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Do infants with neonatal abstinence syndrome (NAS) experience better outcomes when their mothers have been treated with morphine rather than methadone?

As slow-release morphine has been shown to be as effective as methadone in maintaining addicts (Etzersdorfer, 1997), it has been hypothesised that it may produce a less severe NAS. An open, randomised trial in 48 pregnant opiate abusers (Fischer, 1999) compared those maintained on methadone (n = 24) with those given slow-release morphine (n=24). No difference was found in the number of days that NAS was experienced by infants born to either treatment group (mean = 16 and 21 days, respectively). Fewer benzodiazepines (p < 0.05) and fewer additional opiates (p < 0.05) were consumed by the group maintained on morphine compared with the methadone group.

A later study (Lee, 2000) has also not demonstrated greater efficacy for slow-release morphine.

In the treatment of infants with NAS, a statement from the American Academy of Pediatrics (Anon, 1998) advises that “Drug selection should match the type of agent causing withdrawal. Thus, for opioid withdrawal, tincture of opium is the preferred drug”.

A recent, partially randomised controlled trial in 20 infants (Coyle, 2002) compared diluted tincture of opium (DTO) plus placebo (n = 10) with DTO plus phenobarbitol. Duration of hospital stay was reduced by 48% (79 to 38 days, p < .001) in the DTO plus phenobarbitol group.

A comparative study in 53 neonates born to mothers maintained on methadone (n=22), slow-release oral morphine (n=17) or buprenorphine (n=14) throughout pregnancy (Ebner, 2007) found that those receiving morphine needed a significantly shorter period of treatment (9.9 days vs 17.7 days).

Evidence Level: II

What are the most appropriate doses for morphine and phenobarbital?
The BNF for Children gives the following recommendations:
Morphine:
- Neonatal opioid withdrawal under specialist supervision
- By mouth
Neonate initially 40 micrograms/kg every 4 hours until symptoms controlled, increase dose if necessary; reduce frequency gradually over 6–10 days, and stop when 40 micrograms/kg once daily achieved; dose may vary, consult local guidelines https://www.medicinescomplete.com/mc/bnfc/current/PHP12373-morphine-salts.htm

Phenobarbital:
  By mouth or by intravenous injection
Neonate initially 20 mg/kg by slow intravenous injection then 2.5–5 mg/kg once daily either by slow intravenous injection or by mouth; dose and frequency adjusted according to response

Last amended May 2012
Last reviewed September 2015
This guideline has been prepared with reference to the following:

British Association of Perinatal Medicine Service Standards for Hospitals Providing Neonatal Care, 3rd ed. 2010


Last amended August 2013
Last reviewed September 2015
What are the parental risk factors for anorectal malformations (ARM) among neonates?

A systematic review of 22 international studies (Zwink 2011) found that although evidence on risk factors for ARM was limited the few available studies indicate paternal smoking and maternal overweight, obesity and diabetes to be associated with increased risks. This review recommended that further, ideally large-scale multicentre and register-based studies are required to clarify the role of key risk factors for the development of ARM.

A case-control study (Lin 2012) of 2,853 analysed live births, stillbirths, or elective terminations diagnosed with ≥ 1 birth defects compared with 6,726 healthy infants, in relation to maternal periconceptional (1 month prior through third month of pregnancy) use of asthma medication. The study found that maternal use of this asthma medication (bronchodilator or anti-inflammatory) was associated with a moderately increased risk of isolated anorectal atresia (adjusted odds ratio 2.12, 95% CI 1.09-4.12).

An international case-control study (Wijers 2013) of 1417 cases identified the following pregnancy-related disorders associated with an increased risk of anorectal malformation: maternal epilepsy (adjusted OR 5.1, 95% CI 1.7-15.6), fertility treatment (adjusted OR 1.3, 95% CI 0.9-1.8), multiple pregnancy (adjusted OR 1.6, 95% CI 1.2-2.1), primiparity (adjusted OR 1.6, 95% CI 1.4-1.8), pre-eclampsia (adjusted OR 2.2, 95% CI 1.2-4.0) and maternal fever (adjusted OR 2.2, 95% CI 0.8-5.7).

A case-control study (Kallen 2014) looking at maternal hypothyroidism and a range of congenital malformations found a positive association with anorectal malformation (adjusted OR 1.85, 95% CI 1.00-1.85). This study was based on 588 cases of anorectal malformation. A case-control study (Gilboa S, 2014) compared 4525 cases of selected birth defects with 8665 controls and found no association between maternal vitamin E intake and anorectal atresia.

Evidence Level III

Last amended July 2015
Last reviewed September 2015
Counselling may help reduce anxiety and the incidence of invasive testing?
A study in 123 pregnant women aged ≥35 years who underwent nuchal translucency screening (NTS) (Kaiser, 2004) found that, after group counselling, decisional conflict decreased significantly among those reporting at baseline having made a decision about invasive testing (t(222)=2.00, P=0.014) and for those who were uncertain (t(222)=5.74, P<0.0005). After receiving NT-adjusted risks, decisional conflict decreased further for those uncertain about testing at baseline (t(222)=4.64, P<0.0005). There was no change in risk perception and anxiety after group counselling. After NT-adjusted risks were communicated, risk perception decreased significantly (t(230)=5.02, P<0.0005), as did anxiety (t(115)=7.91, P<0.005). Despite reassuring NTS results, the uptake rate for prenatal invasive testing was 78.4%. Risk perception, anxiety, and decisional conflict decreased after individual counseling for reassuring NTS results, but the uptake of invasive testing remained high.


Evidence Level: IV
Caffeine citrate is effective treatment for apnoea and bradycardia?

A Cochrane systematic review of 6 trials (Henderson-Smart, 2010 i) reported on the effect of methylxanthine in the treatment of apnoea (three trials of theophylline and three trials of caffeine). Five trials that enrolled a total of 192 preterm infants with apnoea evaluated short term outcomes; in these studies, methylxanthine therapy led to a reduction in apnoea and use of IPPV in the first two to seven days. The post-hoc analysis of the large CAP Trial comparing caffeine to control in a subgroup of infants being treated for apnoea reported significantly reduced rates of PDA ligation; postmenstrual age at last oxygen treatment, last endotracheal tube use, last positive pressure ventilation; and reduced chronic lung disease at 36 weeks. The authors concluded that caffeine should be the treatment of choice in this condition, and confirmed this in a separate review of 5 trials in 108 infants (Henderson-Smart, 2010 ii). Further sub-group analysis of the CAP trial (Henderson-Smart, 2010iii) has, however, concluded that “The results of this review do not support the use of prophylactic caffeine for preterm infants at risk of apnoea.”


Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD000273


Evidence Level: I

Last amended March 2011
Last reviewed September 2015
Is the dorsalis pedis artery a suitable site for the insertion of arterial lines in neonates?
Although no specific evidence one way or the other has been identified, several current online sources mention the use of this site:
e.g. Vanderbilt Medical Center (2006): "Most frequently used site in the neonate is the radial and dorsalis pedis arteries."

Vanderbilt Medical Center. Arterial Lines Peripheral. 2006.
http://vuno.org/npart1.htm


Evidence Level: V

Last amended June 2013
Last reviewed September 2015
Samples should be analysed immediately in order to avoid inaccurate results?

A study of 38 placentas of infants delivered by elective caesarean section (Armstrong, 2006) looked at arterial samples from 20 placentas, and venous samples from 18 placentas. Arterial and venous lactate was significantly higher than at time 0 by 20 minutes in both clamped and unclamped vessels. Changes in unclamped vessels were greater than in clamped vessels. The pH remained unchanged over 60 minutes in clamped vessels, but changed significantly in unclamped vessels. Base excess changed significantly in both clamped and unclamped vessels. The authors concluded that cord blood samples taken after 20 minutes delay were unreliable for lactate measurement, even if the vessel had been doubly clamped to isolate the blood from the placenta.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672835/

Evidence Level: IV

Last amended January 2011
Last reviewed September 2015
What treatment is indicated for chronic suppurative lymphadenopathy?

A review on this subject (Goraya, 2002) states that "treatment of BCG lymphadenitis has remained controversial…Once suppuration has occurred, the treatment should aim at promoting resolution and preventing spontaneous discharge and sinus formation". Results from controlled trials (Kuyucu, 1998; Noah, 1993; Caglayan, 1987) have demonstrated that antibiotic treatment does not reduce the risk of suppuration or shorten the duration of healing once it has occurred.

The two alternative treatments that remain are needle aspiration and surgical excision. The only RCT on needle aspiration to be identified (Banani, 1994) found that the procedure resulted in significantly higher (95% vs 68%) and rapid (6.7 vs 11.8 weeks) healing compared with no aspiration.

Surgical excision is generally regarded as the treatment of choice for suppulsive cases in which needle aspiration has failed, or in which sinuses have formed in previously-drained nodes (Banani, 1994; Baki, 1991; Caglayan, 1991). Non-suppurative lymphadenopathy requires no treatment (Goraya, 2002).


Evidence Level: II
What is the best way of detecting foetal anaemia and hyperbilirubinaemia?

The most accurate method of testing for foetal anaemia (sampling foetal blood, or cordocentesis) is also the most invasive, and thus is usually the endpoint in a stepwise sequence beginning with less sensitive but non-invasive methods such as measuring maternal serum antibody titres. Cordocentesis has replaced amniocentesis as the definitive test since further evaluation by foetal-blood sampling of a high amniotic-fluid ∆OD_{450} (Sikkel, 2002) has been a requirement before intervention (Saade, 2000).

More accurate non-invasive methods would avoid the risks associated with invasive methods, but more rigorous research is needed (Divakaran, 2001). In a study in 111 foetuses (Mari, 2000), measuring increased peak velocity (1.50 multiples of the median) of systolic blood flow in the middle cerebral artery by Doppler ultrasonography had a sensitivity of 100% for the prediction of moderate or severe anaemia, with a false positive rate of 12%. No larger-scale studies validating these findings have been identified (Oepkes, 2000).

Studies on foetal DNA present in maternal plasma now provide an accurate (99.5%) means of determining the RHD status of the foetus (Rijnders, 2004; Rouillac le Sciiellour, 2004).


Evidence Level: IV

What are the indications for phototherapy?

The trigger for commencement of phototherapy is the total serum bilirubin (TSB) level, but sliding scales based on age and risk level are guided by little evidence and the TSB levels given are approximations (Anon, 2004).

A study in 276 infants (Maurer, 1985) found that phototherapy had no therapeutic effect in reducing the need for exchange transfusion in those with a positive Coombs test for haemolytic
disease, but a 9.4% absolute risk reduction in those with a negative Coombs test (NNT 11; 95% CI 10-12).

http://pediatrics.aappublications.org/content/114/1/297.full


Evidence Level: IV

What follow-up do these babies need, and for how long?
Studies that have investigated developmental outcome between 18 months and 5 years after intrauterine transfusion (Janssens, 1997; Stewart, 1994) have found this to be satisfactory when compared to both normal controls and those babies considered to be "high-risk" but who did not undergo transfusion.
No specific guidance on timing or follow-up for babies with RHD can be identified.


Evidence Level: V

Last amended September 2011
Last reviewed September 2015
BLOODSPOT SCREENING
Supporting information

This guideline has been prepared with reference to the following:


Last amended: January 2015
Last reviewed: September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
BOTTLE FEEDING
Supporting information

This guideline has been prepared with reference to the following:


http://www.bliss.org.uk/baby-charter-audit-tool


https://www.nice.org.uk/guidance/qs4


UNICEF. The Baby Friendly Initiative.

http://www.unicef.org.uk/babyfriendly/


White, A. Parnell, K. 2013. The transition from tube to full oral feeding (breast or bottle) – a cue based developmental approach. Journal of Neonatal Nursing 19, 189-197.

Last amended August 2015
Last reviewed September 2015
This guideline has been prepared with reference to the following:

University Hospitals of North Midlands. Hindmilk Policy. 2015.

Is mechanical expression of breast milk more productive than manual expression?
A Cochrane review (Becker, 2015) found three RCTs that compared mechanical vs. manual pumps with regard to the quantity of milk expressed and found no significant difference between the two methods.


Evidence Level: I

Last amended July 2015
Last reviewed September 2015
This guideline has been prepared with reference to the following:

University Hospitals of North Midlands. Hindmilk Policy. 2015.

What is the optimum temperature at which to store frozen breast milk, in order to preserve its antioxidant content?

A study (Silvestre, 2010) that compared the effects of 2 temperatures (-20 degrees C and -80 degrees C) and different storage times (15, 30, and 60 days) found that freezing induced losses in the antioxidant properties of breast milk and that such losses increased with the duration of storage and differed in intensity according to the temperature. The authors concluded that to maximally preserve the antioxidant properties of breast milk, it was advisable to store the latter at -80 degrees C for a period of less than 30 days, rather than for shorter time periods at the usual temperature of -20 degrees C.


Evidence Level: IV

Last amended July 2015
Last reviewed: September 2015
BREASTFEEDING
Supporting information

This guideline has been prepared with reference to the following:

University Hospitals of North Midlands. Hindmilk Policy. 2015.

Maternal breast milk is to be preferred to formula for enteral feeding in preterm infants?
A Cochrane review (Henderson, 2007) found no randomised trial data comparing breast milk to formula for preterm infants, but concluded nonetheless that breast milk should remain the default choice as it conferred “major non-nutrient advantages”.
A secondary analysis of data from a randomized controlled trial found that extremely preterm infants (28 weeks) explored a number of factors to see which were associated with the following feeding milestones: first enteral feeding, full enteral feeding, first oral feeding, half oral feeding, and full oral feeding. The data suggested that infants fed with breast milk achieved each of five milestones earlier than formula-fed infants.


Evidence Level: IV

Last amended August 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
**EMLA (Eutectic Mixture of Local Anaesthetics) cream is not used in neonates?**

A small RCT in 19 infants (Acharya, 1998) found no significant difference in efficacy between EMLA and placebo creams in physiological and behavioural responses. There was no significant difference in methaemoglobin concentrations one hour after the cream had been applied. At eight hours, however, concentrations were significantly higher after EMLA than placebo ($p = 0.016$). There was no evidence of clinical toxicity. The authors concluded that the results did not support the routine use of EMLA in healthy preterm infants. EMLA has, however, been proved to be safe for single applications in both term and preterm (from 30 weeks gestational age) infants (Taddio, 1998).

http://fn.bmj.com/content/78/2/F138.long

http://pediatrics.aappublications.org/content/101/2/e1.long

**Evidence Level: II**
CARDIAC MURMURS
Supporting information

This guideline has been prepared with reference to the following:


What proportion of cardiac defects is identified by routine postnatal examination?
A prospective study of 7204 infants (Ainsworth, 1999) found that only 44% of cardiac defects were detected by routine postnatal examination, although the predictive value of a murmur at this age was found to be 54%.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720873/pdf/v080p00F43.pdf

Evidence Level: IV

Last amended September 2007
Last reviewed September 2015
CHEST DRAIN INSERTION
Supporting information

This guideline has been prepared with reference to the following:

British Thoracic Society. Pleural disease guideline. 2010. BTS.


Chest X-ray after removal is necessary only if breathing becomes more difficult?
A retrospective chart review of 100 infants with 110 episodes of chest drain removal after 174 chest tube insertions (van den Boom, 2007) showed a low yield for routine radiography: In asymptomatic infants, some reaccumulation of air was detected in 9 of 35 cases of pneumothorax or of fluid in 2 of 5 cases of pleural effusion. In 12 clinically symptomatic infants, chest tubes were reinserted in 5 cases and there was one case of right upper lobe collapse. The authors concluded that “close observation”, rather than routine radiography, was “likely to detect clinically relevant recurrence of pneumothorax”.

This study is the only one to date to focus on neonates. A similar retrospective study on older children also found that clinical signs and symptoms identified “nearly all relevant pneumothoraces” (Pacharn, 2002).


http://fn.bmj.com/content/92/1/F46.long

Evidence Level: IV

Last amended August 2015
Last reviewed September 2015
CHEST PHYSIOTHERAPY
Supporting information

This guideline has been prepared with reference to the following:

Association of Paediatric Chartered Physiotherapists Neonatal Group. Physiotherapy competency
document: A competence framework and evidence based practice guidance for physiotherapists
providing respiratory interventions for preterm infants in the UK. 2014.

http://apcp.csp.org.uk/publications/competence-framework-evidence-based-practice-guidance-
physiotherapists-providing-r

NICE Statement 3b in Specialist neonatal care quality standard. Quality Standards. London,
NICE, 2010

http://www.nice.org.uk/guidance/QS4

Thompson, K, Curson, C, Bedson, Developmentally Appropriate Care – handling and positioning.
South West Midlands Newborn Network. 2012

http://www.networks.nhs.uk/nhs-networks/southern-west-midlands-newborn-
network/documents/Dev%20Care%20Guideline%20January%202012.pdf

Department of Health. Principle 2.5.2.1 in Toolkit for high-quality neonatal services. 2009

https://www.nepho.org.uk/uploads/doc/vid_8769_Toolkit%20for%20high-
quality%20Neonatal%20services.pdf

London.

http://www.bliss.org.uk/Handlers/Download.ashx?IDMF=f6cccb6c-0526-46f7-a02f-312e52fac6e3

British Association of Perinatal Medicine. Standard 6.2.3 and Standard 4.2.2 in Service standards
for hospitals providing neonatal care. 3rd ed. 2010


What evidence is there for adverse effects of physiotherapy on neonatal patients?
The evidence suggests that caution must be taken when dealing with vulnerable extremely
preterm infants.

An updated review of 3 trials that studied 106 infants- Flenady (2010), reported that information
on adverse effects of chest physiotherapy is not adequate enough in the trials included to gauge
safety for practice. In view of this and the lack of clear evidence for benefit, it recommends using
this intervention cautiously.

Early small scale studies reported risks such as intraventricular haemorrhage (Raval 1987) and
encephaloclastic porencephaly. (Harding 1998)

Harding (1998) carried out a retrospective case-control study among 454 infants of birth weight
less than 1500 gm cared for during the 3-year period of 1992 to 1994. Thirteen babies of 24 to 27
weeks of gestation who weighed 680 to 1090 gm at birth had encephaloclastic porencephaly.
Twenty-six control subjects were matched for birth weight and gestation. The patients received
two to three times as many treatments with chest physiotherapy in the second, third, and fourth
weeks of life as did control infants (median 79 vs 19 treatments in the first 4 weeks, p < 0.001).
Patients also had more prolonged and severe hypotension in the first week than did control
subjects (median duration of hypotension 4 vs 0.5 days, p < 0.01), and were less likely to have a
cephalic presentation (31% vs 81%, p < 0.01). Since December 1994 no very low birth weight

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baby has received chest physiotherapy treatment in the first month of life in our nursery, and no further cases have occurred. There were methodological limitations to this study though and there is the possibility that the parallels between discontinuation of physiotherapy and cases of EP is confounding evidence. This link has also been disputed by a number of cohort studies following publication of Harding’s (1998) research. (Beeby et al 1998; Knight et. al 2001)

An updated Cochrane review (Roque I Figuls 2012) focusing on chest physiotherapy on patients with acute bronchitis, found that the nine included trials did not report any severe adverse events, although one of the trials reported a higher number of transient episodes of vomiting and respiratory instability after physiotherapy.


Evidence Level: II

Last amended September 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
What is the definition of chronic lung disease (CLD)?
Definitions of CLD (or bronchopulmonary dysplasia) have in the past been “…broad and hazy, with several competing definitions in the literature” (Charafeddine, 1999). The original description of the condition (Northway, 1967) indicated that oxygen dependency at 28 days of age was diagnostic, and this definition is still widely accepted (Baraldi, 2007; Panickar, 2004). Other definitions include oxygen dependency at 28 days of age with at least 21 days of oxygen supplementation and consistent chest x-ray findings (Bancalari, 1979), and oxygen at 36 weeks corrected gestational age (Shennan, 1988).

The National Institutes of Health (2005) recommend a severity based criteria definition for diagnosis:
- **Mild BPD** defined as need for supplemental oxygen for at least 28 days but not at 36 weeks postmenstrual age or discharge
- **Moderate BPD** defined as need for supplemental oxygen for at least 28 days plus treatment with < 30% oxygen at 36 weeks postmenstrual age
- **Severe BPD** defined as need for supplemental oxygen for at least 28 days plus treatment with ≥ 30% oxygen and/or positive pressure at 36 weeks postmenstrual age


**Evidence Level: IV**

**How do different dexamethasone dosing regimes compare in terms of risks v benefits?**
Three Cochrane systematic reviews (Doyle, 2014; Doyle, 2014a; Halliday, 2003) have concluded that the benefits of early (<96 hours), moderately early (7-14 days) and late (>3 weeks) treatment with corticosteroids may not outweigh the actual or potential adverse effects. In particular, no study to date has been sufficiently powered to detect important adverse long-term neurosensory outcomes (Halliday, 2004i). In view of this, the recommendation is to reserve treatment for those infants who cannot be weaned from mechanical ventilation, and to minimise the dose and duration of any course of treatment.

A further Cochrane review of 5 trials comparing inhaled versus systemic corticosteroids (Shah, 2012) found no advantage for inhaled steroids, either in effectiveness or in side-effect profiles. Significant adverse effects, in terms of spontaneous gastrointestinal perforation, cessation of weight gain, and smaller head circumference have been recorded at moderate dose levels (0.15-0.02mg/kg over 10 days) (Stark, 2001).

A retrospective, two-centre study (van der Heide-Jalving, 2003) compared 25 hydrocortisone-treated patients (tapering dose of 5-1mg/kg for 22 days) and 25 controls with 23 dexamethasone-treated patients (tapering dose of 0.5-0.1 mg/kg for 21 days) and 23 controls. Effectiveness was found to be equal, but both short and long term adverse effects were significantly fewer in the
hydrocortisone group. A more appropriately-powered study needs to be conducted in order to confirm these findings.


Evidence Level: I

What is the role of diuretics?
Lung disease in preterm infants is often complicated with lung oedema. A Cochrane review of 6 small studies (Stewart, 2011i) found that, in preterm infants > 3 weeks of age with CLD, acute and chronic administration of distal diuretics improved pulmonary mechanics. The authors warn that “positive effects should be interpreted with caution as the numbers of patients studied are small in surprisingly few randomized controlled trials.”

Another Cochrane review by the same team (Stewart, 2011ii) concluded that:” In view of the lack of data from randomized trials concerning effects on important clinical outcomes, routine or sustained use of systemic loop diuretics in infants with (or developing) CLD cannot be recommended based on current evidence. Randomized trials are needed to assess the effects of furosemide administration on survival, duration of ventilatory support and oxygen administration, length of hospital stay, potential complications and long-term outcome.


Evidence Level: I

Last amended September 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
CMV (CYTOMEGALOVIRUS INFECTION)
Supporting information

This guideline has been prepared with reference to the following:


http://www.ecci.ac.uk/RecommendationsPDFs/Rec13.pdf


Ganciclovir/valganciclovir is of use in the treatment of congenital CMV infection?
Ganciclovir and valganciclovir are two of a number of agents (including cidofovir and foscarnet) having documented in vitro activity against CMV. Ganciclovir has, to date, been more rigorously evaluated for safety and efficacy in infants with congenital CMV infection (Jones, 2003). Valganciclovir has only been the subject of two small randomised studies (Kimberlin 2008, Lombardi 2009). The pharmacokinetic parameters were found to be similar to Ganciclovir. A placebo-controlled, double blind, randomised study comparing 6 weeks versus 6 months with Valganciclovir is currently being carried out by the CASG. (Kadambari 2011)

Ganciclovir therapy has been associated with a high rate of complications. An open label, phase II trial in 47 symptomatic infants (Whitley, 1997) administered daily doses of 8 or 12 mg/kg in divided doses, 12 hrly for 6 weeks. Thrombocytopenia occurred in 37 babies (78%) and neutropaenia in 29 (61%). Although levels of CMV in the urine decreased during the treatment period, they returned to near pretreatment levels when therapy was discontinued. Hearing improvement or stabilization occurred in 5 (16%) of 30 babies at 6 months or later. A randomised controlled trial in 100 symptomatic infants (Kimberlin, 2003) administered 6mg/kg i.v. 12 hrly for 6 weeks vs no treatment. A large number of patients in this study were non-evaluable at follow-up, leaving 42 patients (25 in the treatment group and 17 controls). Twenty one (84%) of the treatment group had improved or maintained normal hearing at 6 months, vs 10 (59%) of the controls. Twenty nine (63%) of 46 patients in the treatment group had grade 3 or 4 neutropaenia during treatment vs 9 (21%) of 43 controls (P < .01).

At present, there is no evidence-based guidance available on the selection of suitable patients for treatment with ganciclovir, or for appropriate dosing or whether oral valganciclovir is useful for longer-term treatment (Smets, 2006). These questions were to be addressed by a Cochrane Review (Jones, 2003) but as yet it has not been completed.

A controlled Phase III study of symptomatic congenital CMV involving the CNS (Oliver, 2009) randomised 100 neonates to either 6 weeks of intravenous ganciclovir or no treatment. Denver developmental tests were performed at 6 weeks, 6 months, and 12 months. For each age, developmental milestones that > or =90% of normal children would be expected to have achieved were identified. The numbers of milestones not met ("delays") were determined for each subject. The average number of delays per subject was compared for each treatment group. At 6 months, the average number of delays was 4.46 and 7.51, respectively, for ganciclovir recipients and "no treatment" subjects (p=0.02). At 12 months, the average number of delays was 10.06 and 17.14, respectively (p=0.007). In a multivariate regression model, the effect of ganciclovir therapy remained statistically significant at 12 months (p=0.007).

A randomized controlled trial compared 6 weeks of valganciclovir therapy with 6 months of ganciclovir therapy (Kimberlin, 2015). The 6 month group had improved total ear hearing at 12 month follow up (73% vs. 57%, P=0.01) and 24 month follow up (77% vs. 64%, P=0.04). The 6 month group had better neurodevelopmental scores on the Bayley Scales of Infant and Toddler Development, third edition, on the language-composite component (P=0.004) and on the receptive-communication scale (P=0.003).


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http://jid.oxfordjournals.org/content/197/6/836.long

http://www.nejm.org/doi/full/10.1056/NEJMoa1404599#t=articleTop


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2805252/


http://jid.oxfordjournals.org/content/175/5/1080.long

Evidence Level: II

Last amended September 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
This guideline has been prepared with reference to the following:


**What are normal coagulation parameters in the newborn?**

Normal values for term infants are as follows, with values for premature infants in brackets:

- Platelet count: 150-400,000 (ditto)
- Prothrombin time (sec): 11-15 (12-16)
- Partial thromboplastin time (sec): 30-40 (30-80)
- Fibrinogen (mg/dL): 175-350 (150-325)
- Fibrin split products (mcg/mL): <10 (ditto)
- Thrombin time (sec): 15-20 (17-25)

Adult coagulation reference ranges, especially for PT and APTT, cannot be applied to newborns and young infants (Lippi, 2007).


**Evidence Level: V**

**Is there any causative relationship between deranged coagulation and intraventricular haemorrhage (IVH) in the newborn? If so, does treating abnormal coagulation prevent IVH in preterm infants?**

In a study of 106 preterm infants of 34 weeks’ gestation (Beverley, 1984), 25 (23.5%) developed intraventricular haemorrhage in the first 48 hours of life. Although coagulation parameters appeared normal at birth, differences had appeared by 48 hours, with the IVH group showing a prolonged activated partial thromboplastin time and reduced factor II, VII, and X activity. The authors postulated that, although the aetiology of IVH is multifactorial, early correction of coagulation anomalies may prevent progression to more severe grades of haemorrhage. Survivors of grade III or IV IVH have a 40% risk of permanent brain damage (Krishnamoorthy, 1979).

