q8–12h
1,000–2,000 g	≤7 days	30–50 mg/kg/dose q12h
1,000–2,000 g	>7 days	50 mg/kg/dose q8–12h
>2,000 g	All ages	50 mg/kg/dose q8–12h

Adverse reactions: Transient leukopenia and bone marrow suppression, rash, false-positive direct Coombs test, candidiasis, haemolytic anaemia, pseudomembranous colitis, and transient elevation of eosinophils, platelets, renal, and LFTs.

## CEFAZOLIN

Classification: First-generation cephalosporin.

Indications: Treatment of susceptible infections involving the respiratory tract, skin and skin structure, urinary tract; bone and joint, genitals, and septicaemia; perioperative prophylaxis.

Dosage/administration: When given peri-operatively for prophylaxis a one-time dose of 25 mg/kg/dose should be given 30 to 60 minutes prior to the procedure.

Weight	Postnatal Age	Dosage (IV/IM)
<2,000 g	All ages	25 mg/kg/dose q12h
≥2,000 g	≤7 days	25 mg/kg/dose q12h
≥2,000 g	>7 days	25 mg/kg/dose q8h



Adverse reactions: Leukopenia, granulocytopenia, pseudomembranous colitis, serum–sickness-like reaction, and transient elevation of BUN, creatinine, eosinophils, liver enzymes, and rash.

## METRONIDAZOL

Classification: Nitroimidazole - Anaerobic antibiotic.

Indications: Treatment of *B. fragilis* septicaemia, peritonitis, NEC. Not indicated for meningitis.

Dosage/administration:

For infants < 2000 g with ≤ 14 days PNA: loading dose of 15 mg/kg then continue with maintenance dose.

Weight	Postnatal Age	Dosage (IV)
<1,000 g	≤14 days	7.5 mg/kg/dose q48h
<1,000 g	>14 days	15 mg/kg/dose q24h
1,000–2,000 g	≤7 days	7.5 mg/kg/dose q24–48h
1,000–2,000 g	>7 days	15 mg/kg/dose q24h
>2,000 g	≤7 days	15 mg/kg/dose q24h
>2,000 g	>7 days	15 mg/kg/dose q12h

Adverse reactions: Leukopenia, neutropenia, aseptic meningitis, rash, Stevens-Johnson syndrome, vomiting.

## OXACILLIN

Classification: Penicillin, antibiotic.

Indications: Infections due to susceptible penicillinase-producing strains of *Staphylococcus*.

Dosage/administration:

Weight < 1 kg:

PNA ≤ 14 days: 25 mg/kg/dose every 12 hours

PNA > 14 days: 25 mg/kg/dose every 8 hours

Weight 1 to 2 kg:

PNA ≤ 7 days: 25 mg/kg/dose every 12 hours

PNA > 7 days: 25 mg/kg/dose every 8 hours

Weight > 2 kg:

PNA ≤ 7 days: 25 mg/kg/dose every 8 hours

PNA > 7 days: 25 mg/kg/dose every 6 hours

Adverse reactions: fever, rash, diarrhoea, nausea, vomiting, agranulocytosis, eosinophilia, leukopenia, neutropenia, thrombocytopenia, haematuria, acute interstitial nephritis, AST increased.

## VANCOMYCIN

Classification: Glycopeptide Antibiotic.

Indications: Drug of choice for serious infections caused by methicillin-resistant staphylococci, penicillin-resistant pneumococci, and coagulase-negative staphylococcus.

Dosage/administration:



Weight	Postnatal Age	Dosage (IV)
<1,200 g	All ages	15 mg/kg/dose q24h
1,200–2,000 g	<7 days	10–15 mg/kg/dose q12–18h
1,200–2,000 g	≥7 days	10–15 mg/kg/dose q8–12h
>2,000 g	<7 days	10–15 mg/kg/dose q8–12h
>2,000 g	≥7 days	10–15 mg/kg/dose q6–8h

Adverse reactions: Red man syndrome (erythema multiform-like reaction with intense pruritus; tachycardia; hypotension; rash involving face, neck, upper trunk, back, and upper arms) usually develops during a rapid infusion of vancomycin or with doses >15 mg/kg/hour and usually dissipates in 30 to 60 minutes. Lengthening infusion time usually eliminates risk for subsequent doses. Cardiac arrest, fever, chills, eosinophilia, and neutropenia reported after prolonged administration (>3 weeks); phlebitis may be minimised by slow infusion and more dilution of the drug. If extravasation occurs, consider using hyaluronidase around periphery of affected area. Also reported are ototoxicity and nephrotoxicity especially if administered concurrently with other nephrotoxic or ototoxic medications or with elevated serum concentrations.

### MEROPENEM

Classification: Carbapenem antibiotic.

Indications: Broad-spectrum carbapenem antibiotic with anti-pseudomonal activity. Treatment of meningitis; should be reserved for multidrug-resistant infections caused by gram-negative organisms.

Dosage/administration:

Weight	Postnatal Age	Dosage (IV)
<1,000 g	≤14 days	20 mg/kg/dose q12h
<1,000 g	>14 days	20 mg/kg/dose q8h
1,000–2,000 g	≤7 days	20 mg/kg/dose q12h
1,000–2,000 g	>7 days	20 mg/kg/dose q8h
>2,000 g	All	20 mg/kg/dose q8h

Adverse reactions: Rash, candidiasis, haemolytic anaemia, pseudomembranous colitis, and thrombocytopenia, increased LFTs, false-positive direct Coombs test.

### IMIPENEM

(NOT THE PREFERRED CARBAPENEM FOR PRETERM INFANTS DUE TO POSSIBLE SEIZURE RELATED TO CILASTATIN. NOT RECOMMENDED FOR CNS INFECTIONS)

Classification: Carbapenem antibiotic.

Indications: Broad-spectrum carbapenem antibiotic with anti-pseudomonal activity. Treatment of meningitis; should be reserved for multidrug-resistant infections caused by gram-negative organisms.

Dosage/administration:

Weight < 1 kg:

PNA ≤ 14 days: 20 mg/kg/dose every 12 hours

PNA > 14 days: 25 mg/kg/dose every 12 hours

Weight 1 to 2 kg:

PNA ≤ 7 days: 20 mg/kg/dose every 12 hours

PNA > 7 days: 25 mg/kg/dose every 12 hours



Weight > 2 kg:

PNA ≤ 7 days: 25 mg/kg/dose every 12 hours

PNA > 7 days: 25 mg/kg/dose every 8 hours

Adverse reactions: Rash, seizure, diarrhoea, vomiting, candidiasis, haemolytic anaemia, pseudomembranous colitis, and thrombocytopenia, increased LFTs, increased serum creatinine.

## FLUCONAZOL

Classification: Systemic anti-fungal agent.

Indications: Treatment of systemic fungal infections, meningitis, and severe superficial mycoses. Alternative to amphotericin-B in patients with preexisting renal impairment or when concomitant therapy with other potentially nephrotoxic drugs are required. May be used as prophylaxis against invasive fungal infections in VLBW infants in NICUs with high fungal infection rates.

Dosage/administration: Daily dose of fluconazole is the same for PO and IV administration. Administer 6 mg/kg IV dose on syringe pump over 60 minutes. Administer 12 mg/kg IV dose on syringe pump over 2 hours. Usual IV concentration is 2 mg/mL. May dilute in dextrose solutions.

Systemic infections, including meningitis: 12 mg/kg/dose q 24h for 21 days. If serum creatinine is >1.2 mg/dL, then give 12 mg/kg/dose q 48h.

Thrush: 6 mg/kg on day 1 and then 3 mg/kg/dose q 24h.

Prophylaxis dosing:

PMA	Postnatal Age	Dose (IV/PO)	Dosing Interval
<30 weeks	<7 days ≥7 days	6 mg/kg/dose 6 mg/kg/dose	Twice a week q72h
30–40 weeks	All ages	6 mg/kg/dose	q48h

Adverse reactions: Vomiting, diarrhoea, exfoliative skin disorders, and reversible increased AST, ALT, alkaline phosphatase.

## AMPHOTERICIN B

Classification: Systemic anti-fungal agent.

Indication: Treatment of suspected or proven systemic fungal infections.

Dosage/administration: 1 to 1.5 mg/kg IV q 24h infused over 2 to 4 hours. Average duration of therapy is 2 to 4 weeks. Maximum concentration for infusion is 0.1 mg/mL for peripheral line administration and 0.5 mg/mL for central line administration. Mix only with dextrose solutions.

Adverse reactions: Hypokalaemia, hypomagnesaemia, nephrotoxicity, LFT abnormalities, thrombocytopenia, anemia, leukopenia, fever/chills, bronchospasm, and tachycardia.

## ANALGESICS

### ACETAMINOPHEN

Dosage/administration:

<32 weeks: 10 to 12 mg/kg/dose q 12h PO/PR PRN.

32 to 36 weeks: 10 to 15 mg/kg/dose q 8h PO/PR PRN.

≥37 weeks: 10 to 15 mg/kg/dose q 6h PO/PR PRN.





Precautions: Rectal suppositories associated with erratic release. Elimination is prolonged in patients with liver dysfunction.

Monitoring: Complete blood count (CBC), liver function tests (LFTs).

Adverse reactions: Rash, blood dyscrasias (thrombocytopenia, leukopenia, pancytopenia, and neutropenia). Adverse reactions are associated with excessive dosages.

Acute effects: Hepatic necrosis, transient azotemia, and renal tubular necrosis.

Chronic effects: Anaemia, renal damage, and gastrointestinal (GI) disturbances.

Treatment of overdose/severe toxicity: N-acetylcysteine (NAC).

## MORPHINE

Classification: Opiate, narcotic analgesic.

Indication: Analgesia, sedation, treatment of opiate withdrawal.

Analgesia/sedation: 0.05 to 0.1 mg/kg/dose IV/IM/SC/PO q 4–8h PRN for pain. Administer IV bolus over 5 to 15 minutes on syringe pump. May dilute in dextrose or saline solutions.

Continuous IV infusion: Following administration of loading dose, start continuous IV infusion: 0.01 to 0.02 mg/kg/hour (10 to 20 µg/kg/hour). Titrate for clinical indications. Use only preservative-free formulation. May dilute in saline or dextrose solutions (dextrose preferred).

Morphine for Neonatal Abstinence:

Initial Dose	Incremental Increases	Maximum Dose
0.04 mg/kg/dose q3h or q4h	0.04 mg/kg/dose	0.2 mg/kg/dose

Adverse reactions: Hypotension, CNS depression, respiratory depression, bradycardia, transient hypertonia, ileus, delayed gastric emptying, constipation.

## ANITINFLAMATORY

### IBUPROFEN

Classification: Nonselective cyclo-oxygenase enzyme inhibitor. Inhibitor of prostaglandin synthesis. Non-steroidal anti-inflammatory agent.

Indications: Pharmacologic closure of clinically significant ductus arteriosus.

Dosage/administration: Administer THREE doses per course. Begin with 10 mg/kg IV × 1 and then 5 mg/kg IV at 24 and 48 hours after initial dose. Infuse over 15 minutes at a concentration of 5 mg/mL. May dilute in dextrose or saline solutions.

Adverse reactions: oedema, peptic ulcer, GI bleed, GI perforation, neutropenia, anaemia, agranulocytosis, inhibition of platelet aggregation, acute renal failure.

## ANTICONVULSANTS

### PHENOBARBITAL

Classification: Anticonvulsant, sedative, hypnotic.

Indications: Management of neonatal seizures, neonatal withdrawal.



Dosage/administration: May give undiluted or may dilute with an equal volume of dextrose or saline solutions. The IV and PO doses are the same.

Seizures:

Loading dose: 20 mg/kg/dose, administer IV loading dose over >15 minutes (>1 mg/kg/minute) on syringe pump. Administer additional doses of 5 to 10 mg/kg every 15 to 20 minutes until cessation of seizures or a total dose of 40 mg/kg is administered. Use the IV route if possible because of unreliable IM absorption.

Maintenance therapy: 3 to 5 mg/kg/day IV/IM/PO given once or twice daily. Begin maintenance therapy 12 to 24 hours after loading dose.

Neonatal withdrawal syndrome:

Administer loading dose and then titrate based on NAS. Loading dose: 15 to 20 mg/kg/dose. Maintenance dose: 1 to 4 mg/kg/dose PO q12h. Closely follow blood levels after stabilisation of abstinence symptoms for 24 to 48 hours, decrease the daily dose by 20% every other day.

Adverse reactions: Respiratory depression (with serum concentrations >60 µg/mL), hypotension, circulatory collapse, paradoxical excitement, megaloblastic anaemia, hepatitis, and exfoliative dermatitis. Sedation reported at serum concentrations >40 µg/mL.

## PHENYTOIN

Classification: Anticonvulsant.

Indication: Treatment of seizures refractory to phenobarbital.

Dosage/administration: Dilute to a maximum of 10 mg/mL with NS. Use a 0.22-micron in-line filter. Start infusion immediately after preparation. Observe for precipitates. If given in a central line, flush catheter with 1 to 3 mL NS before and after administration because of heparin incompatibility. Infuse over > 30 minutes on syringe pump (maximum rate of 0.5 to 1 mg/kg/minute).

Loading dose: 15 to 20 mg/kg IV.

Maintenance dose: 4 to 8 mg/kg/day divided q 8–12h. Maintenance doses usually start 12 hours after loading dose. Avoid IM route because of erratic absorption, pain on injection, and precipitation of drug at injection site. PO absorption is erratic.

Adverse reactions: Hypersensitivity reaction, arrhythmias, hypotension, hyperglycaemia, cardiovascular collapse, liver damage, blood dyscrasias, hypoinsulinaemia, Stevens-Johnson syndrome/toxic epidermal necrolysis; extravasation may cause tissue necrosis and may be treated with hyaluronidase around the periphery of affected site.

## MIDAZOLAM

Classification: Benzodiazepine, sedative hypnotic, anticonvulsant.

Indications: Sedation.

Dosage/administration: IV dose: 0.05 to 0.15 mg/kg/dose q2–4h PRN. Administer over ≥15 minutes on syringe pump. Severe hypotension and seizures have been reported with rapid infusion in neonates. May dilute in dextrose or saline solutions.

Continuous IV infusion: Following administration of loading dose (0.1 mg/kg), start continuous infusion: 0.01 to 0.02 mg/kg/hour (10 to 20 µg/kg/hour). Titrate for clinical indications.

Adverse reactions: Sedation, respiratory arrest, apnoea, cardiac arrest, hypotension, bradycardia, and seizures (following rapid bolus administration and in neonates with underlying CNS disorders). Encephalopathy reported in several infants sedated for 4 to 11 days with midazolam and fentanyl.

## SEDATIVES

### FENTANYL

Classification: Narcotic analgesic.



Indication: Analgesia, sedation, anaesthesia.

Dosage/administration:

Sedation/analgesia: 1 to 4 µg/kg/dose q 2–4h. Administer slow IV push over 3 to 5 minutes. Larger IV bolus doses (>5 µg/kg) should be administered over 5 to 10 minutes. Consider using syringe pump for administration. If used for rapid sequence intubation in combination with paralytic agent, may be given as IV bolus.

Continuous infusion: Give a bolus dose of 1 to 2 µg/kg and then start the infusion at 1 to 2 µg/kg/hour. Titrate PRN. Tolerance may develop quickly.

Anaesthesia: 5 to 50 µg/kg/dose.

Bolus dose dilution instructions: Mix 1 mL of 100 µg/2 mL fentanyl in 9 mL NS. Mixture = 5 µg/mL.

Adverse reactions: CNS and respiratory depression, skeletal/thoracic muscle rigidity, vomiting, constipation, peripheral vasodilation, miosis, biliary or urinary tract spasms, and antidiuretic hormone release; tolerance/tachyphylaxis develops rapidly with continuous IV infusions for >3 to 5 days.

## NEUROMUSCULAR BLOCKING AGENTS

### PANCURONIUM

Classification: Non-Depolarising neuromuscular blocking agent.

Indications: Skeletal muscle relaxation, increased pulmonary compliance during mechanical ventilation, facilitate endotracheal intubation.

Dosage/administration: 0.05 to 0.15 mg/kg/dose IV q 1–2h PRN. May administer undiluted by slow IV push. Usual dose: 0.1 mg/kg/dose.

Clinical considerations: Should not be used in tachycardic infants or some cardiac conditions due to tachycardia side effect. Because sensation remains intact, administer concurrent sedation and analgesia. Apply ophthalmic lubricant.

Precautions: Preexisting pulmonary, hepatic, or renal impairment. In neonates with myasthenia gravis, small doses of pancuronium may have profound effects (may need to decrease dosage).

Adverse reactions: Tachycardia, hypertension, hypotension, excessive salivation, rashes, bronchospasm.

Antidote: Neostigmine 0.04 mg/kg IV (with atropine 0.02 mg/kg IV given 30 to 60 seconds before neostigmine administration).

### VECURONIUM

Classification: Non-Depolarising neuromuscular blocking agent.

Indications: Skeletal muscle relaxation, increased pulmonary compliance during mechanical ventilation, facilitate endotracheal intubation.

Dosage/administration: 0.1 mg/kg (range: 0.03 to 0.15 mg/kg/dose) IV q 1–2h PRN given by IV push. Continuous IV infusion: 0.05 to 0.15 mg/kg/hour. Mix with saline or dextrose solutions.

Precautions: Preexisting pulmonary, hepatic impairment. Premature neonates may be more sensitive to vecuronium effects.

Monitoring: Continuous cardiac, BP monitoring, assisted ventilation status.

Clinical considerations: Because sensation remains intact, administer concurrent sedation and analgesia PRN. Apply ophthalmic lubricant.

Adverse reactions: Arrhythmias, tachycardia (to a lesser degree than pancuronium), hypotension, hypertension, rash, bronchospasm.

Antidote: Neostigmine 0.025 mg/kg IV (with atropine 0.02 mg/kg IV).



## CARDIOVASCULAR

### SILDENAFIL

Classification: Phosphodiesterase Type-5 (PDE5) Inhibitor

Indications: Treatment for persistent pulmonary hypertension of the newborn.

Dosage/administration: 0.3 to 2 mg/kg/dose every 6 hours PO/IV

Decrease in blood pressure may occur due to vasodilator effects.

Adverse reactions: flushing, erythema, skin rash, diarrhoea, priapism, increased liver enzymes, nasal congestion.

### ATROPINE

Classification: Anticholinergic agent.

Indications: Prolonged cardiopulmonary resuscitation unresponsive to epinephrine; premedication for intubation when there is a high risk of bradycardia.

Dosage/administration: IV: 0.02 mg/kg/dose administered over 1 minute. May repeat once in 3 to 5 minutes.

Endotracheal tube (ETT): 0.04 to 0.06 mg/kg/dose. May repeat once if needed. Immediately follow with at least 1 mL NS.

NOTE: The use of a minimum dose (0.1 mg) is not recommended.

Clinical considerations: Effective oxygenation and ventilation must precede atropine treatment of bradycardia. Monitor HR.

Adverse reactions: Tachycardia, mydriasis, cycloplegia, abdominal distention/ileus, urinary retention, arrhythmias, oesophageal reflux, fever, hyperthermia, elevated white blood cell (WBC) count.

Antidote: Physostigmine.

### DIGOXIN

Classification: Antiarrhythmic agent, inotrope.

Indications: Heart failure, paroxysmal atrioventricular nodal tachycardia, atrial fibrillation/flutter, SVT.

Dosage and administration: Administer total digitalising dose (TDD) over 24 hours in THREE divided doses: First dose is one-half TDD, second dose is one-fourth TDD administered 8 hours after first dose, and third dose is one-fourth TDD administered 8 hours after second dose. Administer IV doses over 5 to 10 minutes on syringe pump. Avoid rapid IV infusion because this may result in systemic and coronary arteriolar vasoconstriction.

PMA	Total Digitalizing Dose (TDD) (Total Loading Dose)*		Maintenance Dose	
	PO	IV	PO	IV
≤29 weeks	20 µg/kg	15 µg/kg	5 µg/kg q24h	4 µg/kg q24h
30–36 weeks	25 µg/kg	20 µg/kg	6 µg/kg q24h	5 µg/kg q24h
37–48 weeks	40 µg/kg	30 µg/kg	5 µg/kg/dose q12h	4 µg/kg/dose q12h
≥49 weeks	50 µg/kg	40 µg/kg	6 µg/kg/dose q12h	5 µg/kg/dose q12h

\*Reserve TDD for the treatment of life-threatening arrhythmias and acute chronic heart failure.

Utilise maintenance dose schedule for non-acute arrhythmias and CHF conditions. Do not administer IM. PO doses should be 25% greater than IV doses. The paediatric IV formulation (100 µg/mL) may be given undiluted.



Adverse reactions: Persistent vomiting, feeding intolerance, diarrhoea, and lethargy, shortening of QTc interval, sagging ST segment, diminished T-wave amplitude, bradycardia, prolongation of PR interval, sinus bradycardia or S-A block, atrial or nodal ectopic beats, ventricular arrhythmias. Toxicity enhanced by hypokalaemia, hyper- and hypomagnesaemia, hypercalcaemia. Treat life-threatening digoxin toxicity with digoxin immune Fab.

### DOBUTAMINE

Classification: Sympathomimetic, adrenergic agonist agent.

Indications: Treatment of hypo-perfusion, hypotension, short-term management of cardiac decompensation. Has more effect on cardiac output than dopamine but less effect on BP.

Dosage/administration: 2 to 20 µg/kg/minute continuous IV infusion on syringe pump. Begin at a low dose and titrate to obtain desired cardiac output. Central venous access is preferred. Do not administer through UAC. May dilute in dextrose or saline solutions.

Adverse reactions: Hypotension if hypovolaemic, arrhythmias, tachycardia (with high doses), cutaneous vasodilation, increased BP and dyspnea.

### DOPAMINE

Classification: Sympathomimetic, adrenergic agonist agent.

Indications: Treatment of hypotension.

Dosage/administration: 2 to 20 µg/kg/minute through continuous IV infusion on syringe pump. Low doses (1 to 5 µg/kg/minute) increase renal blood flow and urine output; intermediate doses (5 to 15 µg/kg/minute) increase renal blood flow, HR, cardiac contractility, cardiac output, and BP; and with high doses (15 to 20 µg/kg/minute), the α-adrenergic effects predominate causing vasoconstriction and increased BP. Begin at a low dose and titrate to obtain desired mean arterial pressure. Once 20 µg/kg/minute is reached, consideration should be given to adding a second agent. Central venous access preferred. Do not administer through UAC. May dilute in dextrose or saline solutions.

Adverse reactions: Arrhythmias, tachycardia, vasoconstriction, hypotension, widened QRS complex, bradycardia, hypertension, excessive diuresis and azotemia, reversible suppression of prolactin and thyrotropin secretion, increased pulmonary artery pressure.

### EPINEPHRINE

Classification: Adrenergic agent.

Indications: Cardiac arrest, refractory hypotension, bronchospasm.

Dosage/administration:

Indication	Dose	Comments
Severe bradycardia and hypotension	<b>IV push:</b> 0.1–0.3 mL/kg of <b>1:10,000</b> concentration (equal to 0.01–0.03 mg/kg or 10–30 µg/kg)	May repeat every 3–5 minutes as needed
	<b>Endotracheal (ET) tube:</b> 0.5–1 mL/kg of <b>1:10,000</b> concentration (equal to 0.05–0.1 mg/kg or 50–100 µg/kg)	Must follow immediately with 1 mL NS flush in ET tube
Continuous IV	Start at 0.02–0.1 µg/kg/minute. Adjust dose to desired response, to a maximum of 1 µg/kg/minute	Use the <b>1:1,000</b> formulation for mixing continuous IV preparations.

Adverse reactions: Ventricular arrhythmias, tachycardia, pallor and tremor, severe hypertension with possible IVH, myocardial ischaemia, hypokalaemia, and decreased renal and splanchnic blood flow. IV infiltration may cause tissue ischaemia and necrosis (consider treatment with phentolamine).



## FUROSEMIDE

Classification: Loop diuretic.

Indications: Management of pulmonary oedema. To provide diuresis and improve lung function.

Dosage/administration:

IV: 1 to 2 mg/kg/dose q 12–24h. May administer undiluted over 2 to 5 minutes or may dilute with saline solutions and administer over 10 to 15 minutes at a concentration of 1 to 2 mg/mL.

PO: 1 to 2 mg/kg/dose q12–24h. For long-term use, consider alternate day therapy or longer (every 48 to 72 hours) in order to prevent toxicities. Give with feeds to reduce GI irritation. Give the alcohol- and sugar-free product to neonates. IV form may be given PO.

Adverse reactions: Fluid and electrolyte imbalance, hyponatremia, hypokalaemia, hypocalcaemia/hypercalciuria, hypochloremic alkalosis, nephrocalcinosis (associated with long-term therapy), potential ototoxicity (especially if receiving aminoglycosides), pre-renal azotemia, hyperuricemia, agranulocytosis, anaemia, thrombocytopenia, interstitial nephritis, pancreatitis, and cholelithiasis (in BPD or CHF and long-term TPN and furosemide therapy).

## OTHERS

### CAFFEINE CITRATE

Classification: Respiratory stimulant.

Indications: Apnoea of prematurity.

Dosage/administration: Give undiluted or dilute to 10 mg/mL with dextrose solutions.

Loading dose: 20 mg/kg IV/PO. Infuse IV loading dose over 30 minutes on syringe pump.

Maintenance dose: 5 to 10 mg/kg IV/PO daily, starting approximately 24 hours after loading dose. Mini bolus: 5 to 10 mg/kg/dose. Infuse IV maintenance dose over 10 minutes on a syringe pump. Do not skip scheduled doses when administering a bolus. It takes approximately 1 week for caffeine citrate to reach steady-state levels due to its long half-life. Do not push IV doses of caffeine citrate.

Adverse reactions: Cardiac arrhythmias, tachycardia (withhold dose for HR >180 beats per minute), insomnia, restlessness, irritability, nausea, vomiting, diarrhoea. Consider a decrease in dose to treat the CNS and/or GI side effects, diuresis, and increased urinary calcium excretion.

### AMINOPHYLLINE

Classification: Respiratory stimulant, bronchodilator. Theophylline derivative.

Indications: Apnoea of prematurity

Dosage/administration: IV

Loading dose: 6 mg/kg/dose

Maintenance: 2 mg/kg/dose every 8 to 12 hours

Adverse reactions: tachycardia, rash, diarrhoea, vomiting, tremor.

### RANITIDINE

Classification: H2 antagonist.

Indications: Duodenal and gastric ulcers, GER, and hyper-secretory conditions.

Dosage/administration:

Oral dose: 2 mg/kg/dose PO q 8–12h.



IV dose: 0.5 to 1 mg/kg/dose IV q 8–12h infused over 30 minutes on syringe pump. Usual concentration for infusion is 0.5 mg/mL mixed with saline or dextrose solutions. Maximum concentration for IV infusion is 2.5 mg/mL.

Continuous IV dose: 1.5 to 2 mg/kg/day.

Adverse reactions: GI disturbance, sedation, thrombocytopenia, hepatotoxicity, vomiting, bradycardia, or tachycardia. Use of acid-suppressing therapies in VLBW infants has been associated with a higher risk of NEC, bacterial, and fungal sepsis.

## METOCLOPRAMIDE

Classification: Antiemetic, pro-kinetic agent.

Indications: Improve gastric emptying and GI motility.

Dosage/administration: GI dysmotility: 0.1 to 0.15 mg/kg/dose q 6h IV/IM/PO; administer PO dose 30 minutes before feeds. Administer IV over 15 minutes on syringe pump. Maximum concentration for IV infusion is 5 mg/mL. May dilute in NS. IV form may be given PO.

Adverse reactions: Warnings: May cause tardive dyskinesia (often irreversible). Treatment duration and total dose are associated with an increased risk. Drowsiness, restlessness, agitation, diarrhoea, methaemoglobinaemia, agranulocytosis, leukopenia, neutropenia, and extrapyramidal symptoms (may occur following IV administration of large doses and within 24 to 48 hours of starting therapy; responds rapidly to diphenhydramine and subsides within 24 hours after stopping metoclopramide).

## URSODIOL

Classification: Gallstone dissolution agent.

Indications: Facilitates bile excretion in infants with biliary atresia and TPN cholestasis. Improves hepatic metabolism of essential fatty acids in infants with cystic fibrosis.

Dosages/administration: For PO use only.

Biliary atresia: 10 mg/kg/dose q 12h.

Cholestasis: 10 mg/kg/dose q 8h or 15 mg/kg/dose q 12h.

Cystic fibrosis: 15 mg/kg/dose q 12h.

Administration: Administer with food.

Precautions: Obtain baseline ALT, AST, alkaline phosphatase, direct bilirubin.

Contraindications: Use with caution in infants with chronic liver disease.

Adverse reactions: Hepatotoxicity, nausea, vomiting, abdominal pain, constipation.

Monitoring: Hepatic transaminases, direct bilirubin.

### Further reading:

Taketomo CK, Hodding JA, Kraus DM. Pediatric and Neonatal Dosage Handbook. Lexicomp Drug Reference Handbooks 2017-2018. 24th ed. Wolters Kluwer Clinical Drug Information; 2017.

Domonoske C. Appendix A: Common Neonatal Intensive Care Unit (NICU) Medication Guidelines. In: Eichenwald E, Hansen AR, Martin CR, Stark AR, editors. Cloherty and Stark's Manual of Neonatal Care. Eighth ed. Philadelphia, PA; Wolters Kluwer; 2017.



# APPENDICES

## A. BALLARD SCORE

### MATURATIONAL ASSESSMENT OF GESTATIONAL AGE (New Ballard Score)

NAME \_\_\_\_\_ SEX \_\_\_\_\_  
 HOSPITAL NO. \_\_\_\_\_ BIRTH WEIGHT \_\_\_\_\_  
 RACE \_\_\_\_\_ LENGTH \_\_\_\_\_  
 DATE/TIME OF BIRTH \_\_\_\_\_ HEAD CIRC. \_\_\_\_\_  
 DATE/TIME OF EXAM \_\_\_\_\_ EXAMINER \_\_\_\_\_  
 AGE WHEN EXAMINED \_\_\_\_\_  
 APGAR SCORE: 1 MINUTE \_\_\_\_\_ 5 MINUTES \_\_\_\_\_ 10 MINUTES \_\_\_\_\_

#### NEUROMUSCULAR MATURITY

NEUROMUSCULAR MATURITY SIGN	SCORE							RECORD SCORE HERE
	-1	0	1	2	3	4	5	
POSTURE								
SQUARE WINDOW (Wrist)								
ARM RECOIL								
POPLITEAL ANGLE								
SCARF SIGN								
HEEL TO EAR								
TOTAL NEUROMUSCULAR MATURITY SCORE								

SCORE  
 Neuromuscular \_\_\_\_\_  
 Physical \_\_\_\_\_  
 Total \_\_\_\_\_

#### MATURITY RATING

SCORE	WEEKS
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

#### PHYSICAL MATURITY

PHYSICAL MATURITY SIGN	SCORE							RECORD SCORE HERE
	-1	0	1	2	3	4	5	
SKIN	sticky friable transparent	gelatinous red translucent	smooth pink visible veins	superficial peeling &/or rash, few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled	
LANUGO	none	sparse	abundant	thinning	bald areas	mostly bald		
PLANTAR SURFACE	heel-toe 40-50 mm: -1 <40 mm: -2	>50 mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole		
BREAST	imperceptible	barely perceptible	flat areola no bud	stippled areola 1-2 mm bud	raised areola 3-4 mm bud	full areola 5-10 mm bud		
EYE / EAR	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear shift		
GENITALS (Male)	scrotum flat, smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae		
GENITALS (Female)	clitoris prominent & labia flat	prominent clitoris & small labia minora	prominent clitoris & enlarging minora	majora & minora equally prominent	majora large minora small	majora cover clitoris & minora		
TOTAL PHYSICAL MATURITY SCORE								

#### GESTATIONAL AGE (weeks)

By dates \_\_\_\_\_  
 By ultrasound \_\_\_\_\_  
 By exam \_\_\_\_\_





## B. APGAR SCORE

Score			
Sign	0	1	2
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent	Slow (irregular)	Good crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Reflex irritability	No response	Grimace	Cough or sneeze
Color	Blue, pale	Pink body, blue extremities	All pink

*Source: Adapted from Apgar V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg 1953;32:260-267.*

## C. SILVERMAN ANDERSON SCORE

Score	Upper chest retraction	Lower chest retraction	Xiphoid retraction	Nasal flaring	Grunt
0	Synchronised	None	None	None	None
1	Lag during inspiration	Just visible	Just visible	Minimal	Audible with Stethoscope
2	See-Saw	Marked	Marked	Marked	Audible with unaided ear

### Interpretation

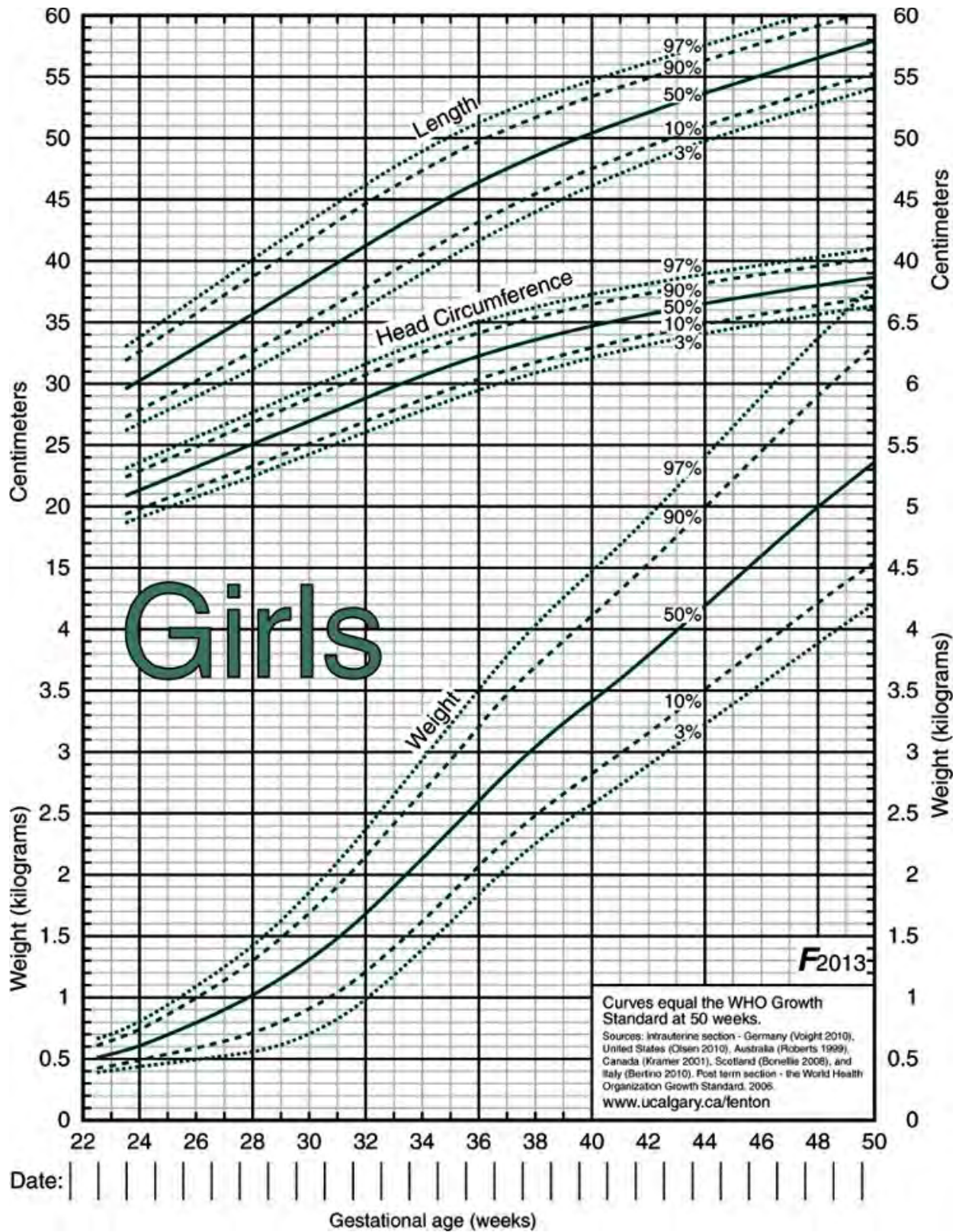
**Score 0-3 = Mild respiratory distress**

**Score 4-6 = Moderate respiratory distress**

**Score > 6 = Impending respiratory failure**



## D. FENTON PRETERM GROWTH CHART GIRLS

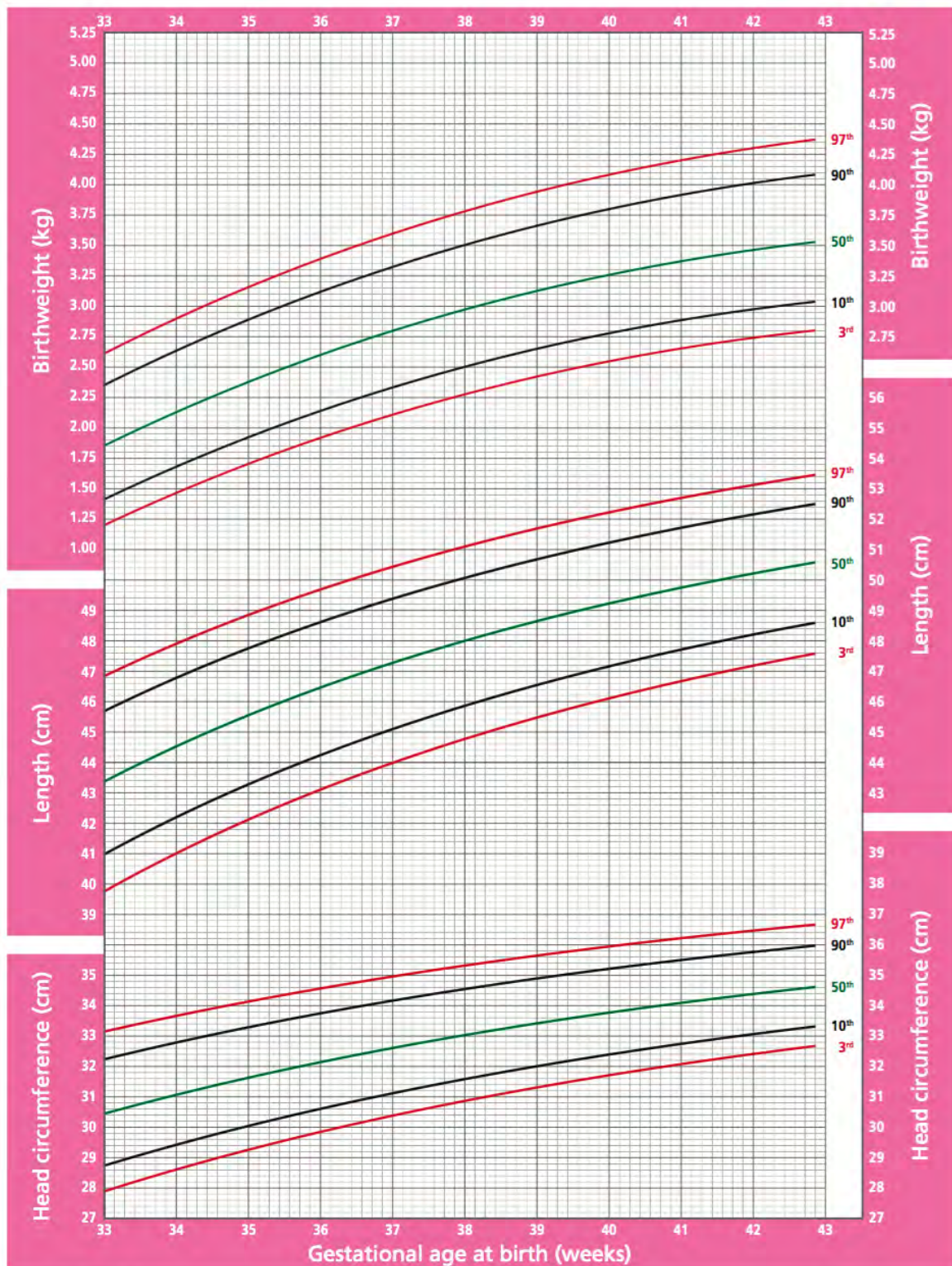




## F. INTERGROWTH-21 TERM NEWBORN GROWTH CHART GIRLS



### International Newborn Size Standards (Girls)



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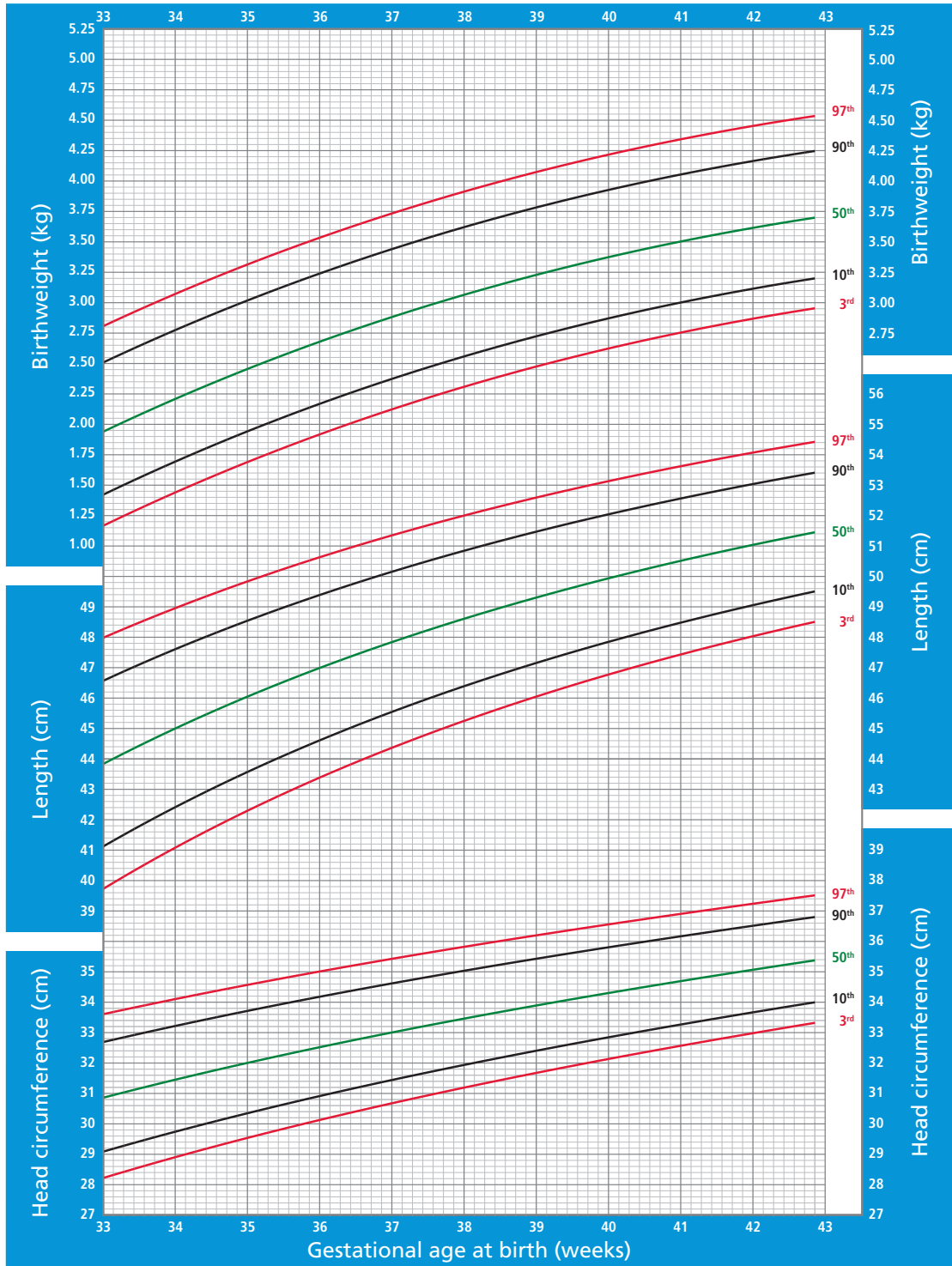
Villar et al. Lancet 2014;384:857-68



# G. INTERGROWTH-21 TERM NEWBORN GROWTH CHART BOYS



## International Newborn Size Standards (Boys)



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Villar et al. *Lancet* 2014;384:857-68



## H. SCHEDULE FOR IMMUNISATION OF PRETERM INFANTS

1. Vaccine doses should not be reduced for preterm infants.
2. Use thimerosal-free vaccines.
3. Intramuscular injections to preterm infants might require a shorter needle than the standard - to 1-inch needle.
4. BCG. Preterm babies can be effectively vaccinated with BCG at the same chronological age and according to the same schedule and using the same precautions as for full-term infants and children once they have a chronological age  $\geq$  35 weeks and weight of  $>$  2000 g.
5. Hepatitis B. All infants should receive Hepatitis B Birth dose or in the first 24 hours if mother is HBsAg negative and in the first 12 hours if mother is HBsAg positive.
  1. For infants with birthweight  $<$  2000 g: If mother is HBsAg positive: continue schedule with three additional vaccine doses at 1, 2 to 3, and 6 to 7 months' chronologic age. If mother is HBsAg negative: continue schedule with the standard additional two doses at 2 to 4, and 6 to 18 months' chronologic age.
    - a. Check anti-HBs and HBsAg at 9 to 15 months of age.
    - b. If anti-HBs and HBsAg are negative, reimmunise with three doses of vaccine at 2-month intervals and retest titers.
  2. For infants with birthweight  $>$  2000 g: If mother is HBsAg positive: continue schedule with the standard additional two doses at 1 and 6 months' chronologic age. If mother is HBsAg negative: continue schedule with the standard additional two doses at 2 to 4, and 6 to 18 months of chronologic age.
    - a. Check antibody to hepatitis B surface antigen (anti-HBs) and HBsAg at 9 to 15 months of age.
    - b. If infant is anti-HBs and HBsAg negative, reimmunise with three doses at 2-month intervals and retest.
  3. Breastfeeding by a mother who is positive for hepatitis B surface antigen (HBsAg) poses no additional risk for acquisition of hepatitis B virus (HBV) infection by the infant.
  4. The following are not contraindications to Hep B vaccination: prematurity, low birth weight, small for gestational age, HIV infection of mother or infant, and jaundice.
6. Preterm infants should receive a full dose of diphtheria and tetanus toxoids and acellular pertussis (DPT), Haemophilus influenzae type B (Hib) conjugate, inactivated poliovirus (IPV), and pneumococcal conjugate (PCV13) at 60 days' chronologic age, regardless of birth weight and gestational age, as long as they are medically stable and consistently gaining weight.
7. Immunisations for preterm infants may be given over 2 or 3 days to minimise the number of injections at a single time.
8. Immunisations (except BCG vaccine) may be given during corticosteroid administration.
9. Immunisations may be given during antibiotic treatment once infant is clinically stable.
10. Palivizumab (Synagis) should be given according to the respiratory syncytial virus (RSV) policy. (NOT available in Belize)
11. Infants with chronic respiratory tract disease should receive the influenza immunisation annually, before or during the influenza season, when they are 6 months postnatal age or older:
  1. The infant should receive two doses of vaccine, 1 month apart.
  2. Family and other caregivers should also receive influenza vaccine annually to protect the infant from exposure.



## I. NEONATAL PAIN ASSESSMENT TOOL

Pain Assessment Tool	Gestational Age/ Post-conceptual Age	Physiologic Components	Behavioral Components	Type of Pain	Adjusts for Prematurity	Scale Metric
PIPP (Premature Infant Pain Profile) <sup>1</sup>	28–40 wk	Heart rate, oxygen saturation	Alertness, brow bulge, eye squeeze, nasolabial furrow	Procedural and Postoperative	Yes	0 to 21
CRIBS (Cries, Requires Oxygen, Increased Vital Signs, Expression, Sleeplessness) <sup>2</sup>	32–56 wk	Blood pressure, heart rate, oxygen saturation	Cry, expression, sleeplessness	Postoperative	No	0 to 10
NIPS (Neonatal Infant Pain Scale) <sup>3</sup>	28–38 wk	Breathing pattern	Facial expression, cry, arms, legs, alertness	Procedural	No	0 to 7
COMFORT (and COMFORTneo) <sup>4,5</sup>	0–3 y (COMFORTneo: 24–42 wk)	Respiratory response, blood pressure, heart rate	Alertness, agitation, physical movements, muscle tone, facial tension	Postoperative (COMFORTneo: prolonged)	No	8 to 40
NFCS (Neonatal Facial Coding System) <sup>6</sup>	25 wk to Term	None	Brow bulge, eye squeeze, nasolabial furrow, open lips, stretch mouth (vertical and horizontal), lip purse, taut tongue, chin quiver	Procedural	No	0 to 10
N-PASS (Neonatal Pain, Agitation, and Sedation Scale) <sup>7</sup>	0–100 d	Heart rate, respiratory rate, blood pressure, oxygen saturation	Crying/irritability, behavior state, facial expression, extremities/ tone	Acute and prolonged pain Also assesses sedation	Yes	Pain: 0 to 10 Sedation –10 to 0
EDIN (Échelle de la Douleur Inconfort Nouveau-Né – Neonatal Pain and Discomfort Scale) <sup>8</sup>	25–36 wk	None	Facial activity, body movements, quality of sleep, quality of contact with nurses, consolability	Prolonged	No	0 to 15
BPSN (Bernese Pain Scale for Neonates) <sup>9</sup>	27–41 wk	Respiratory pattern, heart rate, oxygen saturation	Alertness, duration of cry, time to calm, skin color, brow bulge with eye squeeze, posture	Procedural	No	0 to 27

## J. OPIOIDS FOR PAIN MANAGEMENT

Drug	Advantages	Disadvantages
Morphine	Potent pain relief Better ventilator synchrony Sedation Hypnosis Muscle relaxation Inexpensive	Respiratory depression Arterial hypotension Constipation, nausea Urinary retention Central nervous system depression Tolerance, dependence Long-term outcomes not studied Prolonged ventilator use
Fentanyl	Fast acting Less hypotension	Respiratory depression Short half-life Quick tolerance and dependence Chest wall rigidity Inadequately studied
Remifentanyl	Fast acting Degraded in the plasma Unaffected by liver metabolism	—

*Source:* Reprinted with permission from Hall RW, Anand KJS. Pain management in newborns. *Clin Perinatol* 2014;41(4):895–924.



## K. Y-SITE MEDICATION COMPATIBILITY IN PN SOLUTIONS

### Y-Site Medication Compatibility With 2-in-1 and 3-in-1 PN Solutions.

Medication	PN Solution		Medication	PN Solution	
	2-in-1	3-in-1		2-in-1	3-in-1
Acyclovir	I	I	Mannitol	C	C
Amphotericin B	I	I	Meperidine HCL	C	C
Ampicillin	C/I	C	Meropenem	NA	C
Bumetanide	C	C	Mesna	C	C
Calcium gluconate	C	C	Methotrexate	I	C
Cefazolin	C/I	C	Methylprednisolone sodium succinate	C	C
Cefepime	C	NA	Metoclopramide	I/C	C
Cefotaxime	C	C	Metronidazole	C	C
Ceftazidime	C	C	Micafungin sodium	C	NA
Ceftriaxone	C	C	Midazolam	I/C	I
Cefuroxime	C	C	Milrinone	C	NA
Ciprofloxacin	I	C	Morphine sulfate (concentration 1 mg/mL)	C	C
Cisplatin	I	C	Norepinephrine bitartrate	C	C
Clindamycin	C	C	Octreotide acetate	C	C
Cyclophosphamide	C	C	Ondansetron HCl	C	I
Dexamethasone sodium phosphate	C	C	Pentobarbital sodium	C	I
Digoxin	C	C	Phenobarbital sodium	C	I
Diphenhydramine	C	C	Phenytoin sodium	I	NA
Dobutamine	C	C	Piperacillin sodium-tazobactam sodium	C	C
Dopamine	C	C/I	Potassium chloride	C	C
Epinephrine	C	NA	Potassium phosphate	I	I
Epoetin alfa	C	NA	Propofol	C	NA
Famotidine	C	C	Ranitidine	C	C
Fentanyl citrate	C	C	Sodium bicarbonate	I/C	C
Fluconazole	C	C	Sodium nitroprusside	C	C
5-Fluorouracil	C/I	C/I	Sodium phosphate	I	I
Furosemide	C/I	C	Tacrolimus	C	C
Gentamicin sulfate	C	C	Tobramycin sulfate	C	C
Heparin sodium	C	I	Trimethoprim-sulfamethoxazole	C	C
Hydrocortisone sodium phosphate	C	C	Vancomycin	C	C
Hydromorphone	C	I/C	Vecuronium bromide	C	NA
Ifosfamide	C	C	Zidovudine	C	C
Imipenem-cilastatin	C	C			
Indomethacin	I	NA			
Insulin regular	C	C			
Leucovorin calcium	C	C			
Linezolid	C	NA			
Lorazepam	C	I			
Magnesium sulfate	C	C			

Abbreviations: C, compatible; C/I, conflicting compatibility, but strength of evidence supports compatibility; I, incompatible; I/C, conflicting compatibility and strength of evidence supports compatibility; IU, international units; NA, compatibility data not available; PN, parenteral nutrition, Y-site injection; drug administration via piggyback, IV push, or other IV methods at the Y-site injection port or other access port (ie, stopcock) between the PN solution and the central venous catheter.

\*Modified with permission from Mirtallo.<sup>29</sup>

Source: From Gargasz A. Neonatal and Pediatric Parenteral Nutrition. *Advanced Critical Care. Am Ass of Crit-Care Nurs.* 2012; 23:4





## L. NEWBORN ESTIMATED BLOOD PRESSURE VALUES ACCORDING TO PMA (after two weeks of age)

Postconceptual Age	50th Percentile	95th Percentile	99th Percentile
44 weeks			
SBP	88	105	110
DBP	50	68	73
MAP	63	80	85
42 weeks			
SBP	85	98	102
DBP	50	65	70
MAP	62	76	81
40 weeks			
SBP	80	95	100
DBP	50	65	70
MAP	60	75	80
38 weeks			
SBP	77	92	97
DBP	50	65	70
MAP	59	74	79
36 weeks			
SBP	72	87	92
DBP	50	65	70
MAP	59	72	77
34 weeks			
SBP	70	85	90
DBP	40	55	60
MAP	50	65	70
32 weeks			
SBP	68	83	88
DBP	40	55	60
MAP	49	64	69
30 weeks			
SBP	65	80	85
DBP	40	55	60
MAP	48	63	68
28 weeks			
SBP	60	75	80
DBP	38	50	54
MAP	45	58	63
26 weeks			
SBP	55	72	77
DBP	30	50	56
MAP	38	57	63
SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. Source: From Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. <i>Pediatr Nephrol</i> 2012;27:17-32.			



## M. CEREBROSPINAL FLUID VALUES IN TERM AND PRETERM NEWBORN

Cerebrospinal fluid parameters in term neonates; non-traumatic vs traumatic

	RBC nil	RBC < 500/mm <sup>3</sup>
<b>WBC count/mm<sup>3</sup></b>		
Mean	5.5	6.8
SD	3.6	4.2
<b>Protein (mg/dl)</b>		
Mean	68.2	70.5
SD	15.1	22.8
<b>Glucose (mg/dl)</b>		
Mean	55.0	37.6
SD	25.6	22.2

RBC – Red blood cell; SD – Standard deviation; WBC – White blood cell

Source: Majumdar A, Jana A, Jana A, Biswas S, Bhattacharyya S, Bannerjee S. Importance of normal values of CSF parameters in term versus preterm neonates. *J Clin Neonatol* 2013;2:166-8.

Cerebrospinal fluid parameters in preterm neonates; non-traumatic vs traumatic

	RBC nil	RBC < 500/mm <sup>3</sup>
<b>WBC count/mm<sup>3</sup></b>		
Mean	5.1	7.2
SD	5.2	6.5
<b>Protein (mg/dl)</b>		
Mean	72.6	102.5
SD	15.8	30.6
<b>Glucose (mg/dl)</b>		
Mean	50.3	45.2
SD	27.6	22.4

RBC – Red blood cell; SD – Standard deviation; WBC – White blood cell

Source: Majumdar A, Jana A, Jana A, Biswas S, Bhattacharyya S, Bannerjee S. Importance of normal values of CSF parameters in term versus preterm neonates. *J Clin Neonatol* 2013;2:166-8.



## N. HAEMATOLOGIC VALUES IN TERM AND PRETERM NEWBORN

### Normal Haematologic Values During the First Two Weeks of Life in the Term Infant

Value	Cord Blood	Day 1	Day 3	Day 7	Day 14
Hb (gm/100ml)	16.8	18.4	17.8	17.0	16.8
Haematocrit (%)	53.0	58.0	55.0	54.0	52.0
Red cells (cu.mm. x 10 <sup>6</sup> )	5.25	5.8	5.6	5.2	5.1
MCV (m <sup>3</sup> )	107	108	99.0	98.0	96.0
MCH (γγ)	34	35	33	32.5	31.5
MCHC (%)	31.7	32.5	33	33	33
Reticulocytes (%)	3-7	3-7	1-3	0-1	0-1
Nuc RBC (cu.mm)	500	200	0-5	0	0
Platelets (1000's/cu.mm)	290	192	213	248	252

MCV = mean corpuscular volume

MCH = mean corpuscular haemoglobin

MCHC = mean corpuscular haemoglobin concentration

### The White Blood Cell Count and the Differential Count During the First Two Weeks of Life

Age	Leukocytes	Neutrophils			Eosinophils	Basophils	Lymphocytes	Monocytes
		Total	Seg	Band				
<b>Birth</b>								
Mean	18,100	11,000	9,400	1,600	400	100	5,500	1,050
Range	9.0-30.0	6.0-26			20-850	0-640	2.0-11.0	0.4-3.1
Mean %	-	61	52	9	2.2	0.6	31	5.8
<b>7 Days</b>								
Mean	12,200	5,500	4,700	830	500	50	5,000	1,100
Range	5.0-21.0	1.5-10.0			70-1100	0-250	2.0-17.0	0.3-2.7
Mean %	-	45	39	6	4.1	0.4	41	9.1
<b>14 Days</b>								
Mean	11,400	4,500	3,900	630	350	50	5,500	1,000
Range	5.0-20.0	1.0-0.5			70-1000	0-230	2.0-17.0	0.2-2.4
Mean %	-	40	34	5.5	3.1	0.4	48	8.8

### Haematologic Values in Low Birthweight Infants

Determination	Age of Infant					
	1-3 Days	4-7 Days	2 Weeks	4 Weeks	6 Weeks	8 Weeks
<b>Birthweight less than 1200g</b>						
Haemoglobin	15.6	16.4	15.5	11.3	8.5	7.8
Reticulocytes as % of RBC	8.4	3.9	1.9	4.1	5.4	6.1
Platelets	148,000 ± 61,000	163,000 ± 69,000	162,000	158,000	210,000	212,000
Leukocytes	14,800 ± 10,200	12,200 ± 7,000	15,800	13,200	10,800	9,900
Segmented neutrophils	46	32	41	28	23	23
Band neutrophils	10.7	9.7	8.0	5.9	5.8	4.4
Juvenile neutrophils	2.0	3.9	5.3	3.6	2.6	2.0
Lymphocytes	32	43	39	55	61	65
Monocytes	5	7	5	4	6	3
Eosinophils	0.4	6.2	1.0	3.7	2.0	3.8
Nucleated RBC as % of total RBC	16.7	1.1	0.1	1.0	2.7	2.0
<b>Birthweight 1200-1500g</b>						
Haemoglobin	20.0	18.0	17.1	12.0	9.1	8.3
Reticulocytes as % of RBC	2.7	1.2	0.9	1.0	2.2	2.7
Platelets	151,000 ± 35,000	134,000 ± 49,000	153,000	189,000	212,000	244,000
Leukocytes	10,800 ± 4,000	8,900 ± 2,900	14,300	11,000	10,500	9,100
Segmented neutrophils	47	31	33	26	20	25
Band neutrophils	11.9	10.5	5.9	3.0	1.4	2.1
Juvenile neutrophils	5.1	2.4	2.7	1.8	1.7	1.6
Lymphocytes	34	48	52	59	69	64
Monocytes	3	6	3	4	5	5
Eosinophils	1.3	2.2	2.5	5.1	2.6	2.3
Nucleated RBC as % of total RBC	19.8	0.8	0	0.4	1.4	1.0

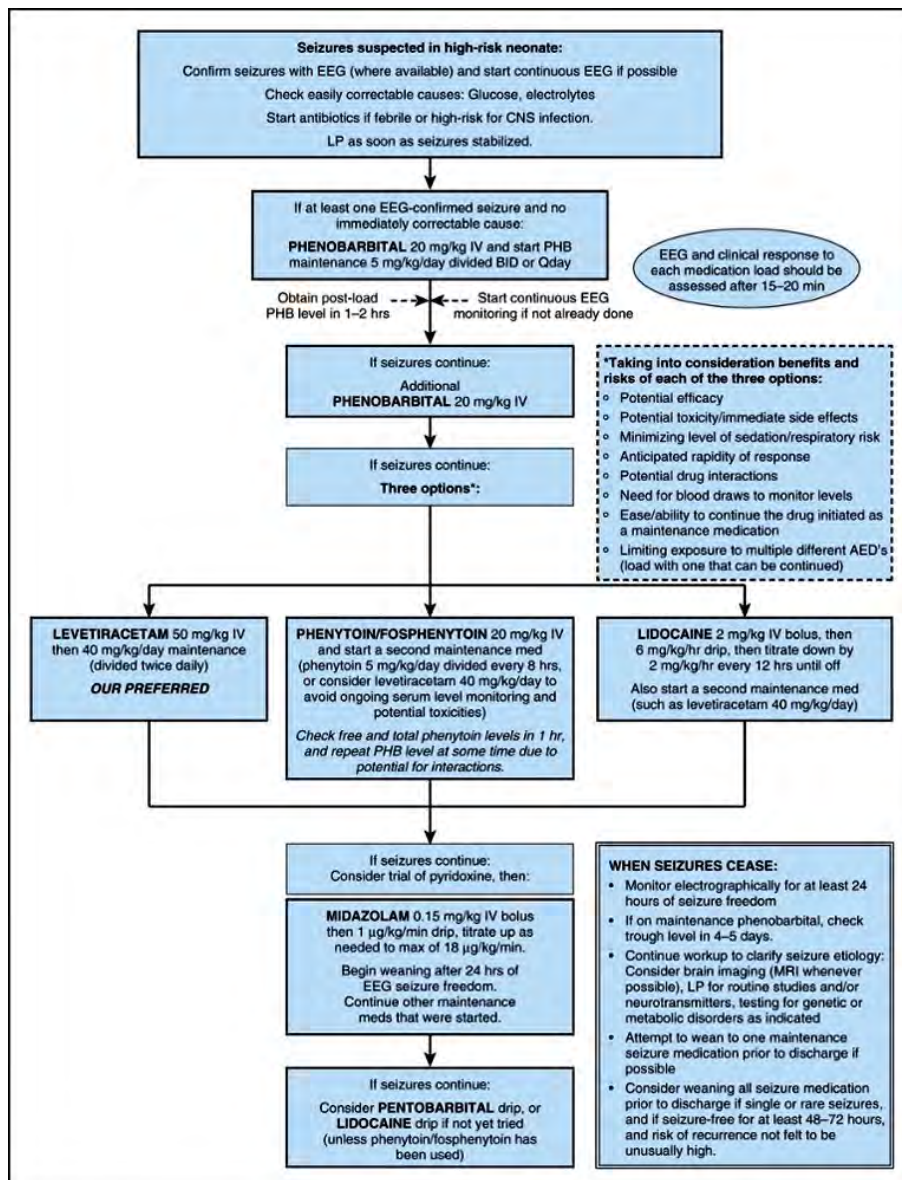
Source: <http://www.adhb.govt.nz/newborn/Guidelines/Blood/HaematologicalValues.htm>



## O. BLOOD GASES NORMAL VALUES

	ARTERIAL	CAPILLARY	VENOUS
pH	7.35 to 7.45	7.35 to 7.45	7.32 to 7.42
pCO <sub>2</sub> (mmHg)	35 to 45	35 to 45	38 to 52
pO <sub>2</sub> (mmHg)	70 to 100	60 to 80	24 to 48
HCO <sub>3</sub> (mEq/L)	19 to 25	19 to 25	19 to 25
TCO <sub>2</sub> (mEq/L)	19 to 29	19 to 29	23 to 33
O <sub>2</sub> saturation (%)	90 to 95	90 to 95	40 to 70
Base excess (mEq/L)	-5 to +5	-5 to +5	-5 to +5

## P. NEONATAL SEIZURE MANAGEMENT ALGORITHM



Source: Volpe's Neurology of the Newborn. Sixth ed. Philadelphia, PA; Elsevier; 2018.



# NOTES

