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Guideline for the management of Neonatal Hypertension

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For use in: East of England Neonatal Units, Guidance specific to the care of neonatal patients.

For use by: Medical Staff, Neonatal Nurse Practitioners, Neonatal Nurses, Pharmacists, Paediatric Nurse Practitioners and Paediatric Nurses for Children below Term + 4 weeks nursed on Children's Wards.

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1. INTRODUCTION

Blood pressure is considered a vital sign as values too low or too high can be associated with mortality and serious morbidity[1]. However, elevated blood pressure in healthy newborn infants is so uncommon that its routine measurement is not recommended as part of standard care [2,3].

Among sick infants on neonatal units, hypertension is reported as occurring in 1-2% of infants [4-6] which is much less than the incidence of hypotension and, as a result, clinicians may be less certain about determining what significantly elevated blood pressure is and when to treat it. Hypertensive crisis is a term used to describe an acute elevation in blood pressure to a level that has the potential to cause end-organ damage and can be life-threatening and should be managed promptly.

This guideline outlines the measurement of neonatal blood pressure, the definition of neonatal hypertension and investigations and management of neonatal hypertension.

2. MEASUREMENT OF NEONATAL BLOOD PRESSURE

- In neonates direct intra-arterial blood pressure monitoring is the gold standard. Whilst many infants are not sufficiently unwell to warrant this, it should be considered in any infant in whom indirect methods of BP measurements suggest significant hypo- or hypertension.[9]

- Most commonly automated oscillometric techniques are used which detect pressure oscillations from the artery to determine mean BP (MAP) and, via various algorithms, calculate systolic (SBP) and diastolic (DBP) blood pressure. Hence, measurements may differ between different oscillometric devices.

- Whilst correlation between oscillometric and invasive measurements is fairly accurate, accuracy falls at lower mean blood pressures, especially MAP < 30mmHg[7] and overall oscillometric techniques tend to overestimate by between 3 and 8mmHg.[8] Therefore any high blood pressure reading should be checked manually with the use of Doppler technique preferable in infants as the Korotkov sounds are less reliably heard.[9] The doppler probe is placed over the brachial artery and the cuff inflated until the signal disappears. The point at which the signal returns is the SBP. DBP and MAP cannot be identified with this method.

- Choice of cuff size is vital. The cuff width should be 45-70% of the upper arm circumference and its bladder should cover 80-100% of the same circumference. In reality errors due to too large a cuff are unlikely but too small a cuff can overestimate the blood pressure.[1,9]

- Blood pressure increases during feeding, sucking, crying and being held head up. In addition, first blood pressure measurements are higher than repeat measurements done after 2 minutes of rest. Therefore, infants should be lying, asleep or quiet and not feeding. If abnormal blood pressure is suspected, three measurements should be taken each time with an appropriately sized cuff on the right upper arm. If the pressure is

elevated or there is clinical suspicion of coarctation of the aorta, blood pressure should be measured in all four limbs. Different cuffs may be required for upper and lower limbs.

3. DEFINITIONS

Epidemiological Definition
SBP in a neonate ≥ 95th percentile for age and sex on three separate occasions.

Clinically significant hypertension requiring treatment[10]

There is little, if any, evidence for a precise, single starting point for treatment but the following acts as a guide.

- SBP ≥ 95th percentile with end-organ involvement OR
- SBP > 99th percentile consistently (usually taken as >110mmHg in term infants) without end-organ involvement

4. NORMAL DATA

The American Second Task Force on Blood Pressure Control in Children[11] incorporated data from over 70,000 American and British children into its centiles. Two large British studies produced reference ranges for preterm babies, recording mean blood pressure using indwelling arterial catheters[12] and systolic blood pressure by Doppler ultrasound.[13] Incorporating the above evidence, the following table gives normal data across various gestations as below.

Guidance values for 95th and 97th centile SBP values in first 2 weeks of life

GESTATION	AGE	SBP 95TH %	SBP 97TH %
Term[11]	Day 1 Day 8-30	96 104	
Term[13]	Day 4 6 weeks (awake)	95 113	
Term[12]	Day 1 Day 10		82 111
24 weeks[12]	Day 1 Day 10		57 71
28 weeks[12]	Day 1 Day 10		62 83
32 weeks[12]	Day 1 Day 10		67 94
36 weeks[12]	Day 1 Day 10		74 104

Dionne et al[14] consolidated available blood pressure measures from the literature for neonates > 2 weeks of age and developed the table below to include 50th, 95th and 99th percentiles for SBP, MAP and DBP.