Another study, in 58 VLBW infants (Setzer, 1982), found that 32 (55%) developed IVH. The affected infants had lower mean platelet count and platelet aggregation response and prolonged mean bleeding time compared to those unaffected.

A study of 54 preterm infants <35 weeks’ gestation (Amato, 1988) found peri-intraventricular haemorrhage (PIVH) in 21 (38%). The affected infants showed lower fibrinogen levels than unaffected infants and significant correlation between platelet count and degree of PIVH.

One prospective study in 49 infants (Van de Bor, 1986) found no difference in coagulopathy between 20 who developed PIVH and 29 who did not, apart from lower levels of factor V in the affected group.

A prospective, randomised trial in 100 infants <32 weeks’ gestation and <1500 gm in weight (Morales, 1988) compared those whose mothers had received 10 mg vitamin K1 i.m. 5 days prior to delivery with a similar number who had not received the vitamin. Infants in the “intervention” group showed significant reduction in the prothrombin time (12.7 vs 15.2 seconds) and partial thromboplastin time (42.6 vs 58.9 seconds). These infants also experienced a lower incidence of total (16% vs 36%) and severe (0% vs 11%) grades of IVH.

A single maternal dose of 10 mg vitamin K1 i.m. 4 hours before delivery may be sufficient to provide significant protection against IVH (Pomerance, 1987).

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One randomised prospective study in 98 infants (Kazzi, 1989) found no improvement in coagulopathy or incidence of IVH when mothers received 10 mg vitamin K1. See also following question on FFP.


Evidence Level: III

What are the indications for giving fresh frozen plasma (FFP)?
The main use of FFP in the neonate is to replace single coagulation deficiencies (factors V, VII, X, XI and XIII), where a specific or combined factor concentrate is unavailable (Contreras, 1992). This is essentially a “second best” solution, as very large volumes are often needed in order to reach sufficiently high plasma levels (Muntean, 2002). A prospective study in 33 neonates (Hyytiainen, 2003) found that FFP had an acute thrombin-reducing effect in those infants with the highest pretransfusional thrombin formation. The authors stress that FFP has poorly-defined effects on coagulation and unproven clinical efficacy. One randomised study in 73 preterm infants (Beverley, 1985) found that 15 (41%) of control patients sustained intraventricular haemorrhage compared with 5 (14%) of 36 patients given FFP 10ml/kg on admission and at 24 hours of age. An earlier controlled trial of the same regimen in 66 infants (Hambleton, 1973) had found no evidence of a protective effect for FFP on IVH. Similarly negative results were obtained in a later and larger trial in 776 infants (Anon, 1996). Osborn and Evans (2009) performed a meta-analysis of randomized trials of early volume expansion in neonates using different volume expanders (including FFP). This meta-analysis concluded that there were no benefits associated with the early administration of FFP to preterm neonates, in terms of improving blood pressure, decreasing rates or severity of IVH, decreasing mortality, or improving neurodevelopmental outcomes.


Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Evidence Level: I (for no evidence in favour of FFP for IVH)

What is the role of Vitamin K in abnormal coagulation in the newborn?

Vitamin K is administered to prevent haemorrhagic disease of the newborn (HDN). A Cochrane review of 13 RCTs (Puckett, 2000) concluded that a single dose (1.0 mg) of intramuscular vitamin K after birth is effective in the prevention of classic HDN. Either intramuscular or oral prophylaxis improved biochemical indices of coagulation status at 1-7 days. Neither route of administration has been tested in RCTs for effect on late HDN (week 2-12), and the oral route has also not been tested for effect on classic HDN (day 1-7). The American Academy of Pediatrics has consistently recommended vitamin K in its guidelines since 1961 (Anon, 2003).

There is no evidence that vitamin K deficiency bleeding is commoner in preterm babies (Hey, 2003), or that cancer risk is raised in infants given intramuscular vitamin K (Roman, 2002).

http://pediatrics.aappublications.org/content/112/1/191.long

http://fn.bmj.com/content/88/2/F80.1.long

Puckett RM, Offringa M. Prophylactic vitamin K for vitamin K deficiency bleeding in neonates. The Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD002776

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746550/

Evidence Level: I

When and how should abnormal coagulation be treated in the newborn (especially the premature)?

Expectant management is sufficient for infants that appear well, but the sick baby may have disseminated intravascular coagulation (Buchanan, 1986). Treatment of the triggering event, low-dose heparin, antithrombin concentrate and selected components may all be used, but good evidence for efficacy is lacking (Bick, 2002).

The presence of cyanosis and a murmur suggests that a response to prostaglandin infusion is likely?
A study in 250 infants with suspected heart disease (Danford, 1986) used decision analysis to demonstrate that “frequency of poor outcome is minimized by early prostaglandin treatment of cyanotic term infants with a murmur or poor pulses, regardless of how ill they appear, and by treating any critically ill term newborn who has either cyanosis or poor pulses.”

Danford DA, Gutgesell HP, McNamara DG. Application of information theory to decision analysis in potentially prostaglandin-responsive neonates. J Am Coll Cardiol 1986;8:1125-30

Evidence Level: IV

Little evidence is available to inform preoperative management of Hypoplastic Left Heart Syndrome (HLHS)?
A questionnaire survey conducted in the US (Johnson, 2008) found that “the management of these infants prior to surgery is anecdotal and variable… a striking lack of consistency in preoperative management techniques for infants with HLHS is apparent. The impact of these preoperative strategies is unknown. Despite challenges in anatomic and hemodynamic variability at presentation, a prospective randomized controlled trial comparing ventilatory management techniques, enteral feeding strategies, and the utility of various monitoring tools on short- and long-term outcome is needed.”


Evidence Level: V

Last amended July 2011
Last reviewed September 2015
This guideline has been prepared with reference to the following:


http://www.bmj.com/content/339/bmj.b4454

Last amended July 2015
Last reviewed September 2015
What are the most common causative organisms in bacterial conjunctivitis?
No evidence-based clinical guidelines on the condition have been identified. A prospective study in 87 children aged 1 month to 18 years in the United States (Patel, 2006) found that non-typeable Haemophilus influenzae accounted for 82% of cases (n=71), Streptococcus pneumoniae for 16% (n=14) and Staphylococcus aureus for 2.2% (n=2).


Evidence Level: IV
Synchronised mechanical ventilation is superior to conventional ventilation?
A Cochrane systematic review of 14 studies (Greenough, 2008) found that synchronised mechanical ventilation was associated with a reduction in the risk of air leak (RR 0.69, 95% CI 0.51 – 0.93) and a shorter duration of ventilation (weighted mean difference -34.8 hrs, 95% CI -62.1, -7.4), compared to conventional ventilation.


Evidence Level: I

Babies who are intubated and ventilated should be sedated unless there is a specific reason not to do so?
A Cochrane review of 13 studies on 1505 infants (Bellu, 2008) concluded that “There is insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. Opioids should be used selectively, when indicated by clinical judgement and evaluation of pain indicators. If sedation is required, morphine is safer than midazolam. Further research is needed.”


Evidence Level: I

Caffeine is beneficial in babies of <30 weeks’ gestation?
A Cochrane Review of 7 studies (Henderson-Smart, 2010) found that methylxanthine treatment resulted in a reduction in failure of extubation within one week (summary RR 0.48, 95% CI 0.32 to 0.71; summary RD -0.27, 95% CI -0.39 to -0.15; NNT 4, 95% CI 3 to 7; six trials, 172 infants). There was significant heterogeneity in the RD meta-analysis perhaps related to the large variation in baseline rate in the control groups (range 20 to 100%). The CAP trial enrolled the largest number of infants, but did not report extubation rates. In the caffeine group, there were lower rates of bronchopulmonary dysplasia, PDA ligation, cerebral palsy and death or major disability at 18 to 21 months. Infants receiving caffeine had reduced postmenstrual ages at time of discontinuing oxygen therapy, positive pressure ventilation and endotracheal intubation.

Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for endotracheal extubation in preterm infants. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD000139

Evidence Level: I

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Passive cooling is beneficial for infants with post-asphyxial (hypoxic-ischemic) encephalopathy (HIE)?

A prospective study was carried out in 39 infants receiving passive cooling before and during inter-hospital transport (Kendall, 2010). Cooling below target temperature (33degreesC-34degreesC) occurred in five babies before the arrival of the transfer team. In two of these infants, active cooling was performed, rectal temperature was not recorded and their temperature was lower than 32degreesC. Of the remaining 37 babies, 33 (89%) demonstrated a reduction in core temperature with passive cooling alone. The percentage of the babies within the temperature range at referral, arrival of the transfer team and arrival at the cooling centre were 0%, 15% and 67%, respectively. On arrival at the cooling centre, four babies had cooled to lower than 33degreesC by passive cooling alone (32.7degreesC, 32.6degreesC, 32.2degreesC and 32.1degreesC). Initiation of passive cooling before and during transfer resulted in the therapy starting 4.6 (1.8) h earlier than if initiated on arrival at the cooling centre.

A systematic review and meta-analysis of 13 trials (Shah, 2010) found that "therapeutic hypothermia was associated with a highly reproducible reduction in the risk of the combined outcome of mortality or moderate-to-severe neurodevelopmental disability in childhood. This improvement was internally consistent, as shown by significant reductions in the individual risk for death, moderate-to-severe neurodevelopmental disability, severe cerebral palsy, cognitive delay, and psychomotor delay. Patients in the hypothermia group had higher incidences of arrhythmia and thrombocytopenia; however, these were not clinically important. This analysis supports the use of hypothermia in reducing the risk of the mortality or moderate-to-severe neurodevelopmental disability in infants with moderate HIE."

A systematic review and meta-analysis of 7 trials in a total of 1214 newborns (Tagin, 2012) found that therapeutic hypothermia resulted in a reduction in the risk of death or major neurodevelopmental disability (RR 0.76; 95% CI, 0.69-0.84) and increase in the rate of survival with normal neurological function (1.63; 1.36-1.95) at age 18 months. Hypothermia reduced the risk of death or major neurodevelopmental disability at age 18 months in newborns with moderate HIE (RR, 0.67; 95% CI, 0.56-0.81) and in newborns with severe HIE (0.83; 0.74-0.92). Both total body cooling and selective head cooling resulted in reduction in the risk of death or major neurodevelopmental disability(RR, 0.75; 95% CI, 0.66-0.85 and 0.77; 0.65-0.93,respectively). This is supported by a further Cochrane review (Jacobs 2013), which examined evidence from 11 RCTs (N=1505 infants) and concluded that therapeutic hypothermia is beneficial in term and late preterm newborns with HIE. Cooling reduces mortality without increasing major disability in survivors and the benefits of cooling on survival and neurodevelopment outweigh any short-term adverse effects.


Evidence Level: I

Does the rate of cooling matter?

A retrospective observational study in 43 children (Kawano, 2011) compared 16 cared for at normothermia with 27 having had mild hypothermia applied. In univariate analysis, ages <= 18 months, marked elevation in serum lactate dehydrogenase (LD) and aspartate

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transaminase, diagnosis of either acute necrotising encephalopathy or haemorrhagic shock and encephalopathy syndrome and longer hypothermic periods were associated with increased risks of death or severe neurological deficit, whereas hypothermia showed pivotal effects: the outcome of children cooled after 12 h of diagnosis was statistically invariant with normothermic children, but was significantly worse compared with children cooled <= 12 h. In multivariate analysis, younger ages and elevated serum LD were associated with adverse outcomes, whereas early initiation of cooling was related to favourable outcomes. For normothermic children, PCPC scores were dependent on the computed tomographic findings suggestive of cerebral oedema, serum LD levels and Glasgow Coma Scale at admission. For hypothermic children, PCPC scores depended on longer delays in cooling initiation.

http://adc.bmj.com/content/96/10/936.long

Evidence Level: IV

Last amended July 2013
Last reviewed September 2015
What are the indications for CPAP?

Recurrent spells of apnoea (pause in breathing > 20 seconds) are “almost universal” in infants < 34 weeks’ gestation (Lemyre, 2002). CPAP is used to support these infants, along with those recently extubated or with respiratory distress soon after birth (De Paoli, 2007). \( P_{aO_2} < 50-60 \text{ mm Hg} \) whilst breathing > 40%-70% oxygen is regarded as a positive indication for CPAP in most units (Carlo, 2001).

A small retrospective randomised study (Dani, 2004) compared nasal CPAP with mechanical ventilation (MV) following surfactant therapy and extubation in preterm infants with respiratory distress syndrome. In the MV group, 6 patients (43%) were still dependent on MV at 7 days of life, vs no patients in the CPAP group.

Nasal CPAP reduces the incidence of adverse effects after extubation including failure (NNT 6; 95% CI 4-15) and chronic lung disease at 28 days (NNT 6; 95% CI 3-22) (Halliday, 2004). Data from a comparison of treatment of premature infants at the University of Vienna tertiary centre and the Vermont Oxford Neonatal Network as a whole (Kirchner, 2005) is also suggestive of an improved rate of retinopathy of prematurity (1-10% vs 8-12%) as well as chronic lung disease (14-32% vs 27-39%), when CPAP is used more often (45-86% vs 37-63%).

A randomised, multicentre trial in 1316 infants (Finer, 2010) assigned babies to intubation and surfactant treatment (within 1 hour after birth) or to CPAP treatment initiated in the delivery room, with subsequent use of a protocol-driven limited ventilation strategy. Infants were also randomly assigned to one of two target ranges of oxygen saturation. The primary outcome was death or bronchopulmonary dysplasia as defined by the requirement for supplemental oxygen at 36 weeks (with an attempt at withdrawal of supplemental oxygen in neonates who were receiving less than 30% oxygen). The rates of the primary outcome did not differ significantly between the CPAP group and the surfactant group (47.8% and 51.0%, respectively; relative risk with CPAP, 0.95; 95% CI, 0.85 to 1.05) after adjustment for gestational age, centre, and familial clustering. The results were similar when bronchopulmonary dysplasia was defined according to the need for any supplemental oxygen at 36 weeks (rates of primary outcome, 48.7% and 54.1%, respectively; relative risk with CPAP, 0.91; 95% CI, 0.83 to 1.01). Infants who received CPAP treatment, as compared with infants who received surfactant treatment, less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia \( (P<0.001) \), required fewer days of mechanical ventilation \( (P=0.03) \), and were more likely to be alive and free from the need for mechanical ventilation by day 7 \( (P=0.01) \). The rates of other adverse neonatal outcomes did not differ significantly between the two groups. The authors concluded that CPAP was a viable alternative to intubation and surfactant in preterm infants.


http://pediatrics.aappublications.org/content/113/6/e560.long


http://www.nejm.org/doi/full/10.1056/NEJMoa0911783#t=articleTop


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Lemyre B, Davis PG, De Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity. The Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD002272

Evidence Level: I

What pressure range should be used?
Conventionally, a nasal CPAP of 5 cm H2O is used, rising in 1 cm increments to 10 cm. if there is no improvement. Higher levels may over-distend the lungs, leading to hypercapnia (De Paoli, 2007; Carlo, 2001).

A 2014 RCT (Buzzella) compared two ranges of nasal continuous positive airway pressure (NCPAP) in oxygen dependent preterm infants. Infants were randomized to low (n = 47) or high NCPAP (n = 46) at day 16.3 ± 14.7 and 15.5 ± 12.4, respectively. Rates of extubation failure per criteria (24% vs 43%, P = .04, OR and 95% CI: 0.39 [0.16-0.96]) and re-intubation (17% vs 38%, P = .023, 0.33 [0.016-0.85]) within 96 hours were significantly lower in the high- compared with the low NCPAP group. This was mainly due to a strikingly lower failure rate in the 500-750 g birth weight strata. These findings suggest the need for higher distending pressure post-extubation in the more immature infants who are still oxygen dependent.

Buzzella B, Claure N, D’Ugard C. A randomized controlled trial of two nasal continuous positive airway pressure levels after extubation in preterm infants. Jnl Paediatrics. 2014:164;46-51


Evidence Level: V

How should infants be weaned from CPAP?
A Cochrane systematic review of 3 trials (Jardine 2011) concluded that: “Infants who have their NCPAP pressure weaned to a predefined level and then stop NCPAP completely have less total time on NCPAP and shorter durations of oxygen therapy and hospital stay compared with those that have NCPAP removed for a predetermined number of hours each day. Future trials of withdrawing NCPAP should compare proposed strategies with weaning NCPAP pressure to a predefined level and then stopping NCPAP completely. Clear criteria need to be established for the definition of stability prior to attempting to withdraw NCPAP.”

A multicentre RCT in 177 infants <30 weeks gestational age (Todd, 2012) randomised the babies to one of the three CPAP weaning methods: 1: Taken ‘OFF’ CPAP with the view to stay ‘OFF’. 2: Cycled on and off CPAP with incremental time ‘OFF’. 3: As with 2, cycled on and off CPAP but during ‘OFF’ periods were supported by 2 mm nasal cannula at a flow of 0.5 l/min. Primary outcomes showed the first method produced a significantly shorter time to wean from CPAP (11.3 +/- 0.8, 16.8 +/- 1.0, 19.4 +/- 1.3 (days +/- 1SE) p<0.0001, respectively) and CPAP duration (24.4 +/- 0.1, 38.6 +/- 0.1, 30.5 +/- 0.1 (days +/- 1SE) p<0.0001, respectively). All the secondary outcomes were significantly shorter with the first method: (oxygen duration: 24.1 +/- 1.5, 45.8 +/- 2.2, 34.1 +/- 2.0 (days +/- 1SE) p<0.0001, BPD: 7/56 (12.5%), 29/69 (42%), 10/52 (19%) p=0.011 and length of admission: 58.5 +/- 0.1, 73.8 +/- 0.1 69.5 +/- 0.1 (days +/- 1SE) p<0.0001, respectively).

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What types of CPAP are available?
The two most widely-used systems are conventional nasal CPAP and the Infant Flow Driver system. Conventional CPAP delivered with a conventional ventilator and nasal prongs was compared to the Infant Flow CPAP (IF CPAP) system in a prospective, randomised study of 162 intubated extremely low birth weight infants (Stefanescu, 2003). Individual extubation success rates were identical at 61.9% (52 of 84) in the CPAP group vs 61.5% (48 of 78) in the IF CPAP group. The IF CPAP group did, however, experience fewer days on supplemental oxygen and shorter hospital stays.

Short binasal prongs (as in the Infant Flow system) produce more stable pressures (De Paoli, 2007) and are more effective than single prongs in reducing the rate of re-intubation (De Paoli, 2008). New generation facemasks that are more effective than those used originally, and that cause minimal nasal trauma, have recently been developed. No clinical comparisons with nasal prongs have yet been completed (De Paoli, 2003).

A small study in 13 premature infants (Boumecid, 2007) suggests that variable-flow NCPAP increases tidal volume and improves thoraco-abdominal synchrony to a greater extent than is the case with constant-flow NCPAP and nasal prongs.

Is bubble CPAP superior to conventional CPAP?
Few randomised studies have compared these two approaches, but those that have (Colaizy, 2004; McEvoy, 2004; Lee, 1998) have recorded reductions of up to 50% in the need for mechanical ventilation in favour of bubble CPAP. Another advantage is low cost: bubble CPAP equipment costs are 15% of those for mechanical ventilation, and the technique can be administered by nursing staff (Koyamaibole, 2006).

A retrospective outcome study (Narendran, 2003) found that early bubble CPAP reduced delivery room intubations, days on mechanical ventilation and postnatal steroid use (p<0.001). Increased postnatal weight gain at 36 weeks was also noted (p<0.05).
Bubbling is assumed to improve pulmonary gas exchange, although no such benefits were observed in a randomised crossover trial in 26 babies (Morley, 2005).


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721902/pdf/v090p0F343.pdf


Evidence Level: II

Last amended September 2015
Last reviewed September 2015
CRANIAL ULTRASOUND SCANS
Supporting information

This guideline has been prepared with reference to the following:


http://www.neurology.org/content/58/12/1726.long

Should all premature newborns be given a cranial ultrasound scan?
The recommendation given in the US guidelines (above) is that cranial ultrasound should be performed routinely on all infants < 30 weeks gestation at 7-14 days of age and repeated between 36-40 weeks postmenstrual age. This has been validated in a retrospective study of 486 infants (Harris, 2007).


Evidence Level: IV

Last amended September 2007
Last reviewed September 2015
Is extended stay (> 28 d) in an intensive care unit predictive of a higher mortality rate?
A retrospective study in 116 infants (mean age 29 days) spending more than 28 days in intensive care (Naghib, 2010) found that they accounted for 3% of total admissions but occupied 63% of total admission days. Median (range) stay was 56 (28-546) days. Mortality during admission for this group was five times higher (22%) than the average intensive care unit mortality rate of 4.6%. Withdrawal or limitation of therapy preceded 70% of deaths.


Evidence Level: IV
DISCHARGE FROM NEONATAL UNIT
Supporting information

This guideline has been prepared with reference to the following:


http://pediatrics.aappublications.org/content/122/5/1119.full

What factors increase the likelihood of parents keeping their follow-up appointments?
A retrospective observational cohort study (Nehra, 2009) found that children of older mothers were more likely to attend follow-up. Factors which significantly improved compliance with follow-up care were patient contact after discharge (compliant: 65% vs. non-compliant: 35%) and early intervention referral (compliant: 64% vs. non-compliant: 36%). Factors which significantly hindered compliance were maternal drug use during pregnancy (compliant: 11.8% vs. non-compliant: 88%), and patient transfer to outside NICUs [(transferred out: compliant: 3 (10.3%), non-compliant 25 (89.3%)].


Evidence Level: IV

Last amended January 2011
Last reviewed September 2015
This guideline has been prepared with reference to the following:


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2936060/


Last amended September 2011
Last reviewed September 2015
What is the incidence of supraventricular tachycardia in the neonatal period?
A review of the subject (Calabro, 2008) states that: “Supraventricular tachycardias are observed in 0.1-0.4% of the paediatric population.”


Evidence Level: V
ENVIRONMENT AND NOISE ON NEONATAL UNIT
(including quiet time)
Supporting information

This guideline has been prepared with reference to the following:


http://pediatrics.aappublications.org/content/100/4/724.full

Last amended September 2011
Last reviewed September 2015
This guideline has been prepared with reference to the following:


http://www.nice.org.uk/guidance/cg37

Should routine examination be carried out at 24-48 hours of age by paediatricians/nurse practitioners?

No randomised trials have addressed the question of whether the routine neonatal examination is useful and necessary (Hall, 1999). Less than 30% of congenital heart defects or hip abnormalities are detected during the examination, although it is regarded as a core component of child health surveillance and expected by parents (Wolke, 2002).

Although the need for a first examination in the first 48 hours is generally accepted, there is disagreement over whether a second is necessary.

The Maternity Services Advisory Committee recommended a routine neonatal discharge examination in 1985, although the joint Working Party on Child Health Surveillance recommended only a repeat examination of hip stability on discharge or within 10 days after birth (Cartlidge, 1992).

An audit of second (discharge) examinations, performed on 97.3% of 1795 newborn infants, was done on the day of discharge in 1428 infants (79.6%) (Moss, 1991). Because of early discharge, 38.5% of babies were examined on or before day 2, the median time of the discharge examination being 4 days of age. This second examination revealed previously undiscovered problems in 63 infants (3.6%). Only 7 of these, however, were considered to be important or significant (0.5%). The study concluded that full second examinations could not be justified, but that a test for hip stability should be performed.

A randomised controlled trial (Glazener, 1999) allocated 4835 newborns to receive one screening examination and 4877 to receive two. Despite more suspected abnormalities being identified in the two examination group (9.9 vs 8.3 diagnoses per 100 babies), there was no significant difference in the number needing active management (12 (0.2%) vs 15 (0.3%)).

A postal questionnaire sent to all maternity units in England, and having an 86% response rate (Hayes, 2003) revealed that routine neonatal examination was usually (83%) carried out by senior house officers. Although 44% of units had at least one midwife qualified to carry out the examination, only 2% of babies nationally were examined by a midwife. Initial examinations were carried out between 6-48 hours of age and 12% of units carried out a second examination prior to discharge.

A randomised trial of 826 mother and baby pairs (Wolke, 2002) found that more mothers were satisfied by neonatal examinations carried out by midwives than by SHOs (OR 0.54, 95% CI 0.39-0.75, p<0.001), largely because midwives were more likely to discuss general healthcare issues and were able to provide continuity of care.

This was also one of the findings of the EMREN study (Townsend, 2004).

A prospective study in 527 infants (Lee, 2001) compared the ability of SHOs in detecting abnormalities compared to advanced neonatal nurse practitioners (ANNPs). ANNPs displayed greater sensitivity than SHOs at detecting hip abnormalities (96% vs 74%; p<0.05) and eye abnormalities (100% vs 33%; p<0.05). There were no significant differences between the two groups in terms of positive predictive values or effectiveness in detecting cardiac abnormalities.

A prospective study in 14,572 infants (Patton, 2006) concluded that effectiveness of the clinical examination in detection of congenital heart disease was more dependent on experience and the existence of a clear, structured, referral pathway than on staff having a medical vs a nursing background.


Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
http://www.bmj.com/content/318/7184/627

Hall DM. The role of the routine neonatal examination: it has many aims, few of them evaluated. BMJ 1999;318:619-20
http://www.bmj.com/content/318/7184/619


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721315/pdf/v085p0F100.pdf


Patton C, Hey E. How effectively can clinical examination pick up congenital heart disease at birth? Arch Dis Child Fetal Neonatal Ed 2006;91:F263-7
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672726/


http://fn.bmj.com/content/86/3/F155.long

Evidence Level: II

Last amended February 2008
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhs.nhs.uk
EXCHANGE TRANSFUSION
Supporting information

What are the indications for exchange transfusion (i.e. haemoglobin level in haemolytic disease of the newborn (HDN); bilirubin level in haemolytic disease jaundice/non-haemolytic disease jaundice)?

The neurodevelopmental risks associated with high total serum bilirubin levels in newborns are "not well defined" (Newman, 2006). The most recent sliding scale for exchange transfusion in infants \( \geq 35 \) weeks' gestation is provided within a clinical practice guideline from the American Academy of Pediatrics (Anon, 2004). Although the general level of total serum bilirubin (TSB) at which exchange transfusion is recommended is 25 mg/dL (428 mol/L), this may be lower in younger infants (as little as 15 mg/dL (257 mol/L) at 24 hours of age) with more risk factors. A study of 41 infants with HDN (Gottvall, 1994) found that a foetal haemoglobin value below 95 g/L was a valid indication for exchange transfusion.

A retrospective cohort study of all infants receiving ET (n=51) in an Australia hospital between 2000 and 2010 found that 96% of patients had Hyperbilirubinaemia, 71% had rhesus haemolytic disease of the newborn and 12& had ABO incompatibility (Chitty, 2013).

http://pediatrics.aappublications.org/content/114/1/297.long


http://www.nejm.org/doi/full/10.1056/NEJMoa054244#:~:text=A%20retrospective%20cohort%20study%20of%20all%20infants%20receiving%20ET%20(n=51)%20in%20an%20Australia%20hospital%20between%202000%20and%202010%20found%20that%2096%25%20of%20patients%20had%20Hyperbilirubinaemia%2C%2071%25%20had%20rhesus%20haemolytic%20disease%20of%20the%20newborn%20and%2012%26%20had%20ABO%20incompatibility%28Chitty%2C%202013%29.

Evidence Level: V

Is the umbilical venous route superior to umbilical artery/vein or peripheral artery/vein?

The umbilical venous route has been associated with portal vein thrombosis in infants with co-existent umbilical infection or traumatic damage resulting from catheterisation (Guimaraes, 1998). Other recorded complications include cardiac arrest or pronounced bradycardia (Rubaltelli, 1978), bladder rupture (Sayan, 1996), bacterial infection (Anagnostakis, 1975), necrotising enterocolitis (Livaditis, 1974), and intestinal perforation (Sommerschild, 1971; Corkery, 1968, Orme, 1968). This route has, however, been shown to be safer than the umbilical artery route, and the majority of adverse events are laboratory abnormalities that are asymptomatic and treatable (Patra, 2004). A study of exchange transfusion using the peripheral vessels, in 201 infants over a 5.5 year period (Fok, 1990), found this route to be safe and effective, with few complications. Recent reviews (Murray, 2004) suggest that there is little or no evidence for one route over another, but that "individual units should maintain a standard practice". No guidance on the preferred route is given in current UK guidelines (Anon, 2004).

A retrospective review (Chen, 2008) of 123 exchange transfusions at a single hospital (24 via umbilical vein and 99 via peripheral vessels) found both approaches equally effective in reducing serum bilirubin. The peripheral approach was associated with fewer severe adverse events. A retrospective cohort study in 109 neonates (Weng, 2011) analysed 128 exchange transfusion (ET) procedures: 33 via femoral vein (FV), 35 via umbilical vein (UV) and 60 via umbilical artery/vein (UA/V) routes. There was no significant difference in the decline of total serum bilirubin between each group. When compared with the UA/V group, the transfusion rate was slower in the FV and UV groups (\( p < .001 \)). Adverse events with clinical significance were more common in ET via the UV route than ET via the FV and UV routes (\( p < .05; \) OR 2.4; 95% CI

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1.2-5.0). Neonates with ET via the UA/V route tended to have more asymptomatic laboratory aberrances (p < .01; OR 2.5; 95% CI 1.3-4.6). There were no significant differences in the transfusion rate (p = .498) and adverse events (p = .822) between the FV and UV groups. The authors concluded that ET through the FV route was “an effective and secure method for the treatment of neonatal hyperbilirubinemia when the UV route is unavailable.”


Chen HN, Lee ML, Tsao LY. Exchange transfusion using peripheral vessels is safe and effective in newborn infants. Pediatrics 2008;122:e905-10


Sommerschild HC. Intestinal perforation in the newborn infant as a complication in umbilical vein infusion or exchange transfusion. Surgery 1971;70:609-13


Evidence Level: III

What investigations/monitoring procedures are required when performing exchange transfusion?

Although there is general agreement that the rate of adverse events associated with exchange transfusion is high (Patra, 2004; Jackson, 1997), no evidence-based guidance currently exists on investigations or monitoring procedures.

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Jackson JC. Adverse events associated with exchange transfusion in healthy and ill newborns. Pediatrics 1997;99:e7
http://pediatrics.aappublications.org/content/99/5/e7.long


Evidence Level: V

Last amended September 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Hyaluronidase should not be used to treat injuries?
A survey of regional neonatal intensive care units (Wilkins, 2004) found that exposure to air, occlusive dressings, and hyaluronidase were all regularly used in the treatment of extravasation injuries. The authors stated that: “Infiltration with hyaluronidase and saline is an invasive procedure recommended in standard texts, and there are case reports showing its use. However, there have been no studies in preterm infants comparing its effectiveness with other treatments. In addition the British National Formulary recommends hyaluronidase to be used with caution in infants.”

Wilkins CE, Emmerson AJ. Extravasation injuries on regional neonatal units. Arch Dis Child Fetal Neonat Ed 2004;89:F274-5
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721664/pdf/v089p0F274.pdf

Evidence Level: V

How many babies develop skin necrosis as a result of extravasation of an IV infusion?
Approximately 4% of babies develop skin necrosis as a result of extravasation of an IV infusion.


Evidence Level: V

Is the risk of extravasation injury different when comparing centrally placed catheters with peripheral cannulae?
A Cochrane systematic review of 3 RCTs (208 subjects) did not detect a statistically significant difference in risk of extravasation injury when comparing central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates (RR: 0.36 CI: 0.07 to 1.75).


Evidence Level: I

Last amended August 2015
Last reviewed September 2015
Most babies born <24 weeks gestation are expected to die, but outcome improves with each additional week of gestational age?

A retrospective, 5 year case-control review of 237 infants with gestational ages < 27 weeks (Genzel-Boroviczeny, 2010) found that, despite successful resuscitation, infants between 23 and 26 weeks had a very poor prognosis for survival when presenting with bradycardia, cyanosis and no respiratory efforts (1-min Apgar=1) at birth. Initiating active treatment for an infant at 23 weeks with bradycardia and apnoea was almost always unsuccessful (with a 1-min Apgar score of 1, a male infant at 23 weeks and 500g had a mortality rate of 92%), whereas by 26 weeks gestation, the chances of survival were higher than the probability of death.


Evidence Level: III
Does positioning have an effect on GOR?

A systematic review of randomised controlled trials (Carroll, 2002) quotes a controlled prospective study of 9 infants with GOR (Orenstein, 1983) which found that positioning at a 60 degree elevation in an infant seat increased reflux compared with the prone position. A later study by the same author (Orenstein, 1990) found no significant difference between the flat and head-elevated prone positions. The "supine reversed-Trendelenburg sleeping position", recommended by some (Taminiau, 1997), was found to increase acid reflux parameters in all 10 consecutively investigated infants in a Belgian study (Bagucka, 1999). A study of 18 preterm infants with GOR (Ewer, 1999) compared prone, left lateral and right lateral positions. Each position was used for 8 hours, with the order randomly assigned. The reflux index was significantly less in prone (6.3) and left lateral (11.0) positions compared to the right lateral (29.4). The left lateral position may be an acceptable alternative, in infants, to the prone position which has been associated with sudden infant death (Tobin, 1997; Vandenplas, 1997) and is recommended in US guidelines (NASPGHAN, 2009) for children older than one year. The effects of positioning have not been studied in children older than 1 year (NASPGHAN, 2009).

A study in 22 premature infants (Corvaglia, 2007) found that oesophageal exposure to acid and nonacid GOR was lower in the prone (4.4% and 0.3%, respectively) and the left lateral (7.5% and 0.7%, respectively) positions than in the right lateral (21.4% and 1.2% respectively) and supine (17.6% and 1.3%, respectively) positions.

A randomised controlled trial by Loots et al. (2014) examined the effects of positioning in the left lateral position (LLP) compared/combined with others therapies in reducing the symptoms of GOR. The authors concluded that LLP may reduce vomiting in infants with GOR.

**References**


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721012/pdf/v081pF201.pdf


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Are thickened feeds of use for GOR?

Two systematic reviews of randomised controlled trials (Huang, 2004; Carroll, 2002;) found no statistically significant reduction in reflux with the use of thickened infant foods compared to placebo. One study in 24 infants (Borrelli, 1997) did, however, detect a significant benefit of formula thickened with carob bean gum compared with rice flour (pH<4 for 5% vs 8% of time). This was replicated by a later study in 14 infants (Wenzl, 2003). Another study in 19 infants (Sutphen, 1989) showed that supplementing with dextrose 5% water was associated with less reflux than dextrose 10% water.

US guidelines (NASPGHAN, 2009) note that, although thickened feeds do not improve reflux index scores, they do decrease the number of episodes of vomiting. A study in 30 formula-fed babies (Vandenplas, 1987) found little change in the reflux index (17.8% vs 18.4%) after 7-14 days of thickened feeds, but in 24 infants a decrease in the number of reflux episodes in 24 hours (15.1 vs 34.5). The duration of the longest recorded episode did, however, increase from 23.3 min to 56.6 min, leading the authors to warn against possible protracted episodes of occult GOR.

Two similar studies, in 20 (Orenstein, 1987) and 52 infants respectively (Bailey, 1987) also came to the same conclusion.

A double-blind, randomised trial in 104 infants (Vanderhoof, 2003) found that a pre-thickened formula (Enfamil AR) was associated with greater symptom reduction by one week compared to placebo: % feedings with any regurgitation (p=0.045), total regurgitation volume score (p=0.035), and % feedings with choke/gag/cough (p=0.004). Sleep was improved in those infants with most symptoms at baseline (p=0.030).

The ESPGHAN Committee on Nutrition recommends that thickened feeds should be used only in selected infants with failure to thrive caused by excessive nutrient losses associated with GOR, and also points out that antireflux milk products “usually do not meet the European Union's compositional standards for infant formula” (Aggett, 2002).

A randomised controlled trial in 96 formula-fed infants (Xinias, 2005) compared a group given standard formula (n=45) with a group given formula thickened with cornstarch/casein (n=51) for 28 days. In the cornstarch group, the percentage of time with a pH < 4.0, number of reflux episodes > 5 min and duration of the longest reflux episode all decreased significantly whilst remaining unchanged in the standard formula group.

A systematic review and meta-analysis of 14 RCTs in 877 infants (Horvath, 2008) found that thickened feeds significantly increased the percentage of infants with no regurgitation (RR: 2.9; 95% CI: 1.7 to 4.9). No one thickening agent demonstrated superiority over another.


NASPGHAN . Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition


Sutphen JL, Dillard VL. Dietary caloric density and osmolality influence gastroesophageal reflux in infants. Gastroenterology 1989;97:601-4


Evidence Level: I (for reduced vomiting)

Is Gaviscon of use in GOR?
A randomised study on 20 infants and children (Buts, 1987) compared Gaviscon with placebo (10 patients in each group). After 8 days of treatment with Gaviscon, all pH monitoring variables were significantly reduced between –35% and –61% of initial recorded values. In the placebo group, mean values changed little (-9.5 - +8.2 of initial values). Reported episodes of regurgitation were also reduced in the Gaviscon group compared to no change in the placebo group.

A randomised, parallel group study conducted on 50 infants with GOR (Greally, 1992) compared Gaviscon plus Carobel (carob seed flour) with oral cisapride (0.8 mg/kg/day over one month). 14 of 26 in the cisapride group (53%) were considered “better” by their parents, compared with 19 of 24 (79%) in the Gaviscon/Carobel group. 5 of 17 pH variables improved from baseline in the cisapride group compared to 11 of 17 given Gaviscon plus Carobel.

Despite this, unpaired analysis of diary and pH data showed no significant difference between the groups. The authors concluded that cisapride was no more effective than Gaviscon plus Carobel.

A third randomised study comparing gaviscon and metoclopramide (Forbes, 1986) found that neither decreased the frequency or duration of GOR.

Gaviscon 100mg/20 ml feed is recommended in a review of GOR (Taminiau, 1997).
A double-blind, non-randomised study in 20 infants (Del Buono, 2005) compared the effects of 6 random administrations of Gaviscon Infant (625 mg in 225 ml milk) with placebo (mannitol and Solvito N, 625 mg in 225 ml milk). There was no significant difference between Gaviscon and placebo in terms of median number or duration of reflux/acid reflux events per hour, nor in minimum distal/proximal pH or total acid clearance time per hour.

A Cochrane systematic review from 2014 (Tighe) found that "the diversity of study designs and the heterogeneity of outcomes, as well as the evolution in formulation, (means) it was not possible to perform a meta-analysis on the efficacy of Gaviscon Infant®. Moderate evidence indicates that Gaviscon Infant® improves symptoms in infants, including those with functional reflux.


Evidence Level: I

Is domperidone of use in GOR?

A double-blind, randomised, placebo-controlled study in 80 children with GOR (Carroccio, 1994) found that symptoms resolved completely in 16 of 20 receiving domperidone plus magnesium hydroxide and aluminium hydroxide. This compared with 8 of 20 given domperidone plus alginate, 9 of 20 given domperidone alone, and 7 of 20 given a placebo. Similar results were achieved in an earlier study by the same team (Iacono, 1991) which compared only the first two groups of the later study. Percentage reflux time was significantly reduced only in the first group.

A double-blind, placebo-controlled trial of domperidone in 17 children (Bines, 1992) found that treatment was necessary for 8 weeks before significant improvement occurred in measures of reflux other than number of episodes in the 2 hour postprandial period. The efficacy of domperidone in children is currently considered to be “unproven” (Cezard, 2004; NASPGHAN, 2009; Brown 2000).

A systematic review of 4 RCTs (Pritchard, 2005) concluded that “there was no robust evidence of efficacy for the treatment of GOR with domperidone in young children. Given the usually benign nature of the condition, the widespread use of unlicensed medicines for GOR is not warranted.”

A 2014 Cochrane systematic review concluded that there was only weak evidence to support the use of domperidone and that the evidence suggested “that although reflux frequency was significantly increased, reflux duration was significantly improved”.


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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884866/


Evidence Level: II

**Is ranitidine/cimetidine plus a proton pump inhibitor of use in relieving oesophagitis caused by GOR?**

A randomised, double-blind trial in 32 children with reflux oesophagitis (Cucchiara, 1989) compared cimetidine 30-40 mg/kg/day (n=17) with placebo (n=15) over a 12 week period. 12 patients in the cimetidine group were healed compared to 3 in the placebo group. Ranitidine is considered as first-line treatment for children with severe oesophagitis and case series have shown successful healing in 75-95% of children aged 3 months to 16 years given 6-8 mg/kg/day for 8 weeks (Kelly, 1994). A dose of 2mg/kg twice daily in infants has been shown to reduce the time that gastric pH was <4 by 44% (Sutphen, 1989). With thrice daily dosing the reduction was 90%. The increased gastric pH effect has been shown to last 9-10 hours in infants (Mallet, 1989). Although there have been no RCTs of ranitidine for oesophagitis in children, expert opinion considers it as effective as cimetidine (Anon, 2001).

A study of 15 children with severe reflux given omeprazole when H2 antagonists and prokinetics had failed (Gunasekaran, 1993) found that doses of between 10mg and 60mg daily were needed to normalise oesophageal pH. A similar study in 12 infants (Alliet, 1998) found that omeprazole 0.5mg/kg/day for 6 weeks resulted in complete resolution in 9 and improvement in the other 3. 6 out of 10 patients who responded well to omeprazole in doses of 20-40mg/day relapsed when therapy was discontinued after 3 months, raising the possibility that long-term treatment may be necessary (De Giacomo, 1997).

Although administering H2RAs and PPIs together can inhibit the efficacy of the latter (Anon, 2001), “step-up” therapy, in which treatment begins with an H2RA at standard dosage, followed by a PPI at standard dosage and then a PPI at higher dosage if necessary, is effective (Gunasekaran, 1993). “Step-down” therapy, which is the reverse approach, has been recommended for adults (Dent, 1999) but the two approaches have not been compared in children.

A randomised controlled trial of famotidine in 35 infants (Orenstein, 2003) found significant improvements in regurgitation frequency (p=0.04) and volume (p=0.01), and crying time (p=0.027) when compared to placebo.

Although no randomised controlled trials on the use of PPIs in children have yet been carried out (Rudolph, 2003), a double-blind, placebo-controlled trial in 30 infants (Moore, 2003) that did not use randomisation found that omeprazole resulted in a significant fall in the reflux index (-8.9% +/- 5.6% vs -1.9% +/-2.0, p<.001). A systematic review of 12 studies (van der Pol, 2011) found no evidence that PPIs were of benefit in newborns.


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http://gut.bmj.com/content/44/suppl_2/S1.long


Kelly DA. Do H2 receptor antagonists have a therapeutic role in childhood? J Pediatr Gastroenterol Nutr 1994;19:270-6


http://pediatrics.aappublications.org/content/127/5/925.long

Evidence Level: II

Last amended September 2015
Last reviewed September 2015

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For patients with high stoma output, capillary blood gas test more appropriate than arterial blood gas test?
The majority of studies show clinically acceptable agreement between capillary and arterial pH. (McLain 1988, Johnson 2000). A prospective study (Johnson 2000) of 21 infants in a NICU, comparing paired capillary and arterial results of pH, PO2, PCO2, lactate, sodium, potassium, ionized calcium, and haematocrit found no capillary-arterial differences were observed for pH, PCO2, lactate, or sodium. Although capillary results were slightly, but significantly (p < .01), higher for potassium (+0.4 mEq/liter), ionized calcium (+0.47 mg/dl), and hematocrit (+4 percent), these differences fell within acceptable Clinical Laboratories Improvement Act (CLIA) performance criteria.


Evidence Level: IV

Last amended July 2013
Last reviewed September 2015
What is the incidence of gastroschisis?
A review of the subject (Holland, 2010) states that “Gastroschisis continues to increase in frequency, with several studies now reporting an incidence of between 4 and 5 per 10,000 live births.”


Evidence Level: V

In NNU, do you give Vitamin K into the deltoid muscle or the thigh?
The Department of Health (2013) recommends the anterolateral thigh muscle as the injection site for newborns or infants (1-12 months.) because it “provides a large muscle mass into which vaccines can be safely injected”, and presumably this can be applied to vitamin K, although it recommends the left deltoid muscle for BCG.


Evidence Level: IV
HEARING SCREENING
Supporting information

This guideline has been prepared with reference to the following:


Newborn screening is superior to later distraction screening for improved developmental outcomes?

A retrospective comparative study in the Netherlands (Korver, 2010) compared developmental outcomes of 263 children with permanent childhood hearing impairment born in regions that performed newborn hearing screening with 171 similarly-affected children born in regions that favoured later distraction hearing screening. Multivariate analysis of variance showed that overall, children in newborn hearing screening regions had higher developmental outcome scores compared with children in distraction hearing screening regions (Wilks = 0.79; F(12) = 2.705; P = .003). For social development, the mean between-group difference in quotient points was 8.8 (95% CI, 0.8 to 16.7) and for gross motor development, 9.1 (95% CI, 1.1 to 17.1). For quality of life, the mean between-group difference was 5.3 (95% CI, 1.7 to 8.9), also in favour of children in newborn hearing screening regions.

A systematic review of 17 non-randomised studies (Wolff, 2010) was unable to reach any firm conclusions on the value of newborn screening, due to the lack of high-quality research. A recent review of past studies (Pimperton and Kennedy 2012) has concluded that “exposure to Universal Newborn Hearing Screening and early identification of Permanent Childhood Hearing Impairment are associated with benefits to language development in deaf children, with more consistent evidence provided for links between early identification and positive language outcomes”

Korver AM, Konings S, Dekker FW et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. JAMA 2010;304:1701-8

http://adc.bmj.com/content/97/7/648.long

http://adc.bmj.com/content/95/2/130.long

Evidence Level: III

Last amended July 2013
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
**HEPATITIS B & C**

**Supporting information**

This guideline has been prepared with reference to the following:


http://www.journal-of-hepatology.eu/article/S0168-8278(05)00417-4/pdf


**Immunisation should be given within 24 hours for infants of HBsAg positive mothers?**

Infants of mothers testing positive for HBeAg should be given HBIG in addition?

A systematic review of 29 RCTs (Lee, 2006) found that immunisation within 24 hours of birth reduced the occurrence of hepatitis B compared with placebo or no intervention (RR 0.28, 95% CI 0.20 – 0.40).

In a small uncontrolled study of 41 infants of HBsAg positive mothers (Reesink, 1979), 21 were immunised within 48 hours of birth and 20 were not treated. None of the treated group became HBsAg positive, compared with 5 of the untreated group (p<0.02). Two of 3 infants who were not immunised until the fourth or fifth day after birth also became HBsAg positive. A RCT in 117 infants (Beasley, 1981) took care to ensure that immunisation occurred as soon as possible after birth (usually within 1 hour). Follow-up continued for at least 15 months, during which time 91% of the 35 infants given placebo became HBsAg positive. This compared with 45% in the 42 infants who received a single dose of HBIG at birth, and 23% of the 40 infants given a course of 3 treatments at birth, 3 months and 6 months. The authors concluded that “Presumably…the earlier administration occurs the better.”

Passive immunisation alone was available in the first six months of life until 1985, when hepatitis B vaccine was first licensed for infants below this age (Polakoff, 1988). Active immunisation was subsequently started at birth.

The presence of HBeAG in the mother is indicative of more severe infection and consequently, the infant may be given 200 IU of HBIG as additional protection (Wallis, 1999).


http://www.bmj.com/content/332/7537/328


http://www.bmj.com/content/297/6643/249.full.pdf+html


Wallis DE, Boxall EH. Immunisation of infants at risk of perinatal transmission of hepatitis B: retrospective audit of vaccine uptake. BMJ 1999;318:1112-3

http://www.bmj.com/content/318/7191/1112

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
HERPES SIMPLEX
Supporting information

This guideline has been prepared with reference to the following:


http://fn.bmj.com/content/99/3/F240.long


http://pediatrics.aappublications.org/content/131/2/e635.full

Is antiviral therapy of value?
A Cochrane systematic review of 2 RCTs in a total of 273 infants (Jones, 2009) failed to establish the value of antiviral agents. One study treated 63 infants with vidarabine or placebo and the other study treated 210 infants with aciclovir or vidarabine. In the study comparing vidarabine with placebo, infants with all forms of neonatal herpes simplex virus (HSV) were included [disseminated disease, central nervous system (CNS) disease alone, and skin, eye and mouth (SEM) disease]. There was no significant reduction in the risk of mortality when analyzed as an entire group; however, mortality was significantly reduced when data from infants with CNS disease or disseminated disease were combined. There was no difference in the rate of neurological abnormalities in survivors at one year when analyzed as an entire group or by disease category. There was no difference between aciclovir and vidarabine in preventing mortality from neonatal HSV disease, in preventing disease progression, in reducing the incidence of neurological abnormality at one year, or in the incidence of drug-induced renal or bone marrow toxicity. In infants with SEM disease, there was no significant difference in neurological outcome with aciclovir compared with vidarabine treatment.


Evidence Level: I

The Polymerase Chain Reaction (PCR) test is an accurate indicator of HSV infection?
A randomised comparison of a new, rapid PCR test and a previously validated “Taqman” PCR test (Gardella, 2010) found the correlation was excellent (R=0.96, P<.001). The rapid test had a positive predictive value of 96.7% and a negative predictive value of 99.6% in a population with HSV shedding prevalence of 10.8%, based on the prevalence of genital HSV previously found among HSV-2 seropositive women in labour.


Evidence Level: II

Last amended July 2015
Last reviewed September 2015

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HFNC is superior to nasal CPAP as a means of respiratory support in preterm infants?

A Cochrane Review of 4 studies (Wilkinson, 2011) concluded that “There is insufficient evidence to establish the safety or effectiveness of HFNC as a form of respiratory support in preterm infants. When used following extubation, HFNC may be associated with a higher rate of reintubation than nasal CPAP. Further adequately powered randomised controlled trials should be undertaken in preterm infants comparing HFNC with nasal CPAP and with other means of respiratory support; or of support following extubation. These trials should measure clinically important outcomes.”

In a recent trial, (Collins 2013) 132 ventilated infants < 32 weeks’ gestation were randomized to receive either heated humidified high-flow nasal cannulae (HHHFNC) or nasal continuous positive airway pressure (NCPAP) (n = 67) or NCPAP (n = 65). Extubation failure occurred in 15 (22%) of the HHHFNC group compared with 22 (34%) of the NCPAP group. There was no difference in the number of infants reintubated in the first week and the two treatments produced similar rates of extubation failure.


Evidence Level: I

Last amended July 2013
Last reviewed September 2015
What are the indications for the use of HFOV in term and in preterm infants?
Infants with respiratory distress syndrome, whether term or preterm, need mechanical ventilation (Greenough, 1999). Conventional ventilation may cause lung injury, and this has been demonstrably reduced, in animal experiments, by the use of HFOV (Delemos, 1987). These results have not, however, been replicated in human studies (Soll, 2006), or confirmed by a Cochrane review and meta-analysis of two RCTs in a total of 199 infants (Henderson-Smart 2009).

A randomised trial in 585 infants treated with either HFOV or conventional ventilation (Marlow, 2006) found that the mode of ventilation had no effect on respiratory or neurological outcomes at 2-year follow-up. A systematic review and meta-analysis (Cools, 2010) found that HFOV was equally effective to conventional ventilation in preterm infants.

A small case series of 18 neonates of from 26-41 weeks gestation (Vierzig, 1994) identified those with a gestational age of at least 35 weeks and persistent pulmonary hypertension complicating pulmonary disease as being most likely to respond to HFOV (n=4 [22%]).

A prospective clinical study in 20 patients (Ben Jaballah, 2006) found that HFOV improved gas exchange in a rapid and sustained fashion: after 1 hour, PaCO2 had significantly decreased (p = .002) and remained in the target range thereafter. Target ventilation was achieved in all patients.

HFOV has also been used in rescue strategies following the failure of conventional ventilation (Clark, 1994; Kohelet, 1988) and in air leak syndromes such as pneumothorax and pulmonary interstitial emphysema (Clark, 1986).


Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. J Pediatr 1994;124:447-54


Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. Arch Dis Child Fetal Neonatal Ed 2006;91:F320-6 http://fn.bmj.com/content/91/5/F320.long


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Evidence Level: IV

Should HFOV be used as a first line treatment or as rescue treatment?

A Cochrane Review (De Paoli, 2009) found no randomised controlled trial data to support the routine use of rescue HFOV in term or near term infants with severe pulmonary disease. Only 2 trials (involving 199 infants) were identified in the review (Clark, 1994 and Rojas, 2005). Neither trial showed evidence of a reduction in mortality at 28 days or in failed therapy on the assigned mode of ventilation requiring cross-over to the other mode. Neither study reported significant differences in the risk of pulmonary air leak, chronic lung disease (28 days or more in oxygen) or intracranial injury. In the study of elective HFOV, there was no difference noted in days on a ventilator or days in hospital. In the one rescue study (Clark, 1994), there was no difference in the risk of needing extracorporeal membrane oxygenation.

Another Cochrane Review by the same team (Bhuta, 1998) found a similar lack of evidence in preterm infants and recommended that “any future use of HFOV as rescue therapy for preterm infants with severe RDS should be within randomized controlled trials and address important outcomes such as longer term pulmonary and neurological function”.

A “BestBETS” report (Shah, 2003) concluded that “HFOV is probably not superior to conventional ventilation as primary mode of ventilation in preterm infants with respiratory distress syndrome for prevention of chronic lung disease or mortality at 36 weeks. However, use of HFOV is safe and not associated with increased risk of intraventricular haemorrhage or airleaks”.

This report included data from two multicentre, randomised trials in 500 infants (Courtney, 2002) and 400 infants (Johnson, 2002) respectively that appeared after the most recent Cochrane update.

A prospective study in 77 infants (Ben Jaballah, 2006) found that HFOV as an early rescue intervention resulted in rapid and sustained decreases in mean airway pressure, FIO(2), OI, and PAO(2) – PaO(2) (P < 0.01). The authors also identified a need for RCTs to confirm the perceived benefits of HFOV vs conventional ventilation.


Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. J Pediatr 1994;124:447-54


Shah S. Is elective high-frequency oscillatory ventilation better than conventional mechanical ventilation in very low-birth-weight-infants? http://www.bestbets.org/cgi-bin/bets.pl?record=00586

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Evidence Level: I

What should the starting settings be when commencing HFOV?
Although frequencies between 3-50 Hz may be used during HFOV, 7-15 Hz “is most commonly employed” (Greenough, 1999). 10-20 Hz is also mentioned frequently as producing the best results (Chan, 1993; Hoskyns, 1991; Froese, 1987). New Zealand guidelines (Battin, 2001) recommend 10 Hz as an appropriate starting frequency.


Evidence Level: V

Should a high volume strategy be used?
A Cochrane Review (Cools, 2014) concluded: “There is evidence that the use of elective high frequency oscillatory ventilation compared with conventional ventilation results in a small reduction in the risk of chronic lung disease, but the evidence is weakened by the inconsistency of this effect across trials. Probably many factors, both related to the intervention itself as well as to the individual patient, interact in complex ways. In addition, the benefit could be counteracted by an increased risk of acute air leak. Adverse effects on short-term neurological outcomes have been observed in some studies but these effects are not significant overall. Most trials reporting long-term outcome have not identified any difference.” In certain situations (gas trapping, severe lobar emphysema), a low-volume strategy appears to be more appropriate (Greenough, 1999).


Evidence Level: I

What are the indications for endotracheal suction during HFOV?
No information with which to answer this question has been identified.

How should an infant be weaned from HFOV?
New Zealand guidelines (Battin, 2001) recommend the following:
- Reduce FiO2 to < 40% before weaning MAP (except when over-inflation is evident)
- Reduce MAP when chest x-ray shows evidence of over-inflation (> 9 ribs)
- Reduce MAP in 1 -2 cm increments to 8-9
- In air leak syndromes (low volume strategy), reducing MAP takes priority over weaning the FiO2
- Wean the amplitude in 4 cm H2O increments
- Do not wean the frequency
- Consider switching to conventional ventilation when MAP < 10 cm H2O, Amplitude 20 - 25 and blood gases satisfactory

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• Suction is indicated for diminished chest wall movement indicating airway or ET tube obstruction or if there are visible/audible secretions in the airway
• Avoid in the first 24 hours of HFV, unless clinically indicated
• Avoid hand-bagging during the suctioning procedure: use PEEP protector and continue with patient on the ventilator
• Increase FiO2 following the suctioning procedure
• MAP may be temporarily increased 2-3 cm H2O until oxygenation improves

A review (Mehta, 2004) states that “Routine scheduled assessments of readiness for weaning and extubation may be more important than specific weaning modes and weaning criteria.”

Battin M. Newborn services clinical guidelines: High frequency ventilation (HFV). 2001


Evidence Level: V

Should an infant be extubated directly from HFOV or weaned to conventional ventilation first?
Weaning to conventional ventilation is common clinical practice (Courtney, 2002), although a technique known as “sprinting” (Seller, 2001) has been used in some difficult cases to achieve extubation directly from HFOV.

http://www.nejm.org/doi/full/10.1056/NEJMoa012750#t=articleTop


Evidence Level: V

Last amended September 2015
Last reviewed September 2015
HIV

Supporting Information

This guideline and has been prepared with reference to the following:


When viral loads in the mother are undetectable (i.e. < 200-500 copies/ml): should anti-retroviral therapy be given to the infant?

A nested case-control study in 105 women (Thea, 1997) found that those with an undetectable viral load were 6 times less likely to transmit the infection than were those with a measurable load (AOR 5.8; 95% CI 2.2-15.5).

In a nonrandomised prospective cohort study of 92 HIV-1-seropositive mothers (Dickover, 1996), none of the 63 women with viral loads of <20,000 copies/ml transmitted the infection to their infants.

A larger study in 480 zidovudine-treated women (Mofenson, 1999) found that "there was no perinatal transmission of HIV-1 among the 84 women who had HIV-1 levels below the limit of detection (500 copies per milliliter) at base line or the 107 women who had undetectable levels at delivery."

In another, similar study of 42 women (Aleixo, 1997), perinatal transmission occurred in 2 ZDV-treated and 3 untreated women with viral loads < 100 copies/ml, raising the possibility that there is no absolute threshold below which transmission will not occur. Equally, there appears to be no upper threshold above which transmission will always occur (Cao, 1997). Anti-retroviral therapy (for both mothers and infants) was shown by the Aleixo study to reduce transmission by 78%, and this was similar to the reduction of 67% noted by the ACTG 076 study (Connor, 1994).

Treating the infants of mothers with a viral load of < 1000 copies may confer some benefit, but it is "not possible to discern from the available data" according to the combined results of 7 European and US prospective studies in a total of 1,202 women (Ioannidis, 2001).

A Cochrane Review of 25 trials with a total of 18,901 participants (Siegfried, 2011) concluded that: "A regimen combining triple antiretrovirals is most effective for preventing transmission of HIV from mothers to babies. The risk of adverse events to both mother and baby appears low in the short-term but the optimal antiretroviral combination and the optimal time to initiate this to maximise prevention efficacy without compromising the health of either mother or baby remains unclear. Short courses of antiretroviral drugs are also effective for reducing mother-to-child transmission of HIV and are not associated with any safety concerns in the short-term. ZDV given to mothers during the antenatal period, followed by ZDV+3TC intrapartum and postpartum for one week, and sd-NVP given to infants within 72 hours of delivery and ZDV for one week, may be most effective when considering short antiretroviral courses. Where HIV-infected women present late for delivery, post-exposure prophylaxis with a single dose of NVP immediately after birth plus ZDV for the first 6 weeks after birth is beneficial. The long term implications of the emergence of resistant mutations following the use of these regimens, especially those containing Nevirapine, require further study."

Aleixo LF, Goodenow MM, Sleasman JW. Zidovudine administered to women infected with human immunodeficiency virus type 1 and to their neonates reduces pediatric infection independent of an effect on levels of maternal virus. J Pediatr 1997;130:906-14


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**Evidence Level: I**

**Should delivery be by elective caesarean section?**

A recent review (Mitchla, 2000) states that “There is still no information as to whether (caesarean section) provides any added benefit for women on highly active antiviral therapy with an undetectable HIV viral load”.

The American College of Obstetricians and Gynecologists originally recommended, in 1999, that caesarean section should be offered to all HIV-seropositive pregnant women. A survey of 2,000 randomly-selected obstetricians and gynaecologists in the U.S. (Rowland, 2001) found, however, that 47% of respondents disagreed with this recommendation, and 72% did not advise caesarean delivery in women with undetectable viral loads.

Current recommendations (Anon, 2001) are that there is no evidence of benefit in women with viral loads < 1000 copies/ml, but that the individual’s wishes regarding mode of delivery should be respected.

The European Collaborative Study (Boer, 2010), a cohort study on 5238 mother-child pairs (MCPs), found that, amongst MCPs with maternal HIV RNA<400 HIV-1 RNA copies/mL (n=960), elective caesarean section (CS) was associated with 80% decreased transfer risk (AOR 0.20; 95% CI 0.05-0.65). Two infants born to 559 women with viral loads <50 copies/mL were infected, one of whom was delivered by elective CS (transmission rate 0.4%; 95% CI 0.04-1.29).


**Evidence Level: V**

**Should breast-feeding be avoided?**

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In a small study involving 17 samples of breast milk from 4 HIV-positive mothers (Chantry, 2000) 15 (88%) showed measurable HIV-1 proviral DNA, despite all mothers having had low or undetectable viral loads. Advice from BHIVA (2012) and the U.S. Public Health Service Task Force (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2015) is that all HIV-seropositive mothers should avoid breast-feeding.

“To prevent the transmission of HIV infection during the postpartum period, the British HIV Association and Children's HIV Association (BHIVA/CHIVA) continue to recommend the complete avoidance of breast feeding for infants born to HIV-infected mothers, regardless of maternal disease status, viral load or treatment.” (see top of page)

https://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf

British HIV Association (BHIVA). Guidelines for the management of HIV infection in pregnant women 2012


Evidence Level: IV

Should the infant be tested with pro-viral DNA/RNA PCR?
A prospective study compared DNA-PCR and viral RNA amplification and detection in 44 HIV-infected infants and 9 uninfected infants (Brown, 1996). Specimens were tested at 3 stages between birth and around 35 days of age, and in each case, viral RNA was found to be more sensitive than DNA-PCR. After the first month of life, the sensitivity of the DNA-PCR increases from 50% to 98% (Cervia, 2003).

As viral RNA levels increase rapidly from birth and reach a peak at 1-2 months of age (Shearer, 1997), testing during this period should be conclusive on the question of whether or not transmission has occurred. The available evidence, however, is at present inconclusive as to the value of testing or treating infants of mothers with undetectable viral load (see 1st question).


Shearer WT, Quinn TC, LaRussa P. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. N Engl J Med 1997;336:1337-42

Evidence Level: V

Last amended September 2015
Last reviewed September 2015
HYDROPS FETALIS
Supporting information

This guideline has been prepared with reference to the following:


Last amended March 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Hyperglycaemia increases mortality risk in premature infants?
A prospective chart study of 93 extremely low birth-weight infants (Hays, 2006) found that more than 50% of the infants had persistent blood glucose concentrations of >150 mg/dL during the first week of life. Twenty-two of these infants (44%) had an early adverse outcome, defined as death or intraventricular haemorrhage of grade 3 or 4 before the 10th day of life.
Another prospective study in 252 premature infants weighing \( \leq 1500 \) g (Heimann, 2007) found a significant increase in mortality (\( p<0.0001 \)) with increasing median blood glucose level and repeated (\( \geq 4 \)) incidents of blood glucose levels \( >150 \) mg/dL associated with low gestational age (\(<27\) weeks). Retrospective analysis of a prospective cohort study of 201 ELBW infants (Kao, 2006) found the odds ratio for either dying or developing a late infection was 5.07 (95% CI 1.06 – 24.3) in those babies with persistent severe hyperglycaemia (\( \geq 180 \) mg/dL).
A review of the literature (Ogilvy-Stuart, 2010) concluded that hyperglycaemia “is associated with increased morbidity and mortality in preterm infants, but what should be considered optimal glucose control, and how best to achieve it, has yet to be defined in these infants”.

Hays SP, O’Brian Smith E, Sunehag AL. Hyperglycaemia is a risk factor for early death and morbidity in extremely low birth-weight infants. Pediatrics 2006;118:1811-18
Heimann K, Peschgens T, Kwicien R, et al. Are recurrent hyperglycemic episodes and median blood glucose level a prognostic factor for increased morbidity and mortality in premature infants \( \leq 1500 \) g? J Perinat Med 2007;35:245-8
http://www.nature.com/jp/journal/v26/n12/full/7211593a.html
Ogilvy-Stuart AL, Beardsall K. Management of hyperglycaemia in the preterm infant. Arch Dis Child Fetal Neonat Ed 2010;95:F126-31
http://fn.bmj.com/content/95/2/F126.long

Evidence Level: IV

Treating hyperglycaemia has a beneficial effect on mortality and morbidity?
A Cochrane Systematic Review of 2 trials in 47 infants (Bottino, 2011) found the evidence was insufficient to answer this question and called for more and larger trials to be conducted.


Evidence Level: I

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
What is the evidence for the use of salbutamol, and is it superior to insulin as a treatment for hyperkalaemia? Has nebulised salbutamol been evaluated?

Intravenous administration of insulin (together with glucose) effectively manages hyperkalaemia in neonates (Ditzenberger, 1999), but the response is unpredictable, and carries the risk of hypoglycaemia, hyperosmolarity, and volume overload (Helfrich, 2001). No good, randomised trials for its use in neonates have been identified.

Intravenous salbutamol is rapidly effective and side effects, including elevated heart rate, mild vasomotor flushing and mild tremor are all short-lasting (Helfrich, 2001; Kemper, 1996; Murdoch, 1991). One prospective, randomised, placebo-controlled double-blind trial of nebulised salbutamol, in 19 neonates <2000g, has been identified (Singh, 2002). Serum potassium levels fell rapidly (from 7.06 +/- 0.23 mmol/L to 6.34 +/- 0.24 mmol/L, P=.003) in the first 4 hours in the treatment group (n=8) in response to 400 mcg given by nebuliser. No significant change was seen in the placebo group (n=11) (6.88 +/- 0.18 mmol/L to 6.85 +/- 0.24 mmol/L).


Evidence Level: II (for inhaled salbutamol)

Is rectal calcium resonium a safe treatment in neonates?

Intestinal perforation has been reported in infants treated with exchange resin enemas (Grammatikopoulos, 2003; Bennett, 1996), although these may have been spontaneous rather than as a result of the treatment.

Nausea and vomiting are common side effects of oral administration, but changing to the rectal route is “less effective” (Helfrich, 2001).

A recent Cochrane review (Vemgal 2012) identified only two randomised trials of resins in the treatment of hyperkalaemia in neonates (Malone 1991 cited Vemgal 2012; Hu, 1999). In the larger, Hu (1999) study, 40 VLBW infants were randomised to receive either glucose/insulin infusion (n=20) or kayexalate resin enema (n=20). Duration of hyperkalaemia was significantly shorter (26.4 +/- 14.9 vs 38.6 +/-13.3 hours) in the insulin group.

An appropriately-sized randomised trial is necessary to evaluate the risks and benefits of this treatment in premature infants (Grammatikopoulos, 2003). Vemgal (2012) continued to call for larger, high quality studies of interventions for patients with hyperkalaemia, but from the three trials it reviewed (which included the Hu study), noted that “it appears that the combination of insulin and glucose is preferred over treatment with rectal cation-resin”


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Do some VLBW infants without renal failure suffer from hyperkalaemia?

Both renal and non-renal causes of neonatal hyperkalaemia have been suggested (Singh, 2002), and the cause of the condition is generally held to be multi-factorial (Ditzenberger, 1999). One study of 48 infants (Fukuda, 1989) implicated metabolic acidosis and catabolic state, but another, in 33 infants (Stefano, 1993), found no difference in muscle protein catabolism between 12 infants with hyperkalaemia and 21 without. In a study of 18 VLBW infants (Gruskay, 1988) no differences in renal glomerular function were noted in 8 who developed hyperkalaemia and 10 who did not. Inability to regulate potassium balance, as a result of immature distal tubule function, may result in hyperkalaemia in the absence of renal failure (Mildenberger, 2002; Lorenz, 1997; Matsuo, 1995; Sato, 1995).


Evidence Level: IV

What level of hyperkalaemia should prompt treatment?
The criteria on which to treat hyperkalaemia have ranged from 6.8 to 7.5 mmol/L, but 6.5 mmol/L may be a better level at which to begin treatment, as rhythm disturbances are to be expected above 7.0 mmol/L (Grammatikopoulos, 2003). If treatment is not initiated until symptoms appear...
(or the serum level exceeds 7.0 mmol/L), the potential for success is reduced (Ditzenberger, 1999). Mortality rates may be as high as 80% once arrhythmias have appeared (Singh, 2002).


Evidence Level: V
Infants losing more than 10% of birth weight should be referred?
A prospective cohort study in 2,788 term newborns (Konetzny, 2009) found that weight loss of $\geq 10\%$ of birth weight was an early indicator for hypernatraemic dehydration of sufficient severity to cause possible convulsions, permanent brain damage, or death. Sixty-seven (2.4%) newborns had a weight loss $\geq 10\%$ of birth weight; 24 (36%) of these had moderate and 18 (27%) severe hypernatraemia. Infants born by caesarean section had a 3.4 times higher risk for hypernatraemia than those born vaginally. All newborns regained weight 24 h after additional fluids.


Evidence Level: III

Weighing babies early (72-96 hrs after birth) helps to prevent hypernatraemic dehydration?
A study of outcomes pre- and post- the introduction of a policy of weighing newborns at 72-96 hrs after birth (Iyer, 2008) found 60 cases of hypernatraemic dehydration: 23 before and 37 after introduction of the policy. After the policy, there was earlier recognition (median 3 vs 6 days), lower percentage weight loss (11% vs 15%), smaller increase in sodium (147 vs 150 mmol/l), and higher breastfeeding rate at discharge (73% vs 22%) and 8 weeks (57% vs 22%). All the differences were significant (p<0.01). There was one death in the pre-policy group, and none in the post-policy group.

http://adc.bmj.com/content/93/4/297.long

Evidence Level: IV

Last amended January 2011
Last reviewed September 2015
Are Hypostop and maxijoule of use in the treatment of neonatal hypoglycaemia?
Evidence for the use of Hypostop in neonatal hypoglycaemia is limited to a single uncontrolled study (Bourchier, 1992). In view of this, current WHO guidance (WHO, 1997) is that Hypostop is not recommended in this situation.
There is a similar lack of evidence for carbohydrate feed additives such as maxijoule, with the only controlled study (Singhal, 1991) failing to address whether increased blood glucose in the supplement group had any beneficial effect on clinical outcome.


Evidence Level: V

At what level can we define glucose levels as “profundely low”?
Comblath et al (2000) state that: “At very low glucose concentrations (<20–25 mg/dL, 1.1–1.4 mmol/L), intravenous glucose infusion aimed at raising the plasma glucose levels above 45 mg/dL (2.5 mmol/L) is indicated.”


Evidence Level: V

At what level should we aim to maintain blood glucose?
Comblath et al (2000) state that: “Although the recommendation for maintaining therapeutic levels in excess of 60 mg/dL (3.3 mmol/L) may be indicated in the symptomatic infant with documented profound, recurrent or persistent hyperinsulinemic hypoglycemia, it should not be the therapeutic goal for the vast majority of newborns with transient or brief episodes of low plasma glucose concentrations”.


Last amended October 2015
Last reviewed September 2015
HYPOKALAEMIA
Supporting information

This guideline has been prepared with reference to the following:


http://www.evidence.nhs.uk/formulary/bnfc/current

Worcester Acute Hospitals NHS trust. Neonatal Formulary


http://ajcn.nutrition.org/content/68/2/345.long

Last amended June 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
This guideline has been prepared with reference to the following:


What is the best method of measuring blood pressure in a neonate?

There is currently no consensus on the best method in all cases (Goonasekera, 2000). Direct transducer readings through an umbilical line are commonly used in sick or very low birth weight neonates (Cordero, 2002), and are “widely accepted as the optimum method” (Dasgupta, 2003).

A combination of oscillometric and Doppler methods has been reported as providing better accuracy than each method on its own in a study in 174 term neonates (Nascimento, 2002). The use of a recently developed algorithm (SuperSTAT(R)) enabled non-invasive blood pressure measurement to comply with ANSI/AAMI accuracy standards (+/- 5 mm Hg, SD <= 8 mm Hg) and to be comparable to invasive methods (Nelson, 2002). It is important that measurements are taken when the infant is in “a restful state” (not necessarily asleep) (Nwankwo, 1997). It is unclear whether indirect measurements taken from the calf are directly equivalent to those taken from the arm (Crupanzano, 1996; Kunk, 1996).

http://www.nature.com/jp/journal/v22/n5/full/7210736a.html


Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. Arch Dis Child Fetal Neonatal Ed 2003;88:F450-F454
http://fn.bmj.com/content/88/6/F450.long

http://adc.bmj.com/content/82/3/261.full


Nwankwo MU, Lorenz JM, Gardiner JC. A standard protocol for blood pressure measurement in the newborn. Pediatrics 1997;99:E10
http://pediatrics.aappublications.org/content/99/6/e10.long

Evidence Level: V

What is a normal blood pressure for a neonate, at term and preterm?

“The normal physiologic blood pressure range ensuring appropriate organ perfusion in the neonate is unknown” (Seri, 2001). “Hypotension affects close to half of all ELBW infants, yet an agreement on its definition is still lacking” (Fanaroff, 2006). A systematic review (Dempsey, 2007) failed to find evidence for a definitive threshold BP that was predictive of poor outcome. In low birthweight or preterm infants, the range of “normal” values is dependent on age in terms of weeks’ gestation and birthweight (Hegyi 1996; Hegyi 1994). New Zealand guidelines
(Knight, 2000) suggest that, for VLBW infants, “a good rule of thumb is to aim for the baby’s gestational age as the desired minimum mean blood pressure”. A postal questionnaire sent to all 120 neonatal ICUs in Canada (Dempsey, 2006), which had a 79% return rate (95 replies), found that 25.8% relied on blood pressure values as the sole criteria for intervention. A blood pressure less than gestational age in weeks was the most common trigger for treatment. “Premature neonates stabilize their BP after 14 days of life, and at this time they have a BP similar to that of term infants” (Kent, 2009).


Dempsey EM, Barrington KJ. Diagnostic criteria and therapeutic interventions for the hypotensive very low birth weight infant. J Perinatol 2006;26:677-81


**Evidence Level: V**

What is the role of clinical assessment (e.g. skin turgor, urine output) in deciding whether or not to treat at a specific blood pressure reading? No evidence can be identified with which to answer this question. There is general agreement that “decisions to treat hypotension should be based on the general condition of the infant, not on the mean arterial blood pressure alone” (Dasgupta, 2003), but no detail is given. Urine output is considered to be an unreliable indicator of hypotension (Dasgupta, 2003).


**Evidence Level: V**

Should IV fluid be used as a first line for the treatment of hypotension? If so, what type and how much? Although hypovolaemia is a relatively uncommon cause of hypotension in the sick preterm infant, moderate fluid replacement is a reasonable precaution and so usually the first line treatment (Dasgupta, 2002). Two RCTs, in 63 (So, 1997) and 41 infants (Oca, 2003) respectively, have demonstrated that saline 0.9% is as effective as 5% albumin for treating neonatal hypotension. Isotonic saline has the further advantages of being cheap, of carrying no infection risk, and of causing less fluid retention in the first 48 hours (So, 1997). A recommended amount to use is 10-20 ml/kg over 30 minutes (Dasgupta, 2002).


So KW, Fok TF, Ng PC, et al. Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. Arch Dis Child Fetal Neonatal Ed 1997;76:F43-F46

Evidence Level: II

**Should dopamine remain the first line drug treatment?**

A Cochrane review of 5 RCTs (Subhedar, 2003) concluded that dopamine was more successful than dobutamine for short-term treatment of hypotension, with fewer infants having treatment failure (RD –0.23; 95% CI –0.34 to –0.13). There was, however, no difference in mortality and no data on long term benefit or safety.

A meta-analysis (Sassano-Higgins, 2011) found that dopamine increases mean arterial blood pressure (12 studies; N=163; r=0.88, 95% CI=0.76 to 0.94) and systolic blood pressure (8 studies; N=142; r=0.81, 95% CI=0.42 to 0.94). For the increase in blood pressure, dopamine administration was associated with a significantly greater overall efficacy than dobutamine (seven studies; N=251; r=0.26; 95% CI=0.20 to 0.32), colloid (two studies; N=67; r=0.60; 95% CI=0.41 to 0.74) and hydrocortisone (one study; N=28; r=0.40; 95% CI=0.034 to 0.67). CBF increased following dopamine administration (five studies; N=75; r=0.36; 95% CI=–0.059 to 0.67) and the increase in CBF was greater in hypotensive than normotensive preterm infants (eight studies; N=153; r=0.16; 95% CI=–0.0080 to 0.32). There were no statistically significant differences in adverse neurological outcome between dopamine and dobutamine (three studies; N=118; r=–0.13; 95% CI=–0.31 to 0.059), epinephrine (two studies; N=46; r=0.06; 95% CI=–0.23 to 0.34), colloid (two studies; N=80; r=0.0070; 95% CI=–0.218 to 0.23) or hydrocortisone administration (one study; N=40; r=–0.10; 95% CI=–0.40 to 0.22).


Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD001242

Evidence Level: I

**What is the role of dobutamine?**

Dobutamine is generally used as a second line drug, in patients unresponsive to dopamine (Dasgupta, 2003). A range of doses from 5-20 mcg/kg/min has been used, and there is no clear evidence as to which of these is “correct” (Subhedar, 2003). New Zealand guidelines (Knight, 2000) suggest starting at the lower dose and increasing incrementally to the higher, after the dopamine dose has been increased to 10-20 mcg/kg/min without response.

Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. Arch Dis Child Fetal Neonatal Ed 2003;88:F450-F454


Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD001242

Evidence Level: II

**What is the role of adrenaline (epinephrine)?**

A Cochrane review (Paradisis, 2004) identified only one on-going randomised study comparing adrenaline (epinephrine) with dopamine and this indicated that both agents significantly increased heart rate and mean BP, with no statistically significant effect on left or right ventricular outputs. No other outcomes were reported. The review concluded that there

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was insufficient data to make any recommendations, and called for larger trials to be carried out.

A retrospective “chart review” in 31 very low birthweight infants not responding to dopamine (Heckmann, 2002) found that the mean arterial blood pressure (=7 (-1 to 13) mmHg, p=0.000001) and the heart rate (+10 (-10 to 42) bpm, p=0.000036) increased significantly in all cases in response to a continuous infusion of adrenaline (epinephrine) in doses of 0.05-2.6 mcg/kg(-1)/min within the first 24 hours. No decrease in urine output was recorded. An increase in metabolic acidosis was noted as a potential adverse effect.


Evidence Level: I

What is the role of steroids?

A single dose of steroids as rescue therapy is successful in “most babies” (Dasgupta, 2003). A randomised, double-blind, controlled trial in 20 premature infants not responding to dopamine and receiving adrenaline (epinephrine) infusion (Gaissmaier, 1999) found that 5/8 given dexamethasone (0.25 mg/kg) vs 1/9 given placebo (3 were excluded) were able to discontinue adrenaline (epinephrine).

A randomised comparison between dopamine and hydrocortisone in 40 very low birthweight infants (Bourchier, 1997) found the two treatments broadly equivalent in efficacy.

A retrospective review of 21 preterm infants given hydrocortisone as rescue therapy (Seri, 2001) noted a rapid increase in blood pressure (from 29.3 +/- 4.1 to 34.1 +/- 5.2 after 2 hours, rising to 41.8 +/- 6.6 mmHg after 6 hours). Steroids may also have a role in the prevention of hypotension in preterm infants with low cortisol levels (Subhedar, 2003).

A Cochrane systematic review (Subhedar, 2007) concluded that in view of the scanty evidence for benefit and lack of long-term safety data, dexamethasone could not be recommended for routine use in preterm hypotension.

A retrospective observational study in 117 infants (Baker, 2008) found that treatment with hydrocortisone increased the mean arterial pressure at 2, 6, 12 and 24 h after initiation, decreased the total inotrope dose at 6, 12 and 24 h and was associated with resolution of oliguria.

A meta-analysis of 12 studies (Higgins, 2010) confirmed that hydrocortisone increases blood pressure (seven studies; N=144; r=0.71, 95%CI=0.18 to 0.92) and decreases the requirement for vasopressors (five studies; N=93; r=0.74, 95%CI=0.0084 to 0.96), but without demonstrating clear clinical benefit.

A Cochrane systematic review of 4 studies in a total of 123 babies (Ibrahim, 2011) found that, in one study, persistent hypotension was more common in hydrocortisone treated infants compared to those who received dopamine as primary treatment for hypotension (RR 8.2, 95% CI 0.47 to 142.6; RD 0.19, 95% CI 0.01 to 0.37). In two studies comparing steroid versus placebo, persistent hypotension (defined as a continuing need for inotrope infusion) was less common in steroid treated infants as compared to controls who received placebo for refractory hypotension (RR 0.35, 95% CI 0.19 to 0.65; RD -0.47, 95% CI -0.68 to -0.26; NNT = 2.1, 95% CI 1.47, 3.8). There were no statistically significant effects on any other short or long-term outcome. The authors concluded that: “With long term benefit or safety data lacking, steroids cannot be recommended routinely for the treatment of hypotension in preterm infants.”


http://fn.bmj.com/content/76/3/F174.long

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. Arch Dis Child Fetal Neonatal Ed 2003;88:F450-F454
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1763241/pdf/v088p0F450.pdf


Subhedar NV. Treatment of hypotension in newborns. Semin Neonatol 2003;8:413-23


Evidence Level: I

What are the best parameters for assessing hypovolaemia in the neonate?
Hypovolaemia is uncommon and also difficult to diagnose in the sick preterm infant, due to the unreliability of indicators such as urine output and capillary refill time (Dasgupta, 2003). In view of the danger of excessive volume expansion (Ewer, 2003), it has been suggested (Evans, 2003) that echocardiography should be used to define systemic blood flow.

Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. Arch Dis Child Fetal Neonatal Ed 2003;88:F450-F454

Evans N. Volume expansion during neonatal intensive care: do we know what we are doing? Semin Neonatol 2003;8:315-23


Evidence Level: V

What is the maximum dose of dopamine, dobutamine and adrenaline (epinephrine) in neonatal hypotension?
The maximum dose of both dopamine and dobutamine is 20 mcg/kg/min (Subhedar, 2004; Osborn, 2002; Knight, 2000). The maximum dose of adrenaline (epinephrine) is 0.5 mcg/kg/min (Paradisis, 2004; Knight, 2000).


Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. The Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD001242

Evidence Level: I

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Does neonatal hypotension increase the risk of developmental delay?
A prospective cohort study in 945 infants (Logan, 2011) found that, after adjustment for potential confounders, no indicators of hypotension were associated with either a Bayley Mental Development Index (MDI) score or a Psychomotor Development Index (PDI) score of <70 at 24 months of age.


Evidence Level: III

Last amended September 2012
Last reviewed September 2015
Placing the baby in a polythene bag prevents heat loss pending transfer to an incubator?
A Cochrane systematic review (McCall, 2010) found that “Plastic wraps or bags were effective in reducing heat losses in infants < 28 weeks’ gestation (4 studies, n = 223; WMD 0.68 °C; 95% CI 0.45, 0.91), but not in infants between 28 to 31 week's gestation.”
Doglioni et al. (2014) conducted an RCT to compare total body wrapping (covering both the body and head) and conventional treatment (covering up to the shoulders) for protection against moderate hypothermia, finding no statistical difference (12% vs. 20% p=0.41).


Evidence Level: I

Heated mattresses are useful in the treatment of mild hypothermia?
A retrospective review (Ibrahim, 2010) studied the occurrence of hypothermia in 105 babies born before, and 124 born after the introduction of heated gel mattresses. Four (3.3%) babies were hypothermic (temperature <36 degrees C) at admission when the mattresses were used, compared to 21 (22.6%) babies during the period it was not (p < 0.001). Hyperthermia (temperature >37 degrees C) rose from 30.1% prior to use of gel mattresses to 49.6% when they were used (p = 0.004).


Evidence Level: IV

Last amended September 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
HYPOTHYROIDISM, CONGENITAL

Supporting information

This guideline has been prepared with reference to the following:

Association for Clinical Biochemistry. UK guidelines for the use of thyroid function tests. London. ACB, 2006


http://pediatrics.aappublications.org/content/117/6/2290.full

Screening

In preterm infants, blood testing should be performed on day 6 and repeated at 36-40 weeks gestational age?

Revised UK guidelines published in April 2005 (see above) made this recommendation, but with the proviso that it should be kept under review. A study (Korada, 2008) compared baseline readings of thyroid stimulating hormone (TSH) in 2238 preterm infants with second samples taken from 2039 infants. No infant with a normal TSH concentration on first sampling was found to have a reading of > 10mU/l on second sampling. The authors concluded that repeat sampling may not be required with a lower screening threshold of 6 mU/l.


http://fn.bmj.com/content/93/4/F286.long

Evidence Level: IV

Immediate management

Infants with congenital hypothyroidism have an increased incidence of other abnormalities?

A study of registry data in the US (Kumar, 2009) showed that children with congenital hypothyroidism had a significantly increased risk of congenital renal and urological anomalies (OR 13.2; 95% CI 10.6-16.5). The other significantly increased defects in congenital hypothyroidism were cardiac, gastrointestinal, and skeletal. Analysis of matched data confirmed an increase of congenital renal and urologic anomalies (OR 4.8; 95% CI 3.7-6.3).


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749842/

Evidence Level: IV

Treatment

A starting dose of 10 mcg/kg/d of thyroxine is appropriate? Do higher dose regimens result in adverse effects on memory, attention or behaviour?

“What constitutes optimal TH therapy is not yet certain” (Rose, 2006). This dose is at the lower end of the range recommended by current American Academy of Pediatrics guidelines (Rose,

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These advise a starting dose of 10-15 mcg/kg/d, depending on the severity of the initial hypothyroidism. When a higher starting dose (12-17 mcg/kg/d) is used, serum T4 normalises in 3 days and TSH returns to the target range within 2 weeks (Bakkar, 2002). However, “evaluation of cognitive outcome is important after use of this increased dose” (Rose, 2006).

A cohort based follow up study of 49 young adults with early treated congenital hypothyroidism compared these with 41 matched sibling controls (Oerbeck, 2005). At age 20, those subjects given high dose (>= 7.8 mcg/kg/d) therapy displayed no adverse effects on higher order cognitive skills, compared to those on low dose (<7.8 mcg/kg/d) treatment. The high dose group did, however, exhibit significant differences on some measures of memory, attention (distractibility) and behaviour. The authors concluded that their findings supported the use of higher dose treatment, but acknowledged that only 12 of their 49 subjects had been given doses of >10 mcg/kg/d, and that “definite answers to the outcome in high dose treatment groups await further studies”.

The largest study to date looking at these outcomes was a systematic review of 14 cohort studies in 1321 patients (Hrytsiuk, 2002). This concluded that “The evidence for an effect of starting dose…on cognitive development, growth, or behavior is too weak to justify recommendations in favor of high- or standard-dose regimens.”

The most severely hypothyroid infants are at risk for a 5-20 point decrease in IQ, and may benefit from a starting dose of 12-17 mcg/kg/d (LaFranchi, 2007).

A Cochrane Systematic Review of a single trial in 47 infants (Ng, 2009) concluded that there was insufficient evidence with which to answer this question.


LaFranchi SH, Austin J. How should we be treating children with congenital hypothyroidism? J Pediatr Endocrinol Metab 2007;20:559-78

Ng SM, Anand D, Weindling AM. High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD006972

http://adc.bmj.com/content/90/2/132.long

http://pediatrics.aappublications.org/content/117/6/2290.full

Evidence Level: III

Last amended April 2011
Last reviewed September 2015
In neonates with HIE, is MRI, EEG, or cranial ultrasonography the most useful technique in predicting outcome?

A study in 46 infants (Rutherford, 1994) found that, although ultrasonography adequately identified those with a poor prognosis, MRI was better at detecting the precise site and extent of the lesion. A resistive index \( \leq 0.55 \) had a PPV of 71% in predicting adverse outcome in a case-control study in 212 patients (Jongeling, 2002).

In a study comparing 47 neonates undergoing CT (n=26), MRI (n=24) or both (n=3) with ultrasonography (Blankenberg, 2000), CT and MRI revealed 25 instances of hypoxic-ischaemic injury compared to 13 identified by ultrasonography. Intraparenchymal haemorrhage was also identified twice as often (10 instances vs 5) by CT and MRI compared to ultrasonography.

A small study in 16 infants (Malik, 2002) found that MR spectroscopy was more sensitive than MRI in detecting the insult due to HIE.

A study of combined standard EEG with MRI in 25 infants (Biagioni, 2001) found that the presence of any EEG background abnormality early in the course of the illness predicted 94% of cases that resulted in an abnormal outcome (mild to severely abnormal). This compared with 85% for MRI. The authors advocate early EEG to distinguish those infants likely to have an abnormal outcome, followed by MRI to provide further information on the nature of the outcome. However, an accompanying editorial (Baumgart, 2001) suggests that focusing on the moderate-to-severely abnormal outcomes results in 100% accuracy for MRI, with little extra benefit from EEG.

Standard EEG may be difficult to obtain in the first hours following birth, but amplitude integrated EEG (aEEG) has been developed to monitor cerebral electrical background activity in the intensive care unit. A study of the technique in 47 infants (Hellstrom-Westas, 1995) found that it predicted outcome correctly in 43 (91.5%). Similar results were obtained from a study of 73 infants (Toet, 1999).

Baumgart S, Graziani LJ. Predicting the future for term infants experiencing an acute neonatal encephalopathy: electroencephalogram, magnetic resonance imaging, or crystal ball? Pediatrics 2001;107:588-90


Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Rutherford MA, Pennock JM, Dubowitz LM. Cranial ultrasound and magnetic resonance imaging in hypoxic-ischaemic encephalopathy: a comparison with outcome. Dev Med Child Neurol 1994;36:813-25

http://fn.bmj.com/content/81/1/F19.long

Evidence Level: IV

**Normal body temperature (36.5 – 37.2°) should be maintained?**

A Cochrane review (Jacobs 2013) found that hypothermia, resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (typical RR 0.75 95%; CI 0.68 to 0.83; typical RD -0.15, 95%; CI -0.20 to -0.10; number needed to treat for an additional beneficial outcome 7, 95% CI 5 to 10 (8 studies, 1344 infants).

An earlier systematic review (Shah, 2007) also found that hypothermia, in 4 studies including 497 infants, resulted in a reduced combined outcome of death or neurodevelopmental disability compared with normothermia (RR 0.76, 95% CI 0.65-0.88, NNT 6, 95% CI 4-14).

There have been conflicting opinions in the US in the past as to whether or not the strength of the existing evidence warrants a change in practice (Perlman, 2008; Kirpalani, 2007).


Evidence Level: I

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Last amended August 2013  
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
This guideline has been prepared with reference to the following:


NHS Choices. The NHS vaccination schedule. 2014.

http://www.nhs.uk/Conditions/vaccinations/Pages/vaccination-schedule-age-checklist.aspx


http://www.nhs.uk/Conditions/vaccinations/Pages/meningitis-B-vaccine.aspx

Immunisation of pre-term babies should not be delayed because of prematurity or low body weight?

There is at present no official guidance on immunisation schedules for pre-term infants (Bonhoeffer, 2006), but the authors of this review suggest that an accelerated 2-3-4 month schedule would achieve protective concentrations of antibodies earlier than a more extended schedule. “The available data support early immunisation without correction for gestational age” (Bonhoeffer, 2006).

A prospective observational study in 473 infants with a birth weight under 1500g (Furck, 2010) concluded that “Premature infants should be vaccinated at the appropriate vaccinating age, without correcting for their gestational week and regardless of their weight.” The frequency of adverse events for local reactions/fever was 2.8% and for apnea/bradycardia it was 10.8%.


Furck AK, Richter JW, Kattner E. Very low birth weight infants have only few adverse events after timely immunization. J Perinatol 2010;30:118-21

Evidence Level: III

What are the high-risk groups for rotavirus-associated morbidity/mortality?

A population-based, case-control study in 1606 infants hospitalised with viral gastroenteritis (Newman, 1999) found that very low birth weight infants (< 1500 g) were at the highest risk (OR 2.6; 95% CI 1.6-4.1), low birth weight infants (1500-2499 g) were at intermediate risk (OR 1.6; 95% CI 1.3-2.1) and large infants (> 4000 g) had a reduced risk (OR 0.8; 95% CI 0.6-0.9) of rotavirus infection.

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Other factors that were associated with increased risk of hospitalisation were male gender (OR 1.4; 95% CI 1.3-1.6), maternal smoking (OR 1.2; 95% CI 1.1-1.4), and maternal age <20 years (OR 1.2; 95% CI 1.0-1.5).


Evidence Level: III

Last amended August 2015
Last reviewed September 2015
INFECTION (EARLY ONSET)
Supporting information

This guideline has been prepared with reference to the following:


http://publications.nice.org.uk/antibiotics-for-early-onset-neonatal-infection-cg149

Last amended August 2013
Last reviewed September 2015
INFECTION – LATE ONSET
Supporting Information

This guideline has been prepared with reference to the following:


http://fn.bmj.com/content/96/1/F4.long


http://www.nice.org.uk/guidance/CG149

Neonatal infection can be predicted by:
- Surface swabs
- White cell count
- C-reactive protein
- Respiratory distress
- Prolonged rupture of membranes
- Discharging eyes
- Inflammation of umbilical cord

A study of 24,584 surface cultures obtained from 3,371 infants over a 3 year period (Evans, 1988) found the optimum sensitivity, specificity and positive predictive value in predicting sepsis was 56%, 82% and 7.5% respectively. The authors concluded that surface swabs were of limited value in this context.

A later, similar study in 35 premature infants (Puri, 1995) found results of 60%, 27% and 60%, respectively and came to a similar conclusion.

Another study (Jolley, 1993) commented that antimicrobial treatment was rarely altered as a result of pathogens isolated from surface swabs and as such the practice was inefficient and not cost-effective.

A study in 221 preterm infants (Berger, 2004) concluded that “Surface swabs add no additional information and hence should not be performed routinely.”

In a systematic review of 14 studies on the use of laboratory tests to identify serious infections in febrile children (Van den Bruel, 2011), the prevalence of serious infections ranged from 4.5% to 29.3%. Tests were carried out for C reactive protein (five studies), procalcitonin (three), erythrocyte sedimentation rate (one), interleukins (two), white blood cell count (seven), absolute neutrophil count (two), band count (three), and left shift (one). The tests providing most diagnostic value were C reactive protein and procalcitonin. Bivariate random effects meta-analysis (five studies, 1379 children) for C reactive protein yielded a pooled positive likelihood ratio of 3.15 (95% CI 2.67 to 3.71) and a pooled negative likelihood ratio of 0.33 (0.22 to 0.49). To rule in serious infection, cut-off levels of 2 ng/mL for procalcitonin (two studies, positive likelihood ratio 13.7, 7.4 to 25.3 and 3.6, 1.4 to 8.9) and 80 mg/L for C reactive protein (one study, positive likelihood ratio 8.4, 5.1 to 14.1) were recommended; lower cut-off values of 0.5 ng/mL for procalcitonin or 20 mg/L for C reactive protein were necessary to rule out serious infection. White blood cell indicators were less valuable than inflammatory markers for ruling in serious infection (positive likelihood ratio 0.87-2.43), and had no value for ruling out serious infection (negative likelihood ratio 0.61-1.14). The best performing clinical decision rule (recently validated in an independent dataset) combined testing for C reactive protein, procalcitonin, and urinalysis and had a positive likelihood ratio of 4.92 (3.26 to 7.43) and a negative likelihood ratio of 0.07 (0.02 to 0.27).


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Evidence Level: I

A study in 6,207 infants (Bonsu, 2003) found that no threshold of the total peripheral white blood cell (WBC) count had both good sensitivity and specificity. At a count cutoff of 5,000 cells/mm³, sensitivity and specificity were 79% and 5%; at a cutoff of 15,000 cells/mm³, 45% and 78%. The authors concluded that the test was relatively inaccurate and that decisions to obtain blood cultures should not rely on it alone. A practice guideline (Baraff, 1993) had previously suggested that a WBC count threshold of 15,000/mm³, having a negative predictive value of 97.6%, but a positive predictive value of only 13%, could be used to avoid unnecessary requests for blood cultures.

Another study, comparing WBC with absolute neutrophil count (ANC) in 170 infants (Gombos, 1998), concluded that both tests were “fair indicators for occult bacteremia”. WBC had a sensitivity of 61% and a sensitivity of 59%, with 61% and 68% for ANC.

A prospective study of 1920 patients (Purcell, 2007) found that “The probability of an abnormal WBC count <5000 and 15,000-30,000 being associated with a concurrent serious bacterial infection was very low and no different from that of a normal WBC count in febrile patients admitted with respiratory syncytial virus lower respiratory tract infection.”

Evidence Level: III

A prospective study of 301 screening episodes for neonatal sepsis (Garland, 2003) found that no single test alone was sufficiently reliable to accurately predict early onset sepsis. C-reactive protein (CRP) had a sensitivity of 67% and a negative predictive value of 86%. This compared to 63% and 80% for full blood examination and 57% and 83% for gastric aspirate. Another prospective study in 1,186 infants (Benitz, 1998) concurred with this view, but concluded that two CRP measurements <1 mg/dl obtained 24 hours apart, 8-48 hours after presentation, indicate that bacterial infection is unlikely and thus that antibiotics are not needed.

Alternatively, many studies have observed that CRP in combination with other tests (such as WBC count) results in improved sensitivity (Arnon, 2004; Hengst, 2003; Laborada, 2003; Manucha, 2002). A prospective study of 711 patients with pneumonia (Clark, 2007) found that C-reactive protein was not associated with the degree of severity of the illness. A systematic review (Sanders, 2008) concluded that poor sensitivity associated with CRP meant that it should not be used as a single test for excluding bacterial infection.

http://pediatrics.aappublications.org/content/102/4/e41.long

http://adc.bmj.com/content/92/5/394.long

Garland SM, Bowman ED. Reappraisal of C-reactive protein as a screening tool for neonatal sepsis. Pathology 2003;35:240-3

Hengst JM. The role of C-reactive protein in the evaluation and management of infants with suspected sepsis. Adv Neonatal Care 2003;3:3-13


**Evidence Level: III**

A study in 3,339 neonates (Galanakis, 2002) found that respiratory distress syndrome was the main risk factor for late-onset sepsis (RR 5.70).

A prospective study in 145 infants referred because of respiratory distress (Dorond, 1979) found a 4.8% incidence of bacteremia, with confirmed septicemia in 3.5%. The authors concluded that antibiotics should not be given routinely in such cases, in view of the low incidence of confirmed septicemia.

In a prospective study of 116 infants with respiratory distress (Boyle, 1978), 9 (8%) were septic. WBC count would have provided early identification of 8 of these, as well as false positive results for 14% (15/105) of the remainder, which, in the authors estimation, would have justified antibiotic treatment for those with a cutoff of <10,000/mm³.


**Evidence Level: III**

A retrospective study of 117 women with PROM (Chua, 1995) found that prolongation of PROM to delivery interval for >48 hours increased the incidence of infection in their infants (33% vs 8.8% and 8.9% for intervals of <12 hours and 12-24 hours respectively.

In a secondary analysis of data from 5,041 women in the International Multicenter Term PROM Study (Seaward, 1998), the following were identified as independent predictors of neonatal infection:
- Clinical chorioamnionitis (OR 5.89, P<.0001)
- Positive maternal group B streptococcal status (vs negative or unknown, OR 3.08, P<.0001)
- 7-8 vaginal digital examinations (vs 0-2, OR 2.37, P=.04)
- 24<=48 hours from membrane rupture to active labour (vs <12 hours, OR 1.97, P=.02)
- >= 48 hours from membrane rupture to active labour (vs <12 hours, OR 2.25, P=.02)
- Maternal antibiotics before delivery (OR 1.63, P=.05)


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Evidence Level: III

Discharging eyes in neonates are commonly due to vertical transmission of a sexually transmitted disease (chlamydia or gonorrhoea) from the mother (Winceslaus, 1987). Group B streptococcus may, however, also be a causative organism (Poschl, 2002).


Evidence Level: V

Acute inflammation of the umbilical cord (funisitis) was associated with a significantly higher rate of congenital sepsis in a study of 315 consecutive singleton preterm births (Yoon, 2000): 12% (8/66) vs 1% (3/216).


Evidence Level: IV

Last amended August 2013
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
This guideline has been prepared with reference to the following:


http://pediatrics.aappublications.org/content/early/2012/09/19/peds.2012-2008.full.pdf+html

Last amended August 2013
Last reviewed September 2015
Treatment with L-carnitine is appropriate in the management of neonatal hyperammonaemia, organic acidaemia, fatty acid oxidation disorders and lactic acidosis? A Cochrane systematic review (Nasser, 2012) was unable to identify any randomised trials in this area and concluded that, “in the absence of any high level evidence, clinicians should base their decisions on clinical experience and in conjunction with preferences of the individual where appropriate. This does not mean that carnitine is ineffective or should not be used in any inborn error of metabolism. However, given the lack of evidence both on the effectiveness and safety of carnitine and on the necessary dose and frequency to be prescribed, the current prescribing practice should continue to be observed and monitored with care until further evidence is available.”


Evidence Level: I (For “no evidence”)

Last amended July 2015
Last reviewed September 2015
Do many antenatally detected cysts resolve spontaneously?
In a study (Sherwood 2008) of prenatally suspected and postnatally confirmed intra-abdominal cysts delivered between 1991 and 2004 at the prenatal diagnosis unit at John Radcliffe Hospital, Oxford, fifty five patients were identified antenatally with a diagnosis of abdominal cystic lesion. Of those, 13 cases (24%) the cyst had resolved on a postnatal scan.
In a prospective study (Bagolan 2002) of 73 ovarian cysts diagnosed in 72 fetuses over a seven year period, 76% of the 34 simple cysts <5 cm resolved spontaneously.


Evidence Level: IV
**What is the optimal timing for adding sodium?**

A randomised controlled trial involving 20 infants (Shaffer, 1989) concluded that administration of sodium “is probably unnecessary during the first few postnatal days” and that hypernatraemia could result from inappropriate supplementation.

Similar conclusions were reached by a prospective randomised trial in 17 infants (Costarino, 1992).

A recent review (Modi, 2004) recommended that maintenance sodium should be deferred until weight loss of approximately 6% has occurred.

“There is no simple formula that will guarantee to prevent either hyponatraemia or hypernatraemia in all children” (Coulthard, 2008).


Coulthard MG. Will changing maintenance intravenous fluid from 0.18% to 0.45% saline do more harm than good? Arch Dis Child 2008;93:335-40 http://adc.bmj.com/content/93/4/335.long


**Evidence Level: II (for no early administration of sodium)**

What is the evidence for appropriate volume replacement on day 1, 2, 3, etc?

A Cochrane review of 5 trials (Bell, 2014) shows what appear to be significant advantages to a restrictive strategy for managing the water intake of premature infants who were in the restricted groups were at lower risk of patent ductus arteriosus and necrotizing enterocolitis, with no significant increase in adverse effects. There were trends toward increased risk of dehydration and decreased risk of bronchopulmonary dysplasia, intracranial hemorrhage and death with restricted water intake but these trends were not significant.

This amount must be flexible, taking into account ambient humidity and gestational/postnatal age, but would be in the range of 30-60 ml/kg/day plus estimated insensible water loss (Armon, 2008; Modi, 2004). Given adequate hydration, stepwise increments on subsequent days following birth should not be necessary unless accompanied by “a clinically relevant increase in nutrition” (Modi, 2004).

Evidence Level: I

Can chronic lung disease, necrotising enterocolitis or patent ductus arteriosus (PDA) be caused by fluid overload, rather than inappropriate sodium supplementation?

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
There is evidence that a positive water and sodium balance with expansion of the extracellular space in preterm infants increases morbidity (Bell, 2014). In this Cochrane Review, restricted water intake significantly reduced the risk of PDA (RR 0.52, 95% CI 0.37 to 0.73) and necrotising enterocolitis (RR 0.43, 95% CI 0.21 to 0.87), although not of chronic lung disease (RR 0.85, 95% CI 0.63-1.14). A recent review (Lorenz, 2004) concluded that, based on a metaanalysis of 3 RCTs, higher fluid intakes did not significantly increase the risk of chronic lung disease. A further retrospective study in 204 extremely low birth weight infants (Stephens, 2008) confirmed the association of high fluid intake (>170 ml/kg(-1)/day(-1)) with increased risk of PDA on day 2 (OR 1.014; 95% CI 1.001 – 1.028) and day 3 (OR 1.022; 95% CI 1.004 – 1.040). Findings from 2 RCTs on sodium supplementation were contradictory.

Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. The Cochrane Database of Systematic Reviews 2014, Art. No.: CD000503


Evidence Level: I

Should infants receiving phototherapy be given extra fluids?
Earlier studies of phototherapy (e.g. Wu, 1985) showed increased insensible water loss during the process. This led to recommendations for fluid supplementation in infants undergoing phototherapy, and a survey in 1996 (Hansen, 1996) recorded 74% of responding neonatal ICUs following this policy. Later studies have produced contradictory results, however, with some suggesting that the earlier findings may have been due to heat stress and that phototherapy in a thermally stable infant does not increase fluid loss (Kjartansson, 1992i &ii), and another recording a 20% increase in transepidermal water loss despite tight control of both skin temperature and relative humidity (Grunhagen, 2002). If these results are accepted, an increase in maintenance fluids of 0.35 mL/kg/h is indicated to correct the deficit.

Two further examples of the more recent studies (Maayan, 2001; Wananukul, 2001) agree with Grunhagen that fluid loss is increased, even in thermally stable infants. A randomised study in 74 term neonates with severe hyperbilirubinaemia (Mehta, 2005) found that fluid supplementation decreased the rate of exchange transfusion (RR 0.30; 95% CI 0.14-0.66) and the duration of phototherapy (52 +/- 18 hours vs 73 +/- 31 hours; P = .004).

http://www.nature.com/pr/journal/v51/n3/full/pr200264a.html


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2532565/

Evidence Level: II

Last amended July 2015
Last reviewed September 2015
**INTUBATION - DIFFICULT**
Supporting information

This guideline has been prepared with reference to the following:

Johansen L, Mupanemunda R & Danha R. Managing the neonate with a difficult airway. Infant. 2012; 8; 116-9


**A visual grading system is useful in identifying which patients will be difficult to intubate?**

The Cormack-Lehane system (Cormack 1984), which classifies into four grades, views of the glottic opening during direct laryngoscopy, has been found anecdotally to be appropriate for neonates (Wheeler 2007). Wheeler (2007) argues however, that additional procedures are required to assess severity and that the four grade system is “more useful as a means to facilitate communication of the degree of difficulty between providers and not as a screening tool for predicting a difficult airway at the bedside”

A number of researchers focusing on adult medicine including Yentis (1998) have argued for a more sensitive scoring system. Yentis, when comparing identification of difficult intubations among 663 adult patients using the Cormack-Lehane system and a modified system which divides grade 2 into 2a (part of the vocal cords are visible) and 2b (only arytenoids or very posterior origin of cords visible), found the latter system to be superior and more useful for anaesthetists.


Wheeler DS “Assessment and Management of the pediatric airway” In Wheeler DS, Wong HR and Shanley THP (eds.) Pediatric Critical Care Medicine: Basic Science and Clinical Evidence, 224-252.


**Evidence Level: III**

Last amended September 2015
Last reviewed September 2015

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This guideline has been prepared with reference to the following:


**Size of ETT is best selected according to the weight of the baby?**

A study in 39 intubated neonates (Luten, 2007) tested the accuracy of a measuring tape (based on a combination of data from the babies in the study and published anthropometric papers) in predicting the correct size of ETT. The average relative difference between tape-predicted weight and actual weight was 9.5% (95% CI 8.3-10.6%) and was evenly distributed throughout all the weight groups. The tape predicted actual ETT size in 96% of cases (95% CI 86.3-99.5%) and was correct within 1 tube size (0.5 mm) in 100% (95% CI 94.8-100%). The authors concluded that length was an accurate predictor of ETT size and weight and could be used in emergency resuscitation when weight was unobtainable.

A small audit in 36 babies (Whyte, 2007) found that nasal-tragus length predicted correct insertional length for ETTs in 94% of cases, compared to 73% when either weight or sternal length was used.

An audit in 33 UK neonatal units (Kempley, 2008) resulted in the provision of a table showing ETT length by gestation and weight.


**Evidence Level: IV**

**Is fentanyl superior to morphine for sedation?**

A small, double-blind, randomised trial in 20 preterm neonates (Pereira e Silva, 2007) compared intubation conditions (ease of laryngoscopy, position of the vocal cords, coughing, jaw relaxation and movement of the limbs) in two equal-sized groups given morphine or remifentanil. Conditions were rated as Excellent, Good or Poor. Morphine scored 0, 6, 4 respectively, compared to 6, 4, 0 for remifentanil. The authors concluded that conditions with remifentanil were significantly better (p = 0.0034) than with morphine. Although small, the study had a statistical power of 83%.

“Many units who give sedation use morphine, probably because of familiarisation rather than proven efficacy” (Wyllie, 2008).

Although fentanyl or morphine are the most commonly used sedative agents, there is a need for larger trials to determine the most effective regimen (Carbajal, 2007).

A small randomised study in 30 infants (Cignacco, 2008) failed to demonstrate any pain relief from the use of morphine as measured by three assessment tools (Bernese Pain Scale for Neonates, Premature Infant Pain Profile and Visual Analogue Scale).


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675432/

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Evidence Level: III

How often do nasogastric tubes need changing routinely and why?
Only two papers addressing this question were identified. The first (Rogahn, 1998) commented that no other previously published articles on the subject had been found. The author carried out a survey of 14 NICUs with 10 or more ventilators to establish their current practice on changing nasogastric tubes and whether or not this was evidence-based. Practice varied from changing the tubes daily to weekly (median 3 days), and was based on experience rather than evidence in all cases.
The second paper (Mears, 2001) observed that little had changed since the publication of the previous paper in 1998. The author surveyed 36 neonatal units in the Thames region and found that, despite her own unit changing the tubes at 48 hour intervals, 64% of those surveyed changed them at 4–7 days, with no reported complications.
The author also contacted the maker of the tubes used in her own unit (Vygon UK Ltd) for advice. This was that tubes may be safely left in situ for up to seven days, after which the integrity of the PVC used in their manufacture could not be guaranteed.
The author’s unit conducted an audit on the basis of this information and altered the frequency of tube change from 48 hours to 5 days, with some tubes being left in situ for up to 7 days if an infant was deemed too unwell to tolerate removal. A re-audit was performed 6 months after completion of the original study, which confirmed that leaving the tubes in situ for up to 7 days was not associated with any recorded adverse effects.

Mears M. Changing nasogastric tubes in the sick and preterm infant: a help or a hindrance? J Neonatal Nurs 2001;7:202-6


Evidence Level: V

Last amended August 2013
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
This guideline has been prepared with reference to the following:


https://www.nice.org.uk/guidance/cg98

**What is the incidence of prolonged neonatal jaundice in term and preterm newborns?**

Jaundice persisting beyond 14 days of age (prolonged jaundice) can (rarely) be a sign of serious underlying liver disease (Hussein, 1991). Jaundice persists beyond 14 days in 15-40% of breastfed infants, depending on the series studied (Hannam, 2000). A prospective study of all 7139 term infants born at King’s College Hospital (London) between January 1997 and June 1998 (Hannam, 2000) found 154 with prolonged jaundice, one of which had conjugated hyperbilirubinaemia (0.14 per 1000 live births). Another study of 3661 babies in Sheffield (Crofts, 1999) found 127 who were jaundiced at 28 days, of which 125 were breastfed (9.2%). Although preterm infants, whose livers are more immature, have prolonged jaundice more commonly than term infants (Fenton, 1998) there appear to be no studies of incidence in this group (Lucas, 1986).

The first large, prospective study of severe hyperbilirubinaemia in UK infants in the first month of life (Manning, 2007) found an incidence of 0.7 per 1,000 live births (95% CI 0.5 – 0.8).


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675352/

**Evidence Level: IV**

**When does serum bilirubin level of a neonate fall to adult level?**

High serum bilirubin levels in the first days of life “decline during the next several weeks to the values commonly found in adults” (Denness, 2001). This time period is inexact, although 14 days is commonly accepted as a cut-off point for investigation of sustained jaundice (Fenton, 1998).


**Evidence Level: V**

**What is the incidence of glucose-6PD deficiency in British white children?**

Glucose-6PD deficiency is most common amongst Greek, Sardinian, Chinese, Jamaican and South East Asian populations (Beutler, 1994; Valaes, 1994; Singh, 1986; Doxiadis, 1961).

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
There appear to be no epidemiological studies in British white children. The prevalence amongst white northern European populations has been estimated as less than 1 in 1,000 (Beutler, 1995).


http://www.bloodjournal.org/content/84/11/3613.full-text.pdf+html

http://ije.oxfordjournals.org/content/21/5/947.long

Singh H. Glucose-6-phosphate dehydrogenase deficiency: a preventable cause of mental retardation. BMJ 1986;292:397-8


Evidence Level: V

What is the incidence of hereditary spherocytosis presenting with prolonged neonatal jaundice only?
The incidence of hereditary spherocytosis in Northern Europeans has been estimated at 1:5,000 (Morton, 1962), although milder forms may be asymptomatic and therefore the true incidence may be higher. A recent review (Delhommeau, 2000) has taken this into consideration and suggested an incidence of 1:2,000. This condition has received little attention in the neonatal period (Delhommeau, 2000) and consequently no information can be identified concerning prolonged jaundice as the sole presenting symptom.


Evidence Level: V

What percentage of urinary tract infection in newborns presents with jaundice only?
The association of urinary tract infection with neonatal jaundice has been well-recognised (Anon, 1971; Arthur, 1967), but no percentages can be identified for newborns presenting with jaundice alone. Most infants in published series have anaemia and/or sepsis in addition to their jaundice (Hannam, 2000). Jaundice as the main presenting symptom of UTI appears to predominate in male infants at a ratio of 3:1 (Seeler, 1969), unlike the female preponderance generally found in paediatric UTI. A study in 102 infants with asymptomatic, unexplained indirect hyperbilirubinaemia in the first two weeks of life (Bilgen, 2006) found UTI in 8 cases (8%). The authors concluded that urine culture should be considered in the bilirubin work-up of infants older than three days of age with an unknown etiology.

Anon. Urinary tract infection presenting as jaundice. BMJ 1971;iii:546-7
http://www.bmj.com/content/3/5774/546.full.pdf+html

http://www.bmj.com/content/3/5559/242.2.full.pdf+html


Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk

Evidence Level: V

At what level of total serum bilirubin (TSB) does kernicterus occur in a) the term baby b) the preterm baby of 32 weeks? At what level should phototherapy be started in the term baby?

The American Academy of Pediatrics (Anon, 2004) states that “It is not known at what bilirubin concentration…significant risk of brain damage occurs or when the risk of damage exceeds the risk of treatment”. Cases of kernicterus have occurred at TSB levels below 200 micromol/l (Gustafson, 1995). This level of uncertainty persists (Wennberg, 2006): “There are insufficient published data to precisely define sensitivity and specificity (of TSB) in determining risk for acute bilirubin neurotoxicity or chronic sequelae (kernicterus).”

One authority (Ives, 1999) suggests that the threshold lies “somewhere between 400 and 650 micromol/l”. The AAP (Anon, 1994) recommends exchange transfusion and intensive phototherapy when serum bilirubin is >/= 430 mmol/l if age 25-48 hours or >/= 510 mol/l if >48 hours. Standard phototherapy should begin at 257 micromol/l or 308 micromol/l for the same age bands, in the term or near term infant.

Data from the Pilot Kernicterus Registry (Johnson, 2002) showed that the median total serum bilirubin (TSB) concentration of infants on readmission to hospital with kernicterus was 600 micromol/l (350 mg/l).

The most recent information on this subject (Bhutani, 2004) indicates that TSB concentrations of >342 micromol/l (>200 mg/l) should be a cause for concern and that values >/= 513 micromol/l (>/= 300 mg/l) should be considered “dangerous”. TSB concentrations are, however, poor predictors of bilirubin toxicity in the sick or preterm infant (Bhutani, 2004). Although “free” or unbound bilirubin may provide a more accurate measure, no tests for this have been validated to date (Bhutani, 2004).

A sliding scale has been suggested, based on infant weight, to indicate when intensive phototherapy should be started, but exchange transfusion is recommended when TSB >190 mL/kg (Bhutani, 2004).

NICE guidelines (2010) found that “There is a lack of good-quality evidence on the association between hyperbilirubinaemia and kernicterus or other adverse sequelae.”


Evidence Level: V

Can gamma-glutamyl transpeptidase (GGT) be useful in distinguishing neonatal hepatitis (NH) from extrahepatic biliary atresia (EHBA)?

A study in 132 patients (Arora, 1992) found that serum GGT at a cut-off level maintaining 100% sensitivity for EHBA (< 150 IU L(-1)), used in conjunction with non-excreting 99mTc-mebrofenin IDA scans, reduced the false positivity of individual tests. In this series, operative cholangiograms would have been avoided in 21 patients having both tests, vs 9 when only IDA scan was performed.

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
A study in 47 infants with EHBA, 10 with NH and 130 age-matched healthy controls (Yamagiwa, 1996), noted significant differences in GGT levels between the EHBA and NH infants at 6 weeks of age (314 +/- 232 IU/L vs 69 +/- 58 IU/L).

A much earlier study in 17 infants aged 5-16 weeks (Wright, 1960) found that the mean maximal GGT level in NH patients (183 +/- 54 IU/L) was significantly lower than that found in EHBA patients (760 +/- 492 IU/L).

Evidence Level: IV

What is the optimal dose and duration of treatment in total parenteral nutrition (TPN) related cholestasis?

“To date, there is no universally accepted treatment for intractable TPN-associated cholestasis” (Al-Hathlol, 2006).

BNF for Children advises ursodeoxycholic acid (UDCA), 10 mg/kg 3 times a day. Most studies have included very small numbers of patients. A pilot study in 7 children (Spagnuolo, 1996) found that UDCA took 4-8 weeks to normalise biochemical markers of cholestasis. Another, in 13 infants (Al-Hathlol, 2006) used a dose of 15-20 mg/kg/day and found that although patients responded from the second week of therapy, about four months of treatment were needed before normalisation occurred.

An alternative treatment is cholecystokinin, which needs to be administered intravenously for 3-5 days in a dose of 2-4 IDU/kg (Teitelbaum, 1997; Teitelbaum, 1995; Rintala, 1995).

Evidence Level: IV

What are the most appropriate tests to be ordered for prolonged jaundice?

A prospective study in 144 infants (Hannam, 2000) concluded that “the number of investigations may safely be reduced to: a total and conjugated bilirubin, packed cell volume, glucose-6-phosphate dehydrogenase level (where appropriate), a urine for culture and inspection of a recent stool sample for bile pigmentation”.

Evidence Level: IV
KANGAROO CARE (KC)
Supporting information

This has been prepared with reference to:


KC can help to reduce procedural pain in preterm infants?
A crossover pilot study in 28 preterm infants (Cong, 2011) tested KC effects on bio-behavioural responses to heel stick, measured by Premature Infant Pain Profile (PIPP) and salivary and serum cortisol. Mother-infant dyads were randomly assigned to KC heel stick (KCH) first or incubator heel stick (IH) first. Study 1 (80-min study, N = 18) tested the effect of 80 min of KC before and throughout the heel stick procedure versus incubator care. Study 2 (30-min study, N = 10) tested 30 min of KC before and throughout the heel stick versus incubator care. KCH and IH began during a pre-measurement phase and continued through four data collection phases: baseline, heel warming, heel stick, and recovery. PIPP responses were measured every 30 s during data collection; salivary cortisol was measured at the end of baseline and recovery; and serum cortisol was measured during heel stick. Study 1 showed no differences between KCH and IH. Study 2 showed lower PIPP scores at four time points during recovery (p < .05 to p < .001), lower salivary cortisol at the end of recovery (p < .05), and lower serum cortisol during heel stick for the KCH condition (p < .05) as well as clinically lower PIPP scores in the KCH condition during heel stick. The authors concluded that 30 minutes of KC before and throughout the heel stick reduced bio-behavioural responses to pain in preterm infants.

A Cochrane Systematic Review of 51 studies in a total of 3396 participants (Pillai Riddell, 2011) found kangaroo care effective in reducing procedural pain in preterm infants (SMD -1.12, 95% CI -2.04 to -0.21).

A Cochrane systematic review (Johnston, 2014) also investigated the pain relieving effect of skin-to-skin care (also known as Kangaroo Care). 19 studies involving 1594 infants were analysed and the authors concluded that “SSC appears to be effective, as measured by composite pain indicators and including both physiological and behavioural indicators, and safe for a single painful procedure such as a heel lance”


Evidence Level: I

For what period of time should skin-to-skin contact be maintained?
Unicef’s Baby Friendly Health Initiative suggests a minimum of 1 hour:


Evidence Level: I

Last amended September 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Are preterm babies that are small for their gestational age at higher risk of parenteral nutrition-associated cholestasis (PNAC)?

A study in 445 VLBW infants (Costa, 2010) found that 55 had PNAC. Infants with cholestasis had lower birth weight and gestational age but similar birth weight z-score compared with infants without cholestasis, and they received a lower amount of enteral feeds (25.8 +/- 20.7 vs 67.9 +/- 33.0 mL/kg, P < .001), a greater amount of intravenous glucose (10.6 +/- 1.3 vs 7.5 +/- 2.5 g/kg, P < .0001), lipids (1.8 +/- 0.4 vs 1.3 +/- 0.5, P < .0001) and proteins (2.7 +/- 0.5 vs 1.9 +/- 0.7, P < .0001), and needed a higher number of days of fasting (13.2 +/- 6.7 vs 6.5 +/- 4.8, P < .001). Enteral intake between 0 and 21 days of life (OR 0.66; 95% CI 0.53, 0.81, P < .0001) and oxygen therapy (OR 1.05; 95% CI 1.01, 1.09; P = .030) were identified as the best independent predictors of PNAC. The authors concluded that small for gestational age infants did not have a higher risk of PNAC.


Evidence Level: IV

Last amended July 2011
Last reviewed September 2015
What are the advantages and disadvantages of these lines?
Silastic catheters are much finer than, for example, Broviac catheters and are less likely to occlude veins, especially when inserted peripherally (Anon, 1991). Silastic is more likely than polyurethane to cause thrombus formation or sepsis (Wheeler, 1991), but is softer and thus more suitable for use in neonates (Goutail-Flaud, 1991). Silastic is less thrombogenic than the older type of PVC catheter (Boros, 1975).


Evidence Level: V

What is the optimum position and the best way of determining the position once placed?
The tip of silastic catheters should be placed just behind the confluence of the superior-inferior vena cava and the right atrium (Hausdorf, 1987), or alternatively in the superior vena cava (Anon, 1991). There is an increased risk of systemic air and fat embolism if the tip is in or close to a patent foramen ovale (Hausdorf, 1987). Ultrasonography accurately confirms positioning of even the thinnest catheters, and reduces the need for radiography (Soong, 1991; Hausdorf, 1987, De Carvalho 2012).


Evidence Level: V

How should any infections be managed? When should the lines be removed?
Catheter infection is more than twice as common in neonates than in older children (Mulloy, 1991), and infection rates as high as 45% have been recorded (Puntis, 1990; Grisoni, 1986). Exit-site infections can be treated with antibiotics, but tunnel infections usually require the catheter to be removed (Anon, 1991). A prospective study of 35 patients (Klein, 1992) included 4 with bacteraemia. Two of these needed catheter removal to clear their infections, but the other 2 were cured by the administration of antibiotics through the catheter. Prophylactic vancomycin or teicoplanin reduces the incidence of catheter-related infection in neonates (Moller, 1995). However, a Cochrane review (Jardine, 2008) found that antibiotic prophylaxis had no effect on overall mortality (RR 0.68, 95% CI 0.31 – 1.51).


Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
What are the most common complications and how can they be avoided?

The most common serious complications of vascular access are infection (Moller, 1995) and catheter occlusion secondary to thrombus formation at the catheter tip (Sherman, 1983). The first prospective study of silastic catheters in neonates, using only peripheral veins of the scalp and extremities (Durand, 1986), found an overall incidence of mechanical complications of 26.4%. These consisted of blockage of the catheter or accidental displacement. Of 53 catheterisations, 4 (7.5%) were complicated by infections.

A study of 535 catheterisations with an average indwelling time of 23 days (Neubauer, 1995) noted one complication for every 153 indwelling catheter days. The most common complication was sepsis, on 22 occasions (4.1%).

A large Chinese study of 1,318 catheterisations (Soong, 1995) found a lower rate of sepsis (2.7%), which was still the most common complication.

The jugular vein route is particularly associated with thrombosis, which was detected in 8 of 24 patients receiving a silastic catheter in a study of 40 neonates (Rand, 1994).

Lines in infants needing total parenteral nutrition or multiple intravenous infusions are particularly susceptible to infection and their use “should be avoided if possible” (Mulloy, 1991). Broviac catheters may be more suitable in these patients (Anon, 1991).

A prospective study of catheter sepsis (Puntis, 1991) found that education of staff in appropriate practice and the utilisation of specialist nurses reduced the rate of infection from 45% to 8% over a 12 month period.

A randomised, controlled, double-blind, single-centre trial in 210 infants (Birch, 2010) compared TPN with heparin (n=102) to TPN without heparin (n=108). There was a statistically significant reduction in all episodes of culture-positive, catheter-related sepsis in those infants with heparin added to the TPN, compared with those without heparin (p=0.04; RR 0.57, 95% CI 0.32 to 0.98; NNT 9, 95% CI 4.6 to 212.4).

A Cochrane review of 2 trials in 267 neonates (Shah, 2008) found some evidence for the prophylactic use of heparin in prevention of thrombotic complications; treatment was associated with a reduced risk of catheter occlusion (RR 0.28, 95% CI 0.15 – 0.53; NNT 5, 95% CI 3 – 8). The only previous systematic review (Randolph, 1998) was not confined to infants.


Birch P; Ogden S; Hewson M. A randomised, controlled trial of heparin in total parenteral nutrition to prevent sepsis associated with neonatal long lines: the Heparin in Long Line Total Parenteral Nutrition (HILLTOP) trial. Arch Dis Child Fetal Neonat Ed 2010;95:F252-7

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk


Neubauer AP. Percutaneous central i.v. access in the neonate: experience with 535 silastic catheters. Acta Paediatr 1995;84:756-60


http://www.bmj.com/content/316/7136/969.long


Evidence Level: V

Last amended August 2013
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
This guideline has been prepared with reference to the following:

NHS Newborn Blood Spot Screening Programme. The MCADD programme. 2012.
http://newbornbloodspot.screening.nhs.uk/mcadd

http://www.bimdg.org.uk/guidelines.asp

Last amended August 2013
Last reviewed September 2015
**Which biochemical marker should be used to identify metabolic disease in preterm infants?**

None of the evaluated metabolites (Ca, P, ALP and vitamin D) alone can be considered a marker of metabolic bone disease (MBD) of prematurity. In a recent study (Figueras-Aloy 2014) in 336 preterm infants who underwent biochemical analyses and bone mineral density (BMD) assessment; the closest correlations between BMD and any other variables were seen for ALP and P. The concentration threshold of ALP to indicate MBD was 500 IU/L, and the maximum value of the correlation (0.290) was obtained by associating the ALP and P concentrations with a cut off point of 4.5 mg/dL (1.45mmol/L) to differentiate mild from severe MBD. According to Hung et al, an ALP level >700 IU/L at 3 weeks postnatal age was predictive of osteopenia at term, with a sensitivity of 73% and a specificity of 74%. In another study (Backstrom 2000) in 43 preterm infants, a combination of the criteria "serum total ALP> 900 IU/l" and "serum P <1.8 mmol/l" yielded a sensitivity of 100% at a specificity of 70% in revealing low BMD by dual energy X-ray absorptiometry. In a cohort study of 64 VLBW infants, higher values of urinary Ca (MBD = 31.9 +/- 20.2, without MBD = 19.8 +/- 15.4; p = 0.017) and ALP (MBD = 369 +/- 114, without MBD = 310 +/- 93; p = 0.04) were found in infants who developed MBD. In a systematic review by Visser et al, it was suggested that none of the frequently used serum measurements are valid biochemical markers of MBD in preterm infants.


**Evidence Level: III**

**What is the role of monitoring urinary mineral excretion to guide mineral supplementation?**

An interventional cohort study (Pohlandt 1994) demonstrated that infants who simultaneously excreted Ca >1.2 mmol/L and P at >0.4 mmol/L (in spot urine specimens) by means of an individual supplementation with Ca and/or P resulting in a slight surplus supply showed the highest bone mineral accretion measured by single-photon absorption densitometry. Hence, an individualized Ca and P supplementation in preterm infants aiming for a slight excess of the actual need, guided by urinary Ca and P concentrations, appears to be able to achieve fetal mineralisation rate. The above strategy appears sensible as both growth velocity and enteral Ca absorption are highly variable. However, monitoring of urinary Ca and P concentrations needs to take into account non-nutritional factors affecting these concentrations in particular drug related calciuria and phosphaturia. Specifically, methylxanthines and diuretics increase the renal Ca losses, and the renal P threshold may be lowered in premature infants. Infants between 26 and 31 weeks were found to have a renal P threshold in the range of normal serum P values (2 mmol/L) but Hellstern et al have shown that extremely preterm infants (23-25 weeks) had a much lower renal P threshold, leading to urinary P excretion even in the presence of low P levels. In a recent study (Mihatsch 2012) in infants born preterm on regular 3 or 4 h feedings, 6 h urine sampling was shown to be sufficiently precise for prediction of Ca and P deficiency homeostasis (PPV 0.92 and 0.83) defined as 24 h urinary concentrations <1 mmol/L Ca or P. As urinary ratios depend heavily on type of feed as mentioned in the guideline, standard reference ranges are less useful.

Evidence Level: III

Which method of monitoring urine mineral excretion should be used- urinary Ca or PO₄ concentrations or Ca/creatinine(Cr) or PO₄ /creatinine ratios?

It is unclear whether the Ca/Cr and PO₄/Cr ratios are superior to the simple urinary Ca and PO₄ concentrations. Aladangady et al reported a reference range for urinary Ca/Cr and UPO₄/Cr ratios and factors influencing these ratios in a representative population of preterm infants between 24-34 weeks gestation but to date no study has shown that these variables are a reliable surrogate measure of bone mineral content. It is well known that urinary Ca and PO₄ concentrations vary and that Cr corrects for varying urine volumes that depend on fluid intake. However, in the slight surplus supply concept, the exact daily amount of Ca/PO₄ excretion is not the primary target as simple urinary Ca and PO₄ concentrations indicate whether there is a surplus (>1 mmol/l) or not (<1 mmol/l). In addition, most stable growing preterm infants are on a constant daily fluid intake and fed at regular intervals during the day and night. Consequently there are no circadian variations in urinary mineral concentrations. Boehm et al described a correlation between the real daily excretion and the mean substrate/Cr ratio of a 24-h collection period, which was weaker than the correlation between the 6-h and the 24-h excretion of the respective substrates. A correction for the urine volume therefore does not seem to be of importance and would actually increase the costs (Cr measurement). In a recent study (Staub 2014), comparison of urinary mineral concentration with mineral/Cr ratio with the intention to supplement the respective mineral, was shown to be moderate for Ca and good for PO₄ but the results did not allow for identifying superiority of either method on the decision to supplement. PO₄ is not bound in the plasma like Ca and so the percent tubular reabsorption of PO₄ (TRP) is the best guide to adequacy of PO₄ supplementation. A percent TRP of >95% shows inadequate supplementation. However, this must be taken in relation to plasma Ca; inadequate Ca intake will lead to hyperparathyroidism and hence tubular leak of PO₄. Similarly, if PO₄ intake is low, there is breakdown of bone and hence release of Ca leading to hypercalcaemia and calciciuria. TRP can be calculated using the formula:

\[
\%TRP = 1 - \frac{Urine \ PO₄}{Urine \ creatinine} \times \frac{Plasma \ creatinine}{Plasma \ phosphate} \times 100.
\]


Evidence Level: III
How much of mineral and vitamin D to be supplemented?

Breast milk Ca is absorbed at a rate of 70%, compared with 25%-30% for formula Ca. Lactose encourages absorption. Rigo et al reported the maximum retention of Ca (91 mg/kg/day) and higher bone accretion at discharge in 9 preterm infants who received breast milk with a fortifier containing 170 mg/kg/day of highly soluble Ca glycerophosphate. Rigo et al recommended administering 100-160 mg/kg/day of highly bioavailable Ca salts with 60-90 mg/kg/day of P and 800-1000 IU/day of vitamin D. The European Society of Paediatric Gastroenterology, Hepatology, and Nutrition’s Committee on Nutrition advises a Ca intake of 120-140 mg/kg/day.


Evidence Level: IV

Last amended February 2015
Last reviews September 2015
METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)
Supporting information

This guideline has been prepared with reference to the following:

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. 2011

http://cid.oxfordjournals.org/content/52/3/e18.full

**Mupirocin ointment is of value in the decolonisation of MRSA carriers?**

A Cochrane systematic review of 9 RCTs involving 3396 participants (van Rijen, 2008) found that, after pooling the 8 studies that compared mupirocin with placebo or with no treatment, there was a statistically significant reduction in the rate of S. aureus infection associated with intranasal mupirocin (RR 0.55, 95% CI 0.43 to 0.70).

A report of an outbreak of MRSA in a hospital in the USA (Lepelletier, 2009) however, found that although the outbreak was controlled with widespread use of mupirocin in both staff and patients, ongoing spread was not eradicated, with nine further sporadic cases being detected over the subsequent 18 month period.


**Evidence Level: I**

Last amended October 2012
Last reviewed September 2015
Evidence pertinent to this guideline may be found in the supporting information for the following Neonatal Guideline:

- Nasogastric tube insertion

Last reviewed August 2013
Last reviewed September 2015
How often do nasogastric tubes need changing routinely and why?
Only two papers addressing this question were identified. The first (Rogahn, 1998) commented that no other previously published articles on the subject had been found. The author carried out a survey of 14 NICUs with 10 or more ventilators to establish their current practice on changing nasogastric tubes and whether or not this was evidence-based. Practice varied from changing the tubes daily to weekly (median 3 days), and was based on experience rather than evidence in all cases.

The second paper (Mears, 2001) observed that little had changed since the publication of the previous paper in 1998. The author surveyed 36 neonatal units in the Thames region and found that, despite her own unit changing the tubes at 48 hour intervals, 64% of those surveyed changed them at 4-7 days, with no reported complications.

The author also contacted the maker of the tubes used in her own unit (Vygon UK Ltd) for advice. This was that tubes may be safely left in situ for up to seven days, after which the integrity of the PVC used in their manufacture could not be guaranteed.

The author’s unit conducted an audit on the basis of this information and altered the frequency of tube change from 48 hours to 5 days, with some tubes being left in situ for up to 7 days if an infant was deemed too unwell to tolerate removal. A re-audit was performed 6 months after completion of the original study, which confirmed that leaving the tubes in situ for up to 7 days was not associated with any recorded adverse effects.

Mears M. Changing nasogastric tubes in the sick and preterm infant: a help or a hindrance? J Neonatal Nurs 2001;7:202-6

Evidence Level: V

Does lingual sucrose reduce pain response to tube insertion?
A small randomised trial in 20 stable preterm infants sampled on 51 occasions (McCullough, 2008) concluded that lingual 24% sucrose (compared to water placebo) administered 2 min before tube insertion reduced pain response. Infants who received sucrose demonstrated a significantly lower Neonatal Facial Coding Score (median 1 (range 0-4) vs 3 (0-4), p=0.055).

http://fn.bmj.com/content/93/2/F100.long

Evidence Level: II

Last amended June 2008
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Are repeat x-ray examinations necessary?
A retrospective chart review of 105 neonates with stage 2 NEC (Najaf, 2010) found those not needing surgery (n=59) were exposed to significantly more x-ray examinations than those needing surgery (n=46). As bowel perforation occurred at a median interval of 1 day after clinical presentation, the authors concluded that x-ray examinations could be “safely minimized or eliminated after 2 days of presentation.”


Evidence Level: IV
NITRIC OXIDE
Supporting information

This guideline has been prepared with reference to the following:


Nitric oxide is contraindicated in congenital heart disease?
An updated Cochrane systematic review of four randomized trials (Bizzarro, 2014) compared the effects of postoperative inhaled nitric oxide versus placebo and/or conventional management on infants and children with congenital heart disease. The study found that there does not appear to be any significant clinical benefit with the use of postoperative iNO to treat pulmonary hypertension in children with congenital heart disease. There does not appear to be convincing evidence that Nitric oxide is contraindicated in these patients though. The reviewers observed no differences between groups with respect to mortality (P = 0.50), PHTC (P = 0.79), change in MPAP (P = 0.36), MAP (P = 0.40), HR (P = 1.00), or PaO2:FiO2 (P = 0.46). Firm conclusions could not be drawn, due to doubt about the validity of some of the studies.


Evidence Level: I

Last amended May 2015
Last reviewed September 2015
NON-NUTRITIVE SUCKING
Supporting information

This guideline has been prepared with reference to:

Anon. Prevention and management of pain in the neonate: an update. American Academy of
Pediatrics Committee on Fetus and Newborn and Section on Surgery; Canadian Paediatric
Society Fetus and Newborn Committee. Pediatrics 2006;118:2231-41

http://pediatrics.aappublications.org/content/118/5/2231.full

What is the evidence for the efficacy of NNS?
A systematic literature review of 13 randomised trials and 2 meta-analyses (Cignacco, 2007)
looked at the effects of non-nutritive sucking, music, swaddling, positioning, olfactory and
multisensorial stimulation, kangaroo care and maternal touch. These had an observable positive
effect on pulse rate, respiration and oxygen saturation, reduction of motor activity and excitation
states following painful procedures. Validated pain assessment instruments were not employed in
these studies, however, and further research was called for.

Cignacco E, Hamers JP, Stoffel L, et al. The efficacy of non-pharmacological interventions in the
management of procedural pain in preterm and term neonates. A systematic literature review. Eur J Pain
2007;11:139-52

Evidence Level: I

Last amended August 2013
Last reviewed September 2015
**NUTRITION AND ENTERAL FEEDING**

Supporting information

This guideline has been prepared with reference to the following:


[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2761573/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2761573/)


At what rate should enteral feeds be increased?

A Cochrane systematic review (Morgan, 2014) concluded that advancing enteral feed volumes at daily increments of 30 ml/kg to 35 ml/kg does not increase the risk of necrotising enterocolitis in very preterm or VLBW infants. Advancing the volume of enteral feeds at slow rates resulted in several days delay in regaining birth weight and establishing full enteral feeds. The applicability of these findings to extremely preterm, extremely low birth weight, or growth-restricted infants is limited.

Approximately 90% of infants developing necrotising enterocolitis (NEC) do so after being fed, with some authorities linking this to rapid incremental rates of enteral feeding (Berseth, 2003). A randomised trial in 141 preterm infants (Berseth, 2003) comparing a minimal (20 mL/kg/d for 10 days) feed group with an advancing (20 mL/kg/d on day 1, increased by 20 mL/kg/d up to 140 mL/kg/d) group was closed early after 7 of the advancing group vs 1 of the minimal group developed NEC.

Other randomised trials have found no difference in incidence of NEC between “fast” and “slow” groups. A prospective randomised trial in 185 infants with birth weight 501-1500g ((Rayyis, 1999) found that a greater than twofold difference in the rate of feed advancement (from 15 cc/kg/d to 35 cc/kg/d) resulted in a 9% incidence of NEC in the “fast” group (n=87) compared to 13% in the “slow” group (n=98). The authors concluded that “Factors other than feed advancement appear to be more important in the pathogenesis or progression of NEC”.

Another randomised trial, in 53 infants <1250g (Salhotra, 2004) compared “slow” (increments of 15 mL/kg/d, n=26) and “fast” (increments of 30 mL/kg/d, n=27) groups, finding that the “fast” group reached full enteral intake (180 mL/Kg/d) considerably earlier (10 +/- 1.8 days) than did the “slow” group (14.8 +/- 1.5 days), without any difference in the incidence of NEC.

Other trials and reviews have also reported better growth with no adverse effects from the use of more “aggressive” enteral feeding programmes (Ziegler, 2002; Evans, 2001; Wilson, 1997).

A randomised controlled trial in 100 neonates (Krishnamurthy, 2010) found that “rapid enteral feeding advancements of 30 mL/kg/day are well tolerated by stable preterm neonates weighing 1000-1499 g.”

Berseth CL, Bisquera JA, Paje VU. Prolonging small feeding volumes early in life decreases the incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2003;111:529-34


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Evidence Level: I

Does delaying the introduction of progressive enteral feeding help prevent necrotising enterocolitis (NEC) in VLBW infants?

An updated Cochrane Review of 9 RCTs in a total of 1106 infants (Morgan, 2014) concluded that: “delaying the introduction of progressive enteral feeds beyond four days after birth did not reduce the risk of developing NEC in very preterm or VLBW infants, including growth-restricted infants. Delaying the introduction of progressive enteral feeds resulted in a few days' delay in establishing full enteral feeds but the clinical importance of this effect was unclear.”


Evidence Level: I

Last amended November 2015
Last reviewed September 2015
This guideline has been prepared with reference to the following guidelines:

- IV Fluid Therapy
- Vitamin K

Last amended August 2013
Last reviewed September 2015
OXYGEN ON DISCHARGE
Supporting information

This guideline has been prepared with reference to the following:


Home oxygen therapy may be of use in bronchiolitis?
A prospective, randomised trial of 92 infants and children with acute bronchiolitis and hypoxia aged 2 to 24 months (Bajai, 2006) assigned 53 (58%) to home therapy and 39 (42%) to inpatient admission. Of 53 patients, 37 (70%) randomly assigned to home oxygen completed the observation period and were discharged from the hospital. The remaining 16 patients were excluded from the study (6), resolved their oxygen requirement (5), or failed to meet the discharge criteria and were admitted (5). One discharged patient (2.7%) returned to the hospital and was admitted for a cyanotic spell at home after the 24-hour follow-up appointment. The patient had an uncomplicated hospital course with a length of stay of 45 hours. The remaining 36 patients (97%) were treated successfully as outpatients with home oxygen.


Evidence Level: II

Last amended May 2011
Last reviewed September 2015
OXYGEN SATURATION TARGETS
Supporting information

Should lower target ranges for oxygen saturation be favoured, in order to minimise the risk of retinopathy of prematurity (ROP)?

A retrospective chart review (Tluczek, 2010) compared babies screened for ROP during the 2 years immediately before (Group 1, n=387) and the 2 years after (Group 2, n=386) the initiation of a new oxygen protocol. In the new protocol, target oxygen saturation was adjusted from 90%-99% to 85%-93%. Mean birth weights (BW) and gestational ages were 1,194 g and 29.2 weeks (ranges, 525-2,085 g; 23 2/7-39 6/7 weeks) for Group 1 and 1,139 g and 28.9 weeks (ranges, 520-2,500 g; 22 6/7-35 3/7 weeks) for Group 2 (p= 0.02/0.10). ROP developed in 32.7% of infants in Group 1 and 27.8% in Group 2 (p =0.17). The incidence of ROP requiring treatment was 19.9% in Group 1 and 20.5% in Group 2 (p = 0.91). Subanalysis of infants with BW <= 1,000g (Group 1, n = 119; Group 2, n = 141) revealed ROP incidence of 75.1% versus 57.1%, respectively (p < 0.01); treatable disease occurred in 37.5% and 21.9% of affected infants (p = 0.19). The authors concluded that lowering target oxygen saturation for inborn premature infants was associated with decreased incidence of ROP only in infants with BW <= 1,000 g. Severity of disease, including need for treatment, was similar in both groups.

A meta-analysis of 10 studies (Chen, 2010) found that low oxygen saturation (70%-96%) in the first several postnatal weeks was associated with a reduced risk of severe ROP (RR 0.48 [95% CI 0.31-0.75]). High oxygen saturation (94%-99%) at > or = 32 weeks' PMA was associated with a decreased risk for progression to severe ROP (RR: 0.54 [95% CI: 0.35-0.82]).

A randomised trial comparing target ranges of oxygen saturation of 85 to 89% or 91 to 95% among 1316 infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation (Carlo, 2010) found that the rates of severe retinopathy or death did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3% and 32.1%, respectively; RR with lower oxygen saturation, 0.90; 95% CI 0.76 to 1.06; P=0.21). Death before discharge occurred more frequently in the lower-oxygen-saturation group (in 19.9% of infants vs. 16.2%; RR 1.27; 95% CI, 1.01 to 1.60; P=0.04), whereas severe retinopathy among survivors occurred less often in this group (8.6% vs. 17.9%; RR 0.52; 95% CI, 0.37 to 0.73; P<0.001). There were no significant differences in the rates of other adverse events.

Manja et al. (2015) systematically reviewed the evidence evaluating the effect of restricted vs liberal oxygen exposure on morbidity and mortality in extremely preterm infants. They found that there was no significant differences in retinopathy of prematurity at 24 months.

Three large international randomised controlled trials also reported an increased risk in death when targeting oxygen saturation below 90%. The trials evaluated the effects of targeting an oxygen saturation level of 85 to 89% compared to a range of 91 to 95% on disability free survival for 2 years in 2488 infants born < 28 weeks.(Stenson 2013) Recruitment had to be stopped early when an analysis showed an increased rate of death in the low oxygen group at 36 weeks. (23.1% vs. 15.9%; relative risk in the lower-target group, 1.45; 95% confidence interval [CI], 1.15 to 1.84; P=0.002). Those in the lower-target group for oxygen saturation did have a reduced rate of retinopathy of prematurity (10.6% vs. 13.5%; relative risk, 0.79; 95% CI, 0.63 to 1.00; P=0.045). However, they also had an increased rate of necrotizing enterocolitis (10.4% vs. 8.0%; relative risk, 1.31; 95% CI, 1.02 to 1.68; P=0.04).

A systematic review and meta-analysis of 10 trials (Saugstad, 2011) concluded that “A low oxygen saturation approach reduces severe retinopathy of prematurity by 50%, i.e., from 20.9 to 9.5%, and bronchopulmonary dysplasia/lung problems by 25%, i.e., from 40.8 to 29.7%.”

http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=articleTop

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4016714/


Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. Neonatology 2011;100:1-8
http://www.karger.com/Article/Pdf/322001

http://www.nejm.org/doi/full/10.1056/NEJMoa1302298#t=articleTop


Evidence Level: I

Last amended September 2015
Last reviewed September 2015
This guideline has been prepared with reference to:


http://pediatrics.aappublications.org/content/118/5/2231.full.pdf+html

What is the evidence for the efficacy of non-pharmacological interventions?

A systematic literature review of 13 randomised trials and 2 meta-analyses (Cignacco, 2007) looked at the effects of non-nutritive sucking, music, swaddling, positioning, olfactory and multisensorial stimulation, kangaroo care and maternal touch. These had an observable positive effect on pulse rate, respiration and oxygen saturation, reduction of motor activity and excitation states following painful procedures. Validated pain assessment instruments were not employed in these studies, however, and further research was called for.

A Cochrane systematic review of 20 trials (Shah, 2012) found that distress measured by heart rate, crying time and two scoring systems (Douleur Aigue Nouveau-ne and Neonatal Facial Coding Score) was significantly reduced by breastfeeding or breast milk supplementation during painful procedures.

A double-blind prospective trial in 110 infants (Thyr, 2007) found that infants given 2 mL of 30% glucose after immunisation at 3, 5 and 12 months cried less than those given water (mean crying time reduced by 22, 62 and 52% respectively).

“Additional research is needed to fully understand the mechanism of action, optimal dose, and safety of repeated doses of oral sucrose in neonates” (Anon, 2006).

A meta-analysis of 20 RCTs involving 1380 infants and children between 1 month and 11 years of age (Chambers, 2009) found that breathing exercises, child-directed distraction, nurse-led distraction, and combined cognitive-behavioural interventions were effective in reducing the pain and distress associated with routine childhood immunisations.

A Cochrane systematic review of 57 studies involving 4,730 infants (Stevens, 2013) found that sucrose significantly reduced the duration of total crying time (seconds) [WMD -39 (95% CI -44 to 34), 88 neonates].

A Cochrane systematic review (Johnston, 2014) also investigated the pain relieving effect of skin-to-skin care (also known as Kangaroo Care). 19 studies involving 1594 infants were analysed and the authors concluded that “SSC appears to be effective, as measured by composite pain indicators and including both physiological and behavioural indicators, and safe for a single painful procedure such as a heel lance”


http://pediatrics.aappublications.org/content/118/5/2231.full.pdf+html


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Evidence Level: I

Last amended September 2015
Last reviewed September 2015
This guideline has been prepared with reference to the following:


Last amended July 2015
Last reviewed September 2015
What are the risk factors for parenteral nutrition-associated cholestasis (PNAC)?
A retrospective study in 62 premature infants (Hsieh, 2009) identified young gestational age, low birth body weight, more sepsis episodes, extended duration of parenteral nutrition and low energy intake during the 2nd and 3rd weeks of life as significant risk factors for PNAC.


Evidence Level: IV
PATENT DUCTUS ARTERIOSUS
Supporting information

Does ibuprofen have advantages over indomethacin?
A number of randomised trials (Su, 2008; Fakhraee, 2007; Lago, 2002; Supapannachart, 2002; Patel, 2000; van Overmeire, 2000; van Overmeire, 1997) have found ibuprofen to be as effective as indomethacin in closing PDA, whilst causing significantly fewer side-effects. A systematic review on the use of ibuprofen in PDA (Aranda, 2006) advises that, as ibuprofen does not reduce the incidence of intraventricular haemorrhage (IVH), indomethacin should be used on the first day of life if IVH prophylaxis is needed. Ibuprofen should then be used on the second and subsequent days of life. An updated Cochrane systematic review of 33 trials (Ohlsson, 2015) concluded that “Ibuprofen is as effective as indomethacin in closing a PDA and currently appears to be the drug of choice. Ibuprofen reduces the risk of NEC and transient renal insufficiency. Oro-gastric administration of ibuprofen appears as effective as iv administration.”

A prospective, randomised controlled study in 80 preterm infants (Erdeve, 2012) compared the efficacy and safety of oral vs intravenous ibuprofen for PDA closure. Closure rate was significantly higher with oral ibuprofen (83.3% vs 61.7%) after the first course of the treatment (p=0.04). Although the primary closure rate was marginally higher in the oral ibuprofen group, the need for a second course of ibuprofen during the whole hospitalisation was similar between groups: 11 of 36 in oral versus 15 of 34 in intravenous groups (p=0.24) because of a higher reopening rate in the oral group. In addition to no increase in side effects with oral ibuprofen use, the need for postnatal steroid use for chronic lung disease was significantly lower in the oral ibuprofen group (p=0.001).

As neither medical nor surgical interventions have been shown to influence mortality rates in PDA, it has been suggested (Nemerofsky, 2008; Bose, 2007; Cordero, 2007; van Overmeire, 2007; Vanhaesebrouck 2007) that a “wait and see” approach may result in more spontaneous closures and avoid potential adverse effects of treatment.


http://fn.bmj.com/content/92/6/F498.long

http://www.nature.com/jp/journal/v27/n3/full/7211659a.html

http://fn.bmj.com/content/97/4/F279.long


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http://fn.bmj.com/content/93/2/F94.long

http://www.nejm.org/doi/full/10.1056/NEJM200009073431001#t=articleTop

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720646/pdf/v076p0F179.pdf

Van Overmeire B. Patent ductus arteriosus: how aggressive should we be? Neonatology 2007;91:318

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675417/

Evidence Level: I

In premature infants with patent ductus arteriosus (PDA), does early treatment with indomethacin improve outcomes?

A randomised prospective trial in 127 infants (van Overmeire, 2001) compared early (day 3, n = 64) with late (day 7, n = 63) iv indomethacin treatment (3 x 0.2 mg/kg 12 hrly). PDA closure rate was higher in the “early” group at both 6 (73% vs 44%, p = .0008) and 9 days of age (91% vs 78%, p = .047). More adverse events (including death, lower urinary output, higher serum creatinine, necrotising enterocolitis, extension of haemorrhage and cystic leukomalacia) occurred in the “early” group, however.

Evidence on the duration of indomethacin therapy is unclear. A randomised trial in 61 premature infants (Tammela, 1999) compared 31 given a short course (3 doses:0.2/0.1/0.1 mg/kg in 24 hours) to 30 given a long course (0.1 mg/kg every 24 hours for 7 days). Primary PDA closure occurred more often in the short course group (94% vs 67%, p = .011), but the sustained closure rates were not significantly different (74% vs 60%). The short course patients suffered fewer adverse effects. The authors concluded that a prolonged, low-dosage regimen offered no advantage over a standard-dosage short course.

A similar conclusion was reached by a Cochrane review of 5 trials in a total of 431 infants (Herrera, 2007).

In a more recent retrospective cohort study (Quinn, 2002), 313 infants with PDA were divided, after an initial 3 doses of indomethacin into “clinically closed” (n = 214), “partially closed” (n = 69) and “nonresponder” (n = 30) groups. The 69 partial responders were then investigated, using a hierarchical regression model, to identify factors associated with permanent closure. Only gestational age and duration of indomethacin treatment were significantly and independently associated, with long course (6 dose rather than 3) recipients also having decreased incidence of symptomatic reopening (OR 0.19, 95% CI 0.04-0.96) and ductus ligation (OR 0.14, 95% CI 0.03-0.68).

A small retrospective study in 46 infants (Dumas de la Roque, 2002) found that omitting the initial bolus of indomethacin and giving 0.1 mg/kg daily until the ductus arteriosus was closed was as effective as the standard protocol. Initial success rate was 84.7%, of which 8.5% reopened. The mean cumulative dose of indomethacin was 0.35 mg/kg.

A multicentre, randomised controlled trial in 105 infants (Jegatheesan, 2008) found that increasing indomethacin concentrations above the levels achieved with a conventional dosing regimen had little effect on the rate of PDA closure and was associated with higher rates of retinopathy of prematurity and renal compromise.

A Cochrane review of 19 trials in 2872 infants (Fowlie, 2010) found the incidence of symptomatic PDA [RR 0.44, 95% CI 0.38 to 0.50] and PDA surgical ligation (RR 0.51, 95% CI 0.37,0.71) was significantly lower in infants treated with prophylactic indomethacin.

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Prophylactic indomethacin also significantly reduced the incidence of severe intraventricular haemorrhage (RR 0.66, 95% CI 0.53 to 0.82). Meta-analyses found no evidence of an effect on mortality (RR 0.96, 95% CI 0.81 to 1.12) or on a composite of death or severe neurodevelopmental disability assessed at 18 to 36 months old (RR 1.02, 95% CI 0.90, 1.15).


http://pediatrics.aappublications.org/content/110/1/e10.long


van Overmeire B. Patent ductus arteriosus: how aggressive should we be? Neonatology 2007;91:318


http://www.nejm.org/doi/full/10.1056/NEJM200009073431001#t=articleTop

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720646/pdf/v076p0F179.pdf

Evidence Level: I

Does the feeding regime need to be altered when the patient is on indometacin?
Early enteral nutrition has been supposed to be associated with an increased risk for necrotising enterocolitis (NEC) in preterm infants. The only study to investigate this in conjunction with indomethacin treatment, however, has found no such association (Bellander, 2003). 32 infants given indomethacin were matched with 32 controls; feeding volumes were the same in both groups. Two infants developed NEC in the treatment group, and two in the control group.
A cohort study by Kelleher analysed 5674 extremely low birth weight infants who survived beyond 12 hours after birth who were treated with indomethacin to determine whether early feeding vs non-early feeding was associated with an increased risk of intestinal perforation. The study authors found no statistically significant difference between the two groups (adjusted relative risk 0.74, 95% CI 0.49-1.11)


Evidence Level: IV

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If a duct fails to close after the first course of indometacin, are further courses indicated?
A study in 32 infants (Keller, 2003) showed that recurrent PDA rarely responds to further courses of indometacin if there is persistent Doppler evidence of ductus flow after completion of the initial course. All 9 of the infants in this category failed the second course of indometacin.

A prospective study in 41 infants (Kumar, 1997) found that an initial course of indometacin therapy was successful in 90% of cases. The recurrence rate after the first course was 3%. The success rate of therapy increased to 95% following a second course of indometacin.

Keller RL, Clyman RI. Persistent Doppler flow predicts lack of response to multiple courses of indomethacin in premature infants with recurrent patent ductus arteriosus. Pediatrics 2003;112:583-7


Evidence Level: IV

Last amended September 2015
Last reviewed September 2015
PERICARDIOCENTESIS
Supporting information

What is the incidence of pericardiocentesis attributable to central venous catheterisation?
The incidence has been reported as being between 0.07% and 2% of all peripherally-inserted central line placements (Pizzuti, 2010).

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821304/

Evidence Level: V

Last amended February 2011
Last reviewed September 2015
POLYCYthaemia
Supporting Information

Partial exchange transfusion slightly increases the risk of necrotising enterocolitis (NEC)?
A systematic review of 6 studies (Dempsey, 2006) found no evidence of long term benefit from partial exchange transfusion, but an increased risk of necrotising enterocolitis (RR 8.68; 95% CI 1.06 – 71.1).
A Cochrane systematic review of 4 studies (Ozek, 2010) concluded that: “There are no proven clinically significant short or long-term benefits of PET in polycythemic newborn infants who are clinically well or who have minor symptoms related to hyperviscosity. PET may lead to an increase in the risk of NEC.”

Dempsey EM, Barrington K. Short and long term outcomes following partial exchange transfusion in the polycythemic newborn: a systematic review. Arch Dis Child Fetal Neonatal Ed 2006;91:F2-6 [http://fn.bmj.com/content/91/1/F2.long]


Evidence Level: I

Sodium chloride 0.9% is the optimal dilutional fluid for exchange transfusion?
A systematic review of 6 studies in a total of 235 neonates (de Waal, 2006) found no clinically significant difference in effectiveness between plasma, 5% albumin, crystalloid solutions and sodium chloride 0.9%. As it is cheap, easily available, and carries no risk of transfusion-associated infection, the authors concluded that sodium chloride 0.9% was the best fluid to use for exchange transfusion.

de Waal KA, Baerts W, Offringa M. Systematic review of the optimal fluid for dilutional exchange transfusion in neonatal polycythemia. Arch Dis Child Fetal Neonatal Ed 2006;91:F7-F10 [http://fn.bmj.com/content/91/1/F7.long]

Evidence Level: II

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Inappropriate positioning may cause head molding?
A randomised trial in 126 infants presenting to a plagiocephaly clinic (Hutchison, 2010) compared positioning strategies with positioning plus the use of a Safe T SleepTM positioning wrap. Head shape was measured using a digital photographic technique, and neck function was assessed. The infants were followed up at home 3, 6 and 12 months later. There was no difference in head shape outcomes for the two treatment groups after 12 months of follow-up, with 42% of infants having head shapes in the normal range by that time. Eighty per cent of children showed good improvement. Those that had poor improvement were more likely to have both plagiocephaly and brachycephaly and to have presented later to clinic.


Evidence Level: I

Last amended September 2011
Last reviewed September 2015
Inhaled nitric oxide decreases the risk from PPH?
An historical cohort study compared 16 infants who received inhaled nitric oxide with 15 who were given 100% oxygen (Tanaka, 200). The incidence of cerebral palsy was 12.5% in the nitric oxide group, vs 46.7% in the oxygen group.


Evidence Level: IV

Magnesium sulphate is a suitable alternative for pulmonary vasodilation if nitric oxide is unavailable?
Approximately 30% of patients fail to respond to inhaled nitric oxide therapy (Shah, 2011). Although magnesium sulphate is a potent vasodilator, a Cochrane Systematic Review (Ho, 2007) found no relevant randomised or quasi-randomised trials looking at this question, and consequently declined to recommend the use of magnesium sulphate on the grounds of lack of evidence.

Ho JJ, Rasa G. Magnesium sulfate for persistent pulmonary hypertension of the newborn. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005588

Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Cochrane Database of Systematic Reviews 2011, Art. No.: CD005494

Evidence Level: V

Last amended July 2015
Last reviewed September 2015
Evidence pertinent to this guideline may be found in the supporting information for the following Neonatal Guidelines:

- Resuscitation
- Hypothermia
- Ventilation
- Cannulation
- Infection

Last reviewed September 2015
Dinoprostone is the recommended prostaglandin?
Madar (1995) found that following a survey of neonatal units in north of England, 50% used alprostadil and 50% dinoprostone but that on grounds of cost alone, dinoprostone was the recommended prostaglandin.
BNF for Children advises that either alpostadil or dinoprostone are effective at maintaining potency of ductus arteriosus in neonates.

BNF for Children. Drugs affecting the ductus arteriosus. 2013.


Evidence Level: V
Can pulmonary haemorrhage be caused by excessive fluids, coagulation abnormalities, or surfactant therapy?
Massive pulmonary haemorrhage may result from severe pulmonary oedema, one of the causes of which is reduced intravascular oncotic pressure associated with fluid overload (Bland, 1982). The role of coagulation abnormalities is “unclear”, although secondary disseminated intravascular coagulation is not uncommon (Greenough, 1999).
A Cochrane systematic review of RCTs infants (Soll, 2010) concluded that prophylactic treatment with synthetic surfactant increased the risk of pulmonary haemorrhage, metaanalysis showing a RR of 3.28 (95% CI 1.50-7.16).
Paradoxically, there is some suggestion that surfactant may be used to successfully treat pulmonary haemorrhage, although a Cochrane review (Aziz, 2012) found no randomised or quasi-randomised trials that would allow a firm conclusion to be reached.
A case-control study in 787 VLBW neonates treated with surfactant (Pandit, 1999) found that 94 (11.9%) developed pulmonary haemorrhage. In these infants, this was associated with increased risk of death (OR 7.8, 95% CI 2.6-28) and short term morbidity (OR 4.4, 95% CI 1.3-15.7) if moderate or severe.


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720955/pdf/v081p00F40.pdf


Evidence Level: V (fluids, coagulopathy); I (synthetic surfactant)

What is the most effective treatment for pulmonary haemorrhage?
Three studies, in 17 (Al Kharfy, 2004), 18 (Ko, 1998) and 6 (Pappas, 1996) infants found that high-frequency ventilation improved survival (59%, 72% and 100%, respectively, survived). In an earlier study in 6 infants (Trompeter, 1975), 4 (66%) survived after treatment with intermittent positive pressure ventilation.
A retrospective study in 30 infants (Dearborn, 2002) found chronic inflammation on lung biopsy in 5 patients who died. This, coupled with the finding that only 1 of the surviving infants had not received steroids, whereas the non-survivors had either not received steroids or had them stopped on hospitalisation, led the authors to recommend methylprednisolone, 1 mg/kg 6 hrly during hospitalisation and 1mg/kg daily thereafter. Treatment was continued until the BAL iron index dropped below 50/300, after which the steroids were tapered and finally stopped over a 4 week period.
A retrospective study in 42 infants (Bhandari, 1999) advised that “Large multicenter studies need to be done using standardized protocols for management of PH before any definite conclusion can be drawn” (about the most effective treatment).


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Evidence Level: IV

Can surfactant treatment be beneficial in pulmonary haemorrhage?

Paradoxically, although the risk of pulmonary haemorrhage increases slightly with any surfactant therapy (Raju, 1993), a small study in 15 neonates (Pandit, 1995) found that respiratory status (as measured by oxygenation index (OI)) improved following treatment with exogenous surfactant. Mean OI improved from 24.6 at 0-3 hours presurfactant to 8.6 at 3-6 hours postsurfactant (P < .001).

Case reports have also shown efficacy for surfactant treatment in term neonates (Kaneko, 2001) and older infants (Mikawa, 1994).


Pandit PB, Dunn MS, Colucci EA. Surfactant therapy in neonates with respiratory deterioration due to pulmonary haemorrhage. Pediatrics 1995;95:32-6


Evidence Level: IV

Last amended October 2012
Last updated September 2015
What are the benefits of this treatment for neonates with Hirschsprung's disease?
Coran (2000) reports how serial rectal irrigation helps decompress the bowel and prevent enterocolitis in patients with Hirschsprung's disease and that this should be the "initial approach in the care of the child".


Evidence Level: IV

Last amended August 2013
Last reviewed September 2015
What evidence is there that this approach is beneficial?
There is limited high quality evidence on stoma loss recycling in neonates. However, Wong (2004) reviewed 12 cases of premature neonates whose proximal bowel contents were re-fed into a mucous fistula. All patients achieved good weight gain after refeeding (18.9 +/- 2.9 g/d) with a reduction of parenteral nutrition requirements. All enterostomies were subsequently closed. 4 patients died of unrelated causes after reanastomosis and the remaining 8 were discharged. The authors found that it can prevent disuse atrophy in the distal loop and facilitate subsequent reanastomosis and that the increased absorptive function provided by the small bowel incorporated in the mucous fistula can reduce the requirement for total parenteral nutrition.

A review of 23 neonates (Haddock, 2015) undergoing mucous fistula refeeding at a hospital in Canada found that 4 patients had complications: 3 had perforation of the MF, 1 had bleeding, 4 patients died, with one death directly attributable to mucous fistula refeeding. As a result of these finding the hospital in question (British Columbia Children's Hospital) decided to place a moratorium on mucous fistula refeeding until any prospective studies are able to provide evidence that the procedure is safe.


Evidence Level: V

Last amended September 2015
Last reviewed September 2015
Most cases resolve if the underlying cause is addressed and supportive treatment is given?
A retrospective study in 119 infants (Wedekin, 2008) recorded a mortality rate of 37%, although causes of death were unrelated to kidney function. Renal function recovered completely in all surviving infants.
A small study in 16 infants with acute renal failure aged 2 to 35 days (Chevalier, 1984) found that 4 of the 8 infants with oliguria died, but all of the remaining 8 who were nonoliguric survived with kidney function intact.


http://ndt.oxfordjournals.org/content/23/5/1575.long

Evidence Level: IV

When treating severe hyponatraemia, what is the correct dosage of hypertonic saline (Sodium Chloride) to be used? (e.g NaCl 3% 4ml/kg over minimum of 15 mins vs 2-5ml/kg over 30-60 mins?)
The BNF for Children (2013), referring to sodium chloride administered intravenously, recommend that “if sodium chloride is required, the deficit should be corrected slowly to avoid the risk of osmotic demyelination syndrome; the rise in plasma-sodium concentration should be no more than 10 mmol/litre in 24 hours” for children.
Aside from this, there appears to be little other than anecdotal evidence for details on dosage levels for severe hyponatraemia in neonates. Gouyon & Guinard (2000) recommend for example that Sodium Chloride (5-8 ml/kg of a 3% solution) is slowly given IV over 2 -3 hours.

BNF For Children. Intravenous sodium. 2015.


Evidence Level: V
This guideline has been prepared with reference to the following:


http://www.cprguidelines.eu/assets/downloads/guidelines/S0300-9572(15)00341-X_main.pdf?


http://pediatrics.aappublications.org/content/126/5/e1400.full

Resuscitation Council (UK). Newborn life support. 2010

https://www.resus.org.uk/EasySiteWeb/GatewayLink.aspx?alId=811

Naloxone should not be administered to infants whose mothers abuse narcotics?
A single case study (Gibbs, 1989) recorded generalised convulsions unresponsive to diazepam in a naloxone-treated baby born to a heroin user maintained throughout her pregnancy on methadone. The authors concluded that, as convulsions due to neonatal abstinence syndrome do not appear until at least 48 hours after birth, the symptoms in this case were due to naloxone administration.


Evidence Level: V

Should resuscitation be carried out with 21% or 100% oxygen?
Guidelines from the Resuscitation Council (see above) give no direction on this question. A systematic review and meta-analysis of 10 studies in a total of 2,133 infants (Saugstad, 2008) found that those given 21% oxygen (n=1,082) had reduced mortality compared to those (n=1,051) given 100% oxygen (RR 0.69; 95% CI 0.54 – 0.88).

A systematic review of 2,011 infants from 7 controlled trials (Rabi, 2007) found a statistically significant reduction in mortality in the room air group at 1 week (OR 0.70, 95% CI 0.50 - 0.98) and at 1 month (OR 0.63, 95% CI 0.42 - 0.94).

A randomised study in 44 preterm infants (Ezaki, 2009) found reduced oxidative stress in the group given 21% oxygen, compared to the group given 100% oxygen. A meta-analysis of 8 studies in a total of 1,500 patients (Guay, 2011) concluded that “The literature is insufficient to make any statement regarding the superiority of oxygen or room air as the initial gas mixture for neonatal resuscitation.”

A RCT study involving preterm babies (n=88) found that a low oxygen strategy resulted in better respiratory outcomes than a high (100%) oxygen strategy (Kepadia, 2013).


Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2613494/


Evidence Level: I

Last amended October 2015
Last reviewed October 2015
RETINOPATHY OF PREMATURENESS (ROP)
Supporting information

This guideline has been prepared with reference to the following:


http://pediatrics.aappublications.org/content/131/1/189.full

“Comfort care techniques” reduce pain and anxiety associated with screening for ROP?
A randomised controlled trial in 40 infants (O’Sullivan, 2010) used swaddling in the control group (n=20), who also received 0.2 ml of sterile water given by mouth using a syringe and a soother. The intervention group (n=20) were also swaddled, and received 0.2 ml of sucrose 24% given by mouth using a syringe and a soother. The sucrose group had a significantly lower median Neonatal Pain, Agitation and Sedation Scale (N-PASS) score during ROP screening, initially following insertion of the speculum (6.5 vs 5, p=0.02) and subsequently during scleral indentation (9.5 vs 7.5, p=0.03). Fewer infants experienced episodes of desaturations or bradycardia in the intervention group (1 vs 4, p=0.18).
A systematic review of 8 studies (Sun, 2010) grouped the results according to intervention: oral sucrose (group 1), anaesthetic eye drops (group 2) and non-pharmacological measures (group 3). Pain was assessed by Premature Infant Pain Profile (PIPP). For group 1, the mean PIPP score with sucrose was 1.38 (WMD) (95% CI: 0.41-2.35) lower than that of placebo (p = 0.005). For group 2, one study showed a reduction of two points on the PIPP score with topical proparacaine, whereas another showed no benefit. For group 3, developmental care improved developmental scores and salivary cortisol in one study. The authors concluded that sucrose reduced pain during the eye examination, whereas the efficacy of proparacaine was not consistent. PIPP scores remained relatively high in all the studies; further research was required to delineate better pain reduction strategies.

http://fn.bmj.com/content/95/6/F419.long


Evidence Level: I

Last amended August 2013
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
When should term or preterm neonates with convulsions be treated with drugs (phenobarbitone, phenytoin, clonazepam or midazolam) and when should these be stopped?

The duration of convulsions or seizures in the neonate may be brief and the signs subtle, making it difficult to decide when drug treatment should be started and stopped. As a generalisation, most neonatologists treat if more than 3 brief seizures occur in an hour, or a single seizure lasts more than 3 minutes (Rennie, 1999).

Neonatal convulsions are resistant to most standard antiepileptic drugs (Sankar, 2005; Booth, 2004; Zupanc, 2003), with, for example, phenobarbitone being effective as a first-line treatment in around one-third of cases (Rennie, 2003). A study in 59 neonates comparing phenobarbitone and phenytoin (Painter, 1999) found that the two drugs were equally effective, but that each failed to control seizures in more than half of cases when administered alone. Failure is often associated with a significantly abnormal background EEG (Boylan, 2002).

Phenytoin as a second-line treatment is generally more effective than a benzodiazepine, although large evaluation studies are lacking (Rennie, 2003). Clonazepam is effective in stopping seizures in doses as low as 0.1 mg/kg (Andre, 1986).

Nasal midazolam stopped 122 of 125 seizures (98%) within 10 minutes (average 3.6 min) in a small study involving 26 children both in and out of hospital (Jeannet, 1999). In another study, in 6 neonates whose convulsions were refractory to high-dose phenobarbitone and phenytoin (Sheth, 1996), midazolam controlled the seizures in all 6 within 1 hour.

In a small retrospective study (Brod, 1988), a normal EEG was found to be a reliable predictor for discontinuing drug treatment in 18 of 22 term infants and 9 of 10 premature infants. As long-term use of phenobarbitone is associated with impaired cognitive function in infants and toddlers, and the risk of recurrent seizures is less than 10% in the absence of neurologic damage, early discontinuation of treatment is advisable (Hellstrom, 1995; Gal, 1985; Labrecque, 1984).

Continuing evidence from animal studies confirms that increased apoptotic neurodegeneration occurs in the developing brain after exposure to phenytoin and benzodiazepines as well as phenobarbitone (Rennie, 2007).


Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
http://www.nejm.org/doi/full/10.1056/NEJM199908123410704#t=articleTop


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675465/

Sankar R, Painter MJ. Neonatal seizures: after all these years we still love what doesn't work. Neurology 2005;64:776-7


Zupanc ML. Infantile spasms. Expert Opin Pharmacother 2003;4:2039-48

Evidence Level: IV

Last amended October 2007
Last reviewed September 2015
Samples should be placed into a culture medium bottle immediately?
This is advised as “best practice”, but if unavailable, viral culture medium or normal saline in a sterile container may be used (Chakrapani, 2001).

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721249/pdf/v084p0F205.pdf

Evidence Level: V

Last amended July 2011
Last reviewed September 2015
SKIN CARE OF THE NEONATE
Supporting information

This guideline has been prepared with reference to the following:


Frequent bathing is not recommended?
A randomised trial in 53 premature infants (Quinn, 2005) compared bathing every other day (n=28) to bathing every 4th day (n=25). No statistically significant difference was noted in the skin flora count of either group and none of the babies developed infections. The authors concluded that bathing every 4th day was adequate and safe.


Evidence Level: II

The use of antibiotic ointment to treat nappy dermatitis should be avoided?
A Cochrane systematic review of 4 RCTs (Conner, 2003) found that infants treated with prophylactic topical ointment were at increased risk of coagulase negative staphylococcal infection (typical RR 1.31; 95% CI 1.02 - 1.70; typical risk difference 0.04; 95% CI 0.00 - 0.08); and any nosocomial infection (typical RR 1.20; 95% CI 1.00 - 1.43; typical risk difference 0.05; 95% CI 0.00 - 0.09).


Evidence Level: I

Gestational Cut-off for use of Electro Cardio leads on babies is <26 weeks gestation?
Insufficient evidence found for any cut-off period.

Last amended July 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
SUDDEN COLLAPSE IN FIRST WEEK OF LIFE
Supporting information

This guideline has been prepared with reference to the following:


What risk factors are associated with Sudden Unexpected Postnatal Collapse (SUPC) in healthy infants?
A case controlled study (Pejovic 2013) of all live born infants during a 30 month period in 5 major delivery wards in Stockholm found that in 26 cases of SUPC in healthy babies, 15 of the 26 children were found in a prone position, during skin-to-skin contact, 18 were offspring of first time mothers, and 13 occurred during unsupervised breastfeeding at <2 h of age.


Evidence Level: IV

Last Updated August 2013
Last reviewed September 2015
SURFACTANT REPLACEMENT THERAPY
Supporting information

This guideline has been prepared with reference to the following:

British Association for Perinatal Medicine. Guidelines for surfactant administration


Does the routine administration of antenatal steroids impact on the need for prophylactic surfactant?
A placebo-controlled randomised double-blind study in 157 pregnant women (Kari, 1994) found that dexamethasone 6 mg 4 times at 12-hour intervals resulted in a lower incidence of RDS (44% vs 79%, P<0.01), lower requirement for surfactant (22% vs 53%, P<.01), and shorter duration of ventilatory support (2.0 days vs 5.3 days, P<.05) and oxygen therapy (2.0 days vs 7.0 days, P<.01) compared to the placebo group. Mortality was also lower (6 vs 9, P<.05).
An earlier retrospective study using data from 2 randomised trials in a total of 1223 infants came to similar conclusions (Jobe, 1993).

Evidence Level: II

What surfactant preparations are recommended?
Both animal derived surfactant extracts and protein free synthetic surfactant extracts are effective in the treatment and prevention of respiratory distress syndrome. Comparative trials demonstrate greater early improvement in the requirement for ventilator support, fewer pneumothoraces (RR 0.65, 95% CI 0.55 to 0.77), and fewer deaths (RR 0.89, 95% CI 0.79 to 0.99) associated with animal derived surfactant extract treatment. Animal derived surfactant may be associated with an increase in necrotizing enterocolitis (RR 1.38, 95% CI 1.08 to 1.76) and intraventricular hemorrhage (RR 1.07, 95% CI 0.99 to 1.15), though the more serious hemorrhages (Grade 3 and 4) are not increased. Despite these concerns, animal derived surfactant extracts would seem to be the more desirable choice when compared to other available protein free synthetic surfactants.


Evidence Level: I

What advantages and disadvantages does surfactant have?
The benefits of surfactant administration (particularly natural preparations as opposed to synthetic) have been demonstrated in several Cochrane reviews (Stevens, 2007; Bahadue 2012; Soll 1997). A systematic review of 13 RCTs in a total of 2218 treated and 2090 control infants (Sinn, 2002) found a lower rate of mild disability in the treated group at follow-up at 1 year (OR

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0.79; 95% CI 0.66-0.95). The treated group also showed a reduction in combined adverse outcome (death or severe disability) at 1 year (OR 0.8; 95% CI 0.72-0.89). Surfactant treatment has, however, failed to have a significant impact on the incidence of chronic lung disease in survivors (Ainsworth, 2002).

Recorded side effects of surfactant treatment include increased cerebral blood flow velocity, which, due to the lack of cerebral vascular autoregulation in many sick preterm infants, can lead to intraventricular haemorrhage or periventricular leukomalacia. Evidence for this is, however, equivocal (Hentsche, 2002).


Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. The Cochrane Database of Systematic Reviews 1997, Issue 4. Art. No.: CD000511 (Assessed as up-to-date: 7 MAR 2010)


Evidence Level: I

How many doses of surfactant are recommended?
An updated Cochrane systematic review (Soll, 2009) of 2 RCTs comparing single with multiple doses of surfactant showed a reduction in the risk of pneumothorax (RR 0.51, 95% CI 0.30-0.88) and a trend towards a reduction in mortality (RR 0.63, 95% CI 0.39-1.02) associated with the use of multiple doses. The review also identified an additional study of multiple vs. single dose synthetic surfactant in infants at high risk of respiratory distress syndrome. This reported a decrease in necrotizing enterocolitis (relative risk 0.20, 95% CI 0.08, 0.51; risk difference-0.05, 95% CI -0.07, -0.02) and mortality (relative risk 0.56, 95% CI 0.39, 0.81; risk difference-0.07, 95% CI -0.12, -0.03)

The OSIRIS (Open Study of Infants at High Risk of or with Respiratory Insufficiency – the role of Surfactant) trial (Anon, 1992) randomised 2690 infants to either 2 doses of surfactant 12 hours apart, or the option of third and fourth doses at 12-36 hour intervals if signs of RDS persisted or recurred. 4067 infants who later developed RDS were also added, giving a total of 3376 infants allocated up to four doses (45% of whom received more than two). No evidence of improved outcomes associated with more than 2 doses was found.


Soll R, Özek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2009, Issue 1

Evidence Level: I
SYNCHRONOUS POSITIVE PRESSURE VENTILATION (SIPPV)

Supporting information

Is SIPPV superior to conventional mechanical ventilation (CMV)?
A Cochrane systematic review of 14 trials (Greenough, 2008) demonstrated that high-frequency positive pressure ventilation (HFPPV) compared to CMV was associated with a reduction in the risk of air leak (typical RR for pneumothorax was 0.69, 95% CI 0.51, 0.93). Assist control ventilation (ACV) or synchronous intermittent mandatory ventilation (SIMV) compared to CMV was associated with a shorter duration of ventilation (weighted mean difference -34.8 hours, 95% CI -62.1, -7.4). ACV compared to SIMV was associated with a trend to a shorter duration of weaning (weighted mean difference -42.4 hours, 95% CI -94.4, 9.6). Neither HFPPV nor triggered ventilation was associated with a significant reduction in the incidence of bronchopulmonary dysplasia. There was a non-significant trend towards a lower mortality rate using HFPPV vs. CMV and a non-significant trend towards a higher mortality rate using triggered ventilation vs. CMV. No disadvantage of HFPPV or triggered ventilation was noted regarding other outcomes. Since the last review, two new patient triggered modes have been included: pressure regulated volume control ventilation (PRVCV) and SIMV plus pressure support. Each of these methods of ventilation has only been tested in single randomised trials with no significant advantages in important outcomes. In none of the trials was complex respiratory monitoring undertaken and thus it is not possible to conclude that the mechanism of producing those benefits is by provocation of synchronized ventilation. Further trials are needed to determine whether synchronized ventilation is associated with other benefits.


Evidence Level: I

Last amended January 2011
Last reviewed September 2015
Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests are useful for risk grouping?

“The reported sensitivity of VDRL/RPR tests for primary syphilis is 60–90% and higher for secondary syphilis. They are associated with high rate of false positive results seen in pregnancy, patients with malignancy, autoimmune conditions, EBV infection and hepatitis” (Doroshenko, 2006).


Evidence Level: V
This guideline has been prepared with reference to the following:

NICE. Screening for latent tuberculosis in neonates who have been in close contact with people with sputum-smear-positive tuberculosis [pathway] from NICE Clinical Guideline Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. 2011. NICE.


Last amended August 2015
Last reviewed September 2015
Severe thrombocytopenia is uncommon?
Although mild thrombocytopenia is common (20% - 35% of all babies admitted to the neonatal intensive care unit), only 2.5% - 5% of these will go on to develop the severe form (Ferrer-Marín, 2010).
A descriptive, population-based UK national study (Knight, 2011) identified 173 cases of severe fetomaternal alloimmune thrombocytopenia (FMAIT) between October 2006 and September 2008. An extra 20 cases were estimated from capture-recapture analysis, giving an estimated incidence of clinically detected FMAIT of 12.4 cases per 100000 total births (95% CI 10.7 to 14.3). Fifty-two cases (30%) were known at the start of pregnancy; 120 (70%) were unknown (n=115) or unrecognized (n=5). Unknown cases were more likely to experience a haemorrhagic complication (67% vs 5%) (P<0.001) and more likely to have an intracranial haemorrhage (20% vs 4%) (P=0.014) than known cases receiving antenatal management.

A systematic review by Knight et al. (2014) of 6 prospective studies found 59,425 newborns screened for severe thrombocytopenia, of which 89 (0.15%) tested positive.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2934854/

http://pediatrics.aappublications.org/content/early/2014/02/25/peds.2013-3320.full.pdf+html


Evidence Level: III

The suggested triggers for platelet transfusion are appropriate?
“The existing evidence to establish platelet transfusion triggers in neonates is very limited, but it suggests that transfusing platelets to non-bleeding neonates with platelet counts >50 x 10(9)/L does not decrease the risk of intraventricular hemorrhage (IVH), and that 30 x 10(9)/L might be an adequate threshold for stable non-bleeding neonates. However, adequately powered multi-center studies are needed to conclusively establish the safety of any given set of neonatal transfusion guidelines” (Sola-Visner, 2008).


Evidence Level: V

Last amended September 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
How do measurements obtained by transcutaneous monitoring compare with those obtained by blood sampling?

A study designed to assess the quality of transcutaneous CO2 data by comparing it to the "gold standard" blood CO2 data (Hejlesen, 2009) found that, for low transcutaneous CO2, the error was relatively high and in most cases the true CO2, represented by the blood CO2, was higher than the measured transcutaneous CO2. The opposite was the case for high transcutaneous CO2.

In contrast, Sandberg (2011) compared transcutaneous (Tc) monitoring of Blood gases (PCO2 and PO2) with simultaneous arterial monitoring of PCO2 and PO2 in 46 newborn infants, (including extremely low birth weight infants), in the neonatal intensive care unit during stable infant conditions. 60 measurements were taken in infants with median (range) birth weight of 0.93 (0.53-4.7) kg and at median (range) age of 8.5 (1-44) days. Comparison of measurements was performed using Bland-Altman plots, and the mean (95% CI) of the difference was calculated. There was good agreement between TcPO(2)/TcPCO(2) and corresponding arterial measurements. The mean (95% CI) difference in PO(2) (TcPO(2)-aPO(2)) was 0.3 (-0.2-0.9) kPa, and the corresponding difference in PCO(2) (TcPCO(2)-aPCO(2)) was 0.4 (0.03-0.8, p < 0.05) kPa. Some differences were related to body weight, age and oxygen requirement, but these differences were small.


Evidence Level: IV

Last amended August 2013
Last reviewed September 2015
TRANSFUSIONS OF RED BLOOD CELLS
Supporting information

This guideline has been prepared with reference to the following:

TSO.

http://www.transfusionguidelines.org.uk/transfusion-handbook/10-effective-transfusion-in-
paediatric-practice/10-2-neonatal-transfusion

Blood should be administered at the rate of 5 mL/kg/hr?
This is the recommendation given (unreferenced) in the British Society of Haematology’s
consensus guidelines (see reference above).
In a study of 78 care givers of packed red blood cell (RBC) transfusions (Kasat, 2011), 18
patients (23%) were transfused based on guidelines, 36 (46%) based on care givers’
perception and 24 (31%) based on both. Neonates transfused based on guidelines alone
were more likely to have received the transfusion in the first week of life, had a higher pre-
transfusion haematocrit, were less symptomatic and had a higher trend to require mechanical
ventilation. Neonates transfused based on caregivers’ perception were more likely to be on
non-invasive ventilatory support and were more symptomatic. Neonates who improved after a
transfusion had a lower pre-transfusion haematocrit (p=0.02), were more symptomatic
(p=0.01) and were more likely to be on non-invasive ventilatory support (p=0.002) when
compared to the group without a clinical improvement. The group without improvement had
an increase in oxygen requirement (+2.8+/−6.4) after the transfusion (p=0.0004). Tachycardia
was the most sensitive predictor of a benefit from packed RBC transfusion (OR 6.48;
p=0.005). The authors concluded that guidelines on when to transfuse stable growing
neonates with packed RBC should be re-evaluated to include more care giver judgement
and perhaps be more restrictive for critically ill neonates.
A systematic review (Venkatesh 2012) reported on two small scale RCTs which compared
neonates receiving transfusions at a high volume (20 ml/kg) vs. standard volume (10 ml/kg)
differences in mesenteric blood flow in babies. One of these trials reported on mortality and
described no differences between the two arms (Wong et al, 2005). Neither trial reported on
Chronic lung disease or neurodevelopmental outcome.

Kasat K, Hendricks-Munoz KD, Mally PV. Neonatal red blood cell transfusions: searching for better
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021402/

Venkatesh V, Khan R, Curley A et al. The safety and efficacy of red cell transfusions in neonates: a

Evidence Level: V

Last amended August 2013
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhrs.nhs.uk
Does the duration of neonatal transport have an impact on mortality?
A cohort study involving 4,966 neonates (Mori, 2007) found that those transported for > 90 min experienced more than twice the mortality of those transported for between 30 and 59 min (RR 2.26; 95% CI 1.26 - 4.04).


Evidence Level: III

Last amended September 2007
Last reviewed September 2015
Prophylactic antibiotics are not needed to prevent infection?
A Cochrane review (Inglis, 2007) found two quasi-randomised trials relevant to this question, but both were of poor quality and their results did not merit pooling. The authors concluded that there was insufficient evidence to either support or refute the use of prophylactic antibiotics in this situation.


Evidence Level: V

How should catheter insertion length be estimated in very low birth weight (VLBW) infants?
A randomised study (Wright, 2008) compared infants <1500g catheterized according to a standard practice nomogram with another group whose catheters were placed according to a new formula (insertional length in cm = 4 x birthweight in kg + 7); a total of 74 insertions. There was a significant increase in correctly-placed catheters with the new formula (p = .003). Overinsertion, a problem in VLBW infants when the standard nomogram was used, was significantly less likely (p < .0001).


Evidence Level: II
Are alcohol swabs useful for disinfection of the skin?

Only one study (Malathi, 1993) on skin disinfection in the neonate was identified. This was carried out in two parts. Initially, 25 peripheral intravascular catheter sites were sampled for the presence of bacteria following routine cannula insertion. Bacterial counts > 100 colony forming units/cm² were found in 10 (40%) sites.

In the second part of the study, sampling was repeated following cleansing with various durations of exposure to chlorhexidine/alcohol swabs or povidone iodine. The overall mean reduction in bacterial colony count after cleansing ranged from 90-99%, with skin sterilization achieved in 33-92% of cases.

Two consecutive 10 second exposures were found to be significantly more effective than a single 10 second wipe. A longer 30 second exposure was also more effective than shorter exposure times.

No difference was seen between those sites cleaned with povidone iodine or chlorhexidine/alcohol. The authors concluded that a brief wipe with a swab was not sufficient to achieve adequate skin disinfection and that either two consecutive cleanings or a longer duration of a single cleaning was needed.

No studies were identified that compared skin disinfection with no action in the prevention of catheter related sepsis.


http://adc.bmj.com/content/69/3_Spec_No/312.full.pdf+html

Evidence Level: IV
What is the incidence of brachial plexus injury?
A prospective study in 30,574 births (Backe, 2008) identified 91 brachial plexus injuries. The incidence was 0.3% and the recovery rate 84%, resulting in 0.5 permanent injuries per 1,000 births.


Evidence Level: IV
In males with posterior urethral valves diagnosed antenatally, can intrauterine drainage procedures provide benefit?

A review on posterior urethral valves (PUV) (Dinneen, 1996) states: “PUV may be one of the conditions suitable for intrauterine intervention, but the timing and type of intervention has yet to be determined”.

It is possible that renal dysplasia may be irreversible by the time it is first detected on ultrasound (Thomas, 1989), and even successful drainage procedures may not return bladder pressures to normal or completely resolve abnormalities of ureteral drainage (Gonzales, 1990).

In the absence of any controlled trials, the evidence for successful prenatal intervention in PUV rests on a small number of case reports (Ropacka, 2001; Quintero, 2000; Shimada, 1998; Nguyen, 1996; Fournie, 1983).


Evidence Level: V

Is there a level of antenatal renal dilatation at a particular stage in pregnancy that is strongly associated with ureteric reflux, irrespective of postnatal scan results?

A study in 111 infants with isolated antenatal hydronephrosis (Phan, 2003) found no correlation between the degree of renal dilatation and the presence or severity of vesicoureteral reflux (VUR). VUR was detected in 16 infants, 10 of whom had mild or absent dilatation.

Another study, in 157 children under 2 years with a family history of VUR in a first-degree relative (Anderson, 2003), found that after 30 weeks gestation, a 4 mm renal pelvis had a sensitivity of 33% and a PPV of 32%. The sensitivity was higher for reflux grades 4 and 5 (75%) than for grades 1-3 (17%). The authors concluded that fetal renal pelvic diameter had a low sensitivity and poor predictive value for detecting VUR, but that this was slightly improved after 30 weeks gestation.

A study of 1,301 fetal renal pelvis measurements over a period of 15 years (Scott, 2001) also found these poorly predictive of VUR, but recommended further investigation of cases >/= 7 mm at 18 weeks gestation.

A prospective study in 257 neonates with prenatally detