PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 19: PREMATURITY AND NEONATAL CONDITIONS
NEMLC 8 DECEMBER 2022 – REPORT
Clinical Editor comment updates

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
19.2.2 Respiratory Distress **19.3 Prematurity/preterm neonate** **19.3.1 Enterocolitis, necrotizing** **19.6.1 Hypoxia-ischaemia of the newborn**	Packed Red Cells	Thresholds amended
		Duration of administration amended
19.2.2 Respiratory Distress **19.3.1 Enterocolitis, necrotizing** **19.5.1 Meningitis bacterial** **19.5.2 Septicaemia of the newborn** **19.5.3 Group B Streptococcus** **19.6.1 Hypoxia-ischaemia of the newborn**	Ampicillin	Gestational age dosing added
19.5.1 Meningitis bacterial	Cefotaxime	Gestational age dosing added

General

PaO_2
Both units mmHg and kPa included throughout the chapter.

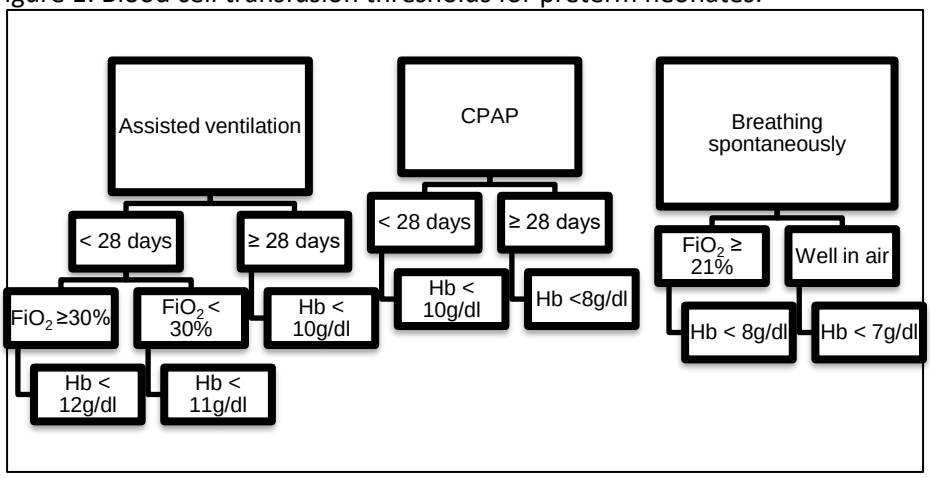
Packed Red Cells
Packed red cells: Thresholds amended
Packed red cells: Duration of administration amended

The Clinical Editor proposed the consideration of thresholds to transfuse depending on the oxygen/CPAP requirements, to present huge amounts of transfusions occurring with a single number of < 13 g/dL. The transfusion protocol was used in a study assessing whether adopting a restrictive blood transfusion policy resulted in fewer transfusions.[1] This study collected data retrospectively from a hospital nursery following implementation of the restrictive blood transfusion policy. After the introduction of the policy, 42 of the 1097 patients admitted (3.8%) received 64 blood transfusions; in comparison to 102 patients out of 940 admitted (10.9%) prior to restrictive policy over same length of period, $p < 0.001$.

The text was amended as follows:

[1] Harrison MC, Pillay S, Joo

Figure 1: Blood cell transfusion thresholds for preterm neonates.



**Thresholds from Harrison et.al. Resource implications of adopting a restrictive neonatal blood transfusion policy, SAMJ, 2013.*

If anaemia is present according to thresholds in figure 1 above:

~~If anaemia if present, Hct < 40% and Hb < 13 g/dL~~

- Packed red cells, IV, 10–15 mL/kg over ~~1-2~~ 3-4 hours in haemodynamically stable patients. More rapid transfusions may be appropriate in bleeding and haemodynamically unstable patients.

Gestational age dosing: Ampicillin and Cefotaxime

Gestational age dosing was previously not included in this chapter for ampicillin and cefotaxime, this was proposed as a beneficial addition. This was added as shown below.[2,3,4,5]

- Cefotaxime, IV, 50 mg/kg over 30 minutes.
  - ~~If < 7 days of age: 50 mg/kg 12 hourly.~~
  - ~~If 7 days–3 weeks of age: 50 mg/kg 8 hourly.~~
  - ~~If > 3 weeks of age: 50 mg/kg 6 hourly.~~

Gestational age	Postnatal age	Dose
< 32 weeks	< 14 days	50 mg/kg/dose every 12 hours
	14 to 28 days	50 mg/kg/dose every 8 hours
≥ 32 weeks	≤ 7 days	50 mg/kg/dose every 12 hours
	8 to 28 days	50 mg/kg/dose every 8 hours

- Ampicillin, IV.

[2] Le J, Greenberg RG, Yoo Y, et al. Ampicillin dosing in premature infants for early-onset sepsis: exposure-driven efficacy, safety, and stewardship. *J Perinatol*. 2022;42(7):959-964. doi:10.1038/s41372-022-01344-2 [PubMed 35210541]

[3] American Academy of Pediatrics (AAP). In: Kimberlin DW, Barnett E, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. 32nd ed. American Academy of Pediatrics; 2021.

[4] Tremoulet A, Le J, Poindexter B, et al. Characterization of the population pharmacokinetics of ampicillin in neonates using an opportunistic study design. *Antimicrob Agents Chemother*. 2014;58(6):3013-3020. [PubMed 24614374]

[5] Bradley JS, Nelson JD, Barnett ED, et al, eds. *Nelson's Pediatric Antimicrobial Therapy*. 28th ed. American Academy of Pediatrics; 2022:chap 2.

- ~~If < 7 days of age: 50 mg/kg 12 hourly.~~
- ~~If > 7 days–3 weeks of age: 50 mg/kg 8 hourly.~~
- ~~If > 3 weeks of age: 50 mg/kg 6 hourly.~~

Gestational Age	Postnatal Age	Dose
≤ 34 weeks	≤ 7 days	50 mg/kg/dose every 12 hours
	8 to 28 days	75 mg/kg/dose every 12 hours
>34 weeks	≤ 28 days	50mg/kg/dose every 8 hours

PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 19: PREMATURITY AND NEONATAL CONDITIONS
NEMLC 23 JUNE 2022 – REPORT

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
19.2.2 Respiratory Distress in the newborn	Surfactant	No type specified
19.3.2 Patent Ductus Arteriosus (PDA)	Paracetamol, oral	Added
19.3.4 Apnoea, neonatal	Caffeine	Oral route emphasized as first-line
	Aminophylline IV	Retained
19.4.1 Heart Failure in Neonates	Captopril	Dose Amended
19.4.2 Cyanotic Heart disease in the Newborn	Alprostadil	Infusion dosage added
19.5.3 Group B Streptococcus *(new section)*	Ampicillin	Added
	Gentamicin	Added
19.6.1 Hypoxia/ischaemia of the newborn *(seizure control)*	Midazolam	Added
	Levetiracetam	Not added
19.6.2 Seizures, neonatal	Midazolam	Added
	Levetiracetam	Not added

General

A note to always assess gestation age as accurately as possible was added, and the Ballard Scoring Assessment was added to the chapter.

Oxygen saturation:
Oxygen saturation targets amended to: 90 to 95% throughout chapter.[6]

Headbox
Use of headbox oxygen was removed from all sections in chapter.

19.1 Resuscitation of the newborn

Resuscitation algorithm
The latest resuscitation algorithm from the Resuscitation Council of South Africa was added (2021).[7]

19.2.1.1 Hyperbilirubinaemia, unconjugated

Phototherapy and total serum bilirubin monitoring in first week of life tables inserted for guidance.[8]

[6] Askie, LM et al. Effects of targeting lower vs higher arterial oxygen saturations on death and disability on preterm infants. Cochrane Database of Systematic Reviews. 2017(4).
[7] Resuscitation Council of South Africa. 2021. https://resus.co.za/Documents/Algorithms/Newborn%20Resuscitation%20Algorithm.pdf
[8] Horn AR, Kirsten GF, Kroom SM, Henning PA, Moller G, Pieper C, et.al. Phototherapy and exchange transfusion for neonatal hyperbilirubinaemia. SAMJ. 2006, 96 (9):819-824.

19.2.2 Respiratory Distress in the newborn

Surfactant: Type of surfactant not specified.

The recommendation to include surfactant was kept general recommending surfactant 100mg/kg. No new evidence to suggest superiority of a specific surfactant was found, and the recommendations from the Medicine Review: Poractant alfa and Beractant (2018) for surfactants to be considered a therapeutic class with the most affordable agent procured was retained. [9]

19.3.1 Enterocolitis, necrotising

Modified Bells Staging Criteria for Necrotising Enterocolitis was added.

19.3.2 Patent Ductus Arteriosus (PDA) in the newborn

Closure of PDA in preterm infants less than 14 days of age

Paracetamol, oral: added

Paracetamol was added as an alternative to ibuprofen for closure of PDA in preterm infants. Paracetamol has been shown to be as effective as ibuprofen in closing a PDA.

Cochrane systematic review[10]:

- A Cochrane review including 5 studies comparing treatment of PDA with paracetamol versus ibuprofen (n=559) found no significant difference between paracetamol and ibuprofen for failure of ductal closure after first course of drug administration (typical risk ratio (RR) 0.95, 95% CI 0.75 to 1.21; typical risk difference (RD) -0.02, 95% CI -0.09 to 0.09). This evidence is assessed to be moderate-quality *(allocation concealment unclear in one study, concerns of performance and detection bias).*
- Three studies reported all-cause mortality during initial hospital stay, and showed no significant difference between paracetamol and ibuprofen, (typical RR 0.96, 95% CI 0.55 to 1.67). Moderate quality evidence *(down graded due to precision issues, small sample size – point estimate not precise).*
- Four studies (n = 537) reported on gastrointestinal bleed. This was found to be lower in the paracetamol group versus the ibuprofen group (typical RR 0.28, 95% CI 0.12 to 0.69; typical RD −0.06, 95% CI −0.09 to −0.02); number needed to treat for an additional beneficial outcome (NNT) 17 (95% CI 11 to 50). This is based on moderate quality of evidence *(downgraded due to concerns of performance and detection bias)*.
- Only one study reported on long-term follow-up to 18 to 24 months of age following treatment with paracetamol versus ibuprofen. There were no significant differences in the neurological outcomes at 18 to 24 months (n = 61). This finding is however based on low quality evidence *(downgraded due to issues of precision)*.

Paracetamol offers an alternative to ibuprofen where ibuprofen is contraindicated, and may have a better adverse event profile.

Level of evidence: II

[9] National Essential Medicines List Committee. Medicine Review: Poractant alfa and beractant for respiratory Distress in Newborns, March 2018.

[10] Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants (Review). Cochrane Database of Systematic Reviews. CD010061. 2020.

19.3.4 Apnoea, neonatal

Caffeine: Oral route emphasized as first line
Aminophylline, IV: retained.

- Text was added to emphasize that the oral route is strongly recommended, and that this can be extemporaneously compounded (a more affordable option than the IV solution orally).
- Aminophylline was retained only for consideration if caffeine is not available. Caffeine has a better drug profile: longer half-life, higher therapeutic index and lack of need for drug-level monitoring. However the Paediatric Committee suggested aminophylline be retained as an alternative in settings where caffeine may not be available.

19.4.1 Heart failure in neonates

Captopril: dose amended

Starting dose and maximum dose amended in line with the South African Medicines Formulary.[11]

The text was amended as follows:

- Captopril, oral, ~~0.01–0.05~~ 0.2 mg/kg/dose, 8–12 hourly, initially.
  - Adjust dose and interval based on response to a maximum of 1 mg/kg/dose.
  - Administer 1 hour before feeding.
  - Continue as long as needed to control the heart failure

19.4.2 Cyanotic heart disease in the newborn

Alprostadil: infusion dosage added

The infusion dose and appropriate mixing was added for ease of administration.

The text was amended as follows:

- Prostaglandin therapy, i.e.:

~~- Alprostadil, IV, 0.12mg/kg in 20ml dextrose water at 0.5ml/hr-1ml/hr (0.05–0.1 mcg/kg/minute), initial dose, (under specialist consultation) :~~

- Alprostadil, IV(under specialist consultation) :
  - Add 1 amp (500mcg) to 50mls dextrose water at 0.3-0.6mls/hr (0.05-0.1mcg/kg/minute)
  - Discard the solution after 24 hours.

19.5.3 Group B Streptococcus

Ampicillin: added
Gentamicin: added

Added as new section as follows:

[11] Division of Pharmacology, Faculty of Health Sciences, University of Cape Town and Health and Medical Publishing group. South African Medicines Formulary, 12th Edition. 2016.

19.5.3 GROUP B STREPTOCOCCUS

DESCRIPTION

Group B streptococcus is an encapsulated Gram-positive coccus that colonises the gastrointestinal and genitourinary tracts.

Infection in the first 6 days of life is referred to as early-onset disease (EOD).
Late-onset disease (LOD) refers to infection from day 7 - 89 of life.

DIAGNOSTIC CRITERIA

» Infants may present in respiratory distress or with signs of septicaemia.
» Complications include meningitis, cellulitis, osteomyelitis or septic arthritis.
» A blood culture should be performed, before initiation of antibiotics, in infants that are at risk of sepsis, namely, maternal fever, prolonged rupture of membranes or prematurity due to an unknown cause.
» Meningitis should be excluded in all patients that have a positive blood culture for group B streptococcus.

GENERAL AND SUPPORTIVE MEASURES

Refer to section on septicaemia of the newborn

MEDICINE TREATMENT

- Ampicillin, IV, 50 mg/kg/dose for 10 days.
  - If age < 7 days: 50 mg/kg 12 hourly.
  - If 7 days – 3weeks of age: 50 mg/kg 8 hourly.
  - If > 3 weeks of age: 50 mg/kg 6 hourly.
- Uncomplicated meningitis: 14 days of ampicillin plus
- Gentamicin, IV, for 5 days for synergy.
  - If < 32 weeks gestation: 5 mg/kg/36 hours in the first week of life.
  - If ≥ 32 weeks gestation: 5 mg/kg/24 hours in the first week of life.
  - Monitor blood levels.

REFERRAL

- For surgical complications such as hydrocephalus, septic arthritis, osteomyelitis
- Septicaemia not responding to treatment.

19.6.1 Hypoxia/ischaemia of the newborn

Seizure control

Levetiracetam: not added
The data is still lacking for use of levetiracetam in neonatal seizures.[12]

Midazolam: added as second-line option

Lidocaine was listed as the second-line option for patients that are refractory to phenobarbitone. The use of lidocaine in the clinical practice is not something that is done commonly and thus it was proposed that midazolam be added as an alternative due to the familiarity with its use. There is not strong evidence for either midazolam

[12] Mruk Al, Garlit KL, Leung NR. Levetiracetam in Neonatal Seizures: A Review. J Pediatr Pharmacol Ther. 2015; 20 (2):76 – 89.

of lidocaine, however both are recommended for consideration in the second-line setting after use of phenobarbitone. [13,14]

The following text was added:

- Midazolam, IV.
  - Loading dose: 0.05mg/kg IV over 10 minutes.
  - Followed by a continuous infusion of 0.03-0.3mg/kg/hour

For preterm neonates:

- Midazolam, IV.
  - Loading dose: 0.05mg/kg IV over 10 minutes.
  - Followed by a continuous infusion of 0.03-0.3mg/kg/hour

19.6.2 Seizures, neonatal

Seizure control

Midazolam: added as second-line option

As above.

The following text was added:

- Midazolam, IV.
  - Loading dose: 0.05mg/kg IV over 10 minutes.
  - Followed by a continuous infusion of 0.03-0.3mg/kg/hour

For preterm neonates:

- Midazolam, IV.
  - Loading dose: 0.05mg/kg IV over 10 minutes.
  - Followed by a continuous infusion of 0.03-0.3mg/kg/hour

19.7.3 The infant of a diabetic mother

The following section was added:

19.7.3 THE INFANT OF A DIABETIC MOTHER (IDM)

Description

Infants born to mother with established or newly diagnosed diabetes mellitus. The fetus will be exposed to high levels of insulin in utero if maternal glycaemic control is not achieved, with fetal pancreatic hypertrophy as an adaptive measure. The infant of a diabetic mother is at increased risk of morbidity and mortality.

Diagnostic criteria

IDM babies may show signs related to insulin and/or glucose toxicity, as well as complications of the withdrawal of insulin. As maternal diabetes may be undiagnosed, the condition should be suspected in infants with the following:

» Hypoglycaemia
» Polycythaemia
» Hyperbilirubinemia
» Respiratory distress syndrome

[13] Slaughter LA, Patel AD, Slaughter JL. Pharmacological Treatment of Neonatal Seizures: A Systematic Review. J Child Neurol. 2013, 28 (3): 351-364.

[14] Booth D, Evans DJ. Anticonvulsants for neonates with Seizures (Review). Cochrane Database of Systematic Reviews. 2004, 3. CD004218.

» Hypertrophic cardiomyopathy
» Congenital malformations especially cardiac malformations and sacral agenesis
» Macrosomia which predisposes to birth injuries

General and supportive measures
» Strict glucose monitoring: after birth, at 30 minutes, 1 hour, 2 hours and before each feed for all LGA babies or confirmed IDM

Medicine treatment
Refer to Chapter 7: Endocrine, section 7.6 Hypoglycaemia in Children.

Referral
- Severe, persistent hypoglycaemia requiring more than 12.5% intravenous dextrose to maintain normal glucose levels.
- Congenital malformations or birth injuries requiring specialist management.

19.9 Underweight for Gestational Age (UGA)

The following section was added:

19.9 UNDERWEIGHT FOR GESTATIONAL AGE (UGA)

DESCRIPTION
UGA is failure of an infant to achieve their genetic growth potential. This may be due to maternal, placental or fetal factors in utero.

DIAGNOSTIC CRITERIA
» The birth weight of the underweight for gestational age infant plots below the 10th centile.
» Symmetrically wasted: weight, length and head circumference is below the 10th centile. Causes include chromosomal disorders, genetic abnormalities, chronic intra-uterine infection, maternal under-nutrition, and teratogenic agents such as alcohol.
» Asymmetrically wasted: only the weight is below the 10th centile. Causes include placental insufficiency, hypertension and diabetes mellitus during pregnancy and smoking during pregnancy.

The neonate is at risk of:
» Preterm delivery
» Birth asphyxia
» Hypoglycaemia
» Polycythaemia
» Hypothermia
» Increased mortality

GENERAL AND SUPPORTIVE MEASURES:
» Admit unwell/unstable infants to neonatal high/intensive care facility.
» Temperature control:
- Kangaroo mother care: Initiate if baby is well and vital signs are stable.
- Keep infants temperature, axilla or skin of anterior abdominal wall, at 36.5–37.5°C.

» Whole blood glucose (heel prick) < 2.6 mmol/L.
- Monitor the blood glucose, at least 2 hourly, to prevent the development of hypoglycaemia.

See management of hypoglycaemia (section 19.7.2 Hypoglycaemia, neonatal) if the glucose < 2.6mmol/L.

» If renal function is compromised, use a potassium-free solution.

» Hospital discharge if:
  - clinically well,
  - able to breastfeed or formula feed,
  - able to maintain body temperature, and
  - weight > 1.8 kg, and on an upward trend

Follow-up visits to assess growth parameters and neurodevelopment.

REFERRAL

Presence of one or more of the following complications that cannot be managed at the facility:

» Respiratory distress requiring ventilatory support.
» Feeding difficulties where the underlying cause is unclear.
» Congenital abnormalities requiring surgical intervention.
» Hypoglycaemia not responding to treatment.