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Estimated normal BP values in neonates > 2 weeks of age.

Post-menstrual 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	**57**	**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

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MAP	38	57	63

5. HOW OFTEN SHOULD BLOOD PRESSURE BE MEASURED IN NICU?

There is no accurate guidance on this. Routine screening with blood pressure in every term healthy baby is not indicated.[2] In the absence of any evidence the following is recommended (guidance only).

- all critically unwell ITU babies to have an invasive BP measured either through central or peripheral arterial line, mainly to monitor for hypotension.
- any baby on inotropes to titrate inotropes to keep systolic BP < 97th centile for gestational age
- all ITU babies without an arterial line to have BP recorded **4 hourly** as part of observations, or more frequently if concerns about BP
- all HDU babies without an arterial line to have BP recorded **12 hourly** at least, or more frequently if clinically indicated
- all well SCBU babies with risk factors for hypertension as above (eg previous UAC, chronic lung disease) to have at least one BP recording **twice a week**
- all stable SCBU babies who have not needed any HDU/ITU support to have BP at least **once on admission and one on discharge**

6. AETIOLOGY

Hypertension is more common in premature infants and those of low birth weight; possibly because they have a lower nephron mass. A cause or risk factor for hypertension is almost always identified in the neonatal population.[6] The most common causes are renal parenchymal and renovascular, cardiac, iatrogenic and respiratory.

Causes of neonatal hypertension

Renal parenchymal	Congenital eg autosomal dominant polycystic kidney disease Acute tubular necrosis eg sepsis, asphyxia Renal hypoplasia Severely obstructed urinary tract Haemolytic uraemic syndrome Congenital rubella syndrome
Renovascular	Renal artery thrombosis (especially if previous UAC) Renal vein thrombosis Renal artery stenosis or compression (eg from tumour or post tight abdominal wall closure) Idiopathic arterial calcification
Cardiovascular	Coarctation of the aorta Interrupted aortic arch Distal aortic thrombosis (particularly if previous UAC) Patent ductus arteriosus Fluid overload
Endocrine	Congenital adrenal hyperplasia Hyperaldosteronism Hyperthyroidism Adrenal haemorrhage Hypercalcaemia
Medications	Dexamethasone Adrenergic agents Bronchodilators Caffeine Neonatal TPN through salt and water overload or hypercalcaemia Indomethacin Ibuprofen
Neurological	Pain Seizures Intracranial hypertension Drug withdrawal HIE
Miscellaneous	Chronic lung disease (may manifest late after leaving NICU) ECMO

7. INVESTIGATIONS[1,9,10]

1. Repeat blood pressure measurement manually using Doppler sphygmomanometry; pay close attention to cuff size.
2. Clinical examination
    - abdominal mass?
    - palpable kidneys?
    - normal genitalia (CAH)?
    - pulses – are the femoral and brachial pulses the same?
    - are the fontanelles and sutures normal?
3. Four limb blood pressures (remember to use appropriately sized cuffs which may be different for upper and lower limbs)
    - do not rely on oscillometric BP to exclude coarctation
    - ideally use Doppler sphygmomanometry
4. Bloods
    - electrolytes, urea and creatinine, estimated GFR
    - full blood count
    - calcium, phosphate
    - albumin
    - thyroid function
    - plasma renin and aldosterone (discuss with individual labs, needs immediate transport for immediate separation and freezing)
5. Urinalysis
    - protein, creatinine, microalbumin,
    - microscopy for cells, casts and infection
    - culture
    - urinary catecholamines
6. Renal ultrasound - ideally including renal vessel Dopplers (especially if baby had UAC) – this may require a tertiary centre
7. CXR
8. Echocardiogram
9. Consider
    - urine VMA, urine HVA
    - urine steroid profiles
    - 17-OH progesterone
    - DMSA, MCUG

8. MANAGEMENT[1,9]

It is important to recognise that the majority of antihypertensive medications are not approved or licensed for the neonatal population. Hypertensive crises are best managed with short-acting antihypertensive medications that can be carefully titrated with an infusion. The principal short acting IV agents are labetalol, nicardipine, hydralazine. No studies compare one against the other but the Nottingham Children's Hospital Hypertension Guideline[9] 1st, 2nd and 3rd line recommendations are given below. A low threshold should be maintained for discussion with a tertiary paediatric renal team.

- Investigations as above
- Withdraw iatrogenic medications that may cause hypertension

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- Treat underlying cause
- Consider pharmacological treatment in neonates with
  - asymptomatic hypertension (BP > 99th centile)
  - BP 95th-99th centile and symptomatic or evidence of end-organ damage (eg LVH)
  - symptomatic hypertension with BP > 99th centile should be considered a hypertensive emergency especially if evidence of end-organ damage

↓

Hypertensive crisis

Use IV treatment to reduce BP **SLOWLY to < 90th centile**

- 1/3 total reduction in first 12 hours
- next 1/3 total reduction in 2nd 12 hours
- final 1/3 reduction over next 24 hours

If BP drops suddenly, treat with fluid bolus

- 1st line: IV labetalol or esmolol
- 2nd line: IV hydralazine

↓

Not hypertensive crisis

Use oral agents:

- Ca channel blockers
- vasodilators (hydralazine)
- beta blockers
- diuretics (modest effect on BP)

ACE inhibitors not routinely used, effective at lowering BP but significant side effects

The following tables give medications used in neonates and BNF dosages (accessed August 2019); please refer to BNF for Children/Medusa for full details. Sodium nitroprusside was previously commonly used, however the incidence of thiocyanate toxicity is substantial, which may limit its use.[1] Whilst ACE inhibitors have also been used, they may result in a profound blood pressure reduction (>40%) which can be unresponsive to fluids and inotropes and are associated with acute kidney injury, hyperkalaemia and neurological symptoms The renin-angiotensin-aldosterone system is important in renal development and therefore inhibitors of this system are not recommended for general use in the neonatal population, especially in premature infants.[1,15,16,17]

IV MEDICATION	DRUG CLASS	DOSE	INTERVAL	COMMENTS
Labetalol	Alpha and beta blocker	0.2-1mg/kg bolus Max 4mg/kg 0.5-4mg/kg/hr	q10mins until effect Infusion	Caution in chronic lung disease, heart block, heart failure and neurological injury
Esmolol	Beta 1 receptor blocker	0.5mg/kg loading dose then 50-300microg/kg/min	Bolus Infusion	Reduce rate if BP or HR fall too low BNF recommends reloading each time before increasing the infusion rate in steps of 50mcg/kg/min. Doses over 300mcg/kg/min not recommended.
Hydralazine	Vasodilator	0.1-0.5mg/kg Max 3mg/kg/day 12.5-50 microg/kg/hr Max 2mg/kg/day	q4-6hrs Infusion	Rare agranulocytosis, caution in cerebrovascular disease. Contraindicated in high output cardiac failure.
Sodium nitroprusside	Vasodilator	Initially 0.5microg/kg/min, increased in steps of 0.2microg/kg/min per dose, max 8microg/kg/min, max 4micro/kg/min if used for > 24 hrs	Infusion	Monitor for cyanide toxicity, caution in renal and hepatic failure

Oral medication	Drug class	Dose	Interval	Comments
Amlodipine	Ca channel blocker	0.1-0.2mg/kg	Once daily	Adjust 1-2 weekly to max 0.4mg/kg
Hydralazine	Vasodilator	0.5mg/kg	TDS Max 3mg/kg 8 hourly	Rare agranulocytosis, caution in cerebrovascular disease. Contraindicated in high output cardiac failure.
Nifedipine	Ca channel blocker	0.25-0.5mg/kg	BNF states repeat once if necessary but in practice given TDS if tolerated.[18]	Difficult to administer as oral strength is 20mg/ml and is very light sensitive. Risk of profound hypotension and unpredictability of response. Monitor BP half hourly post dose, caution with neurological injury.
Propranolol	Beta blocker	250microg/kg Increase if necessary to max 2mg/kg TDS	TDS	Monitor BP half hourly post first dose and dose increases. Symptoms of thyrotoxicosis may be masked.
Furosemide	Loop diuretic	0.5-2mg/kg	OD-BD	Only modest effect on BP but can be useful in association with chronic lung disease. Same dose may be given IV. Monitor electrolytes.
Spironolactone	Aldosterone receptor antagonist	0.5-1mg/kg	BD	Only modest effect on BP but can be useful in association with chronic lung disease. Monitor electrolytes.

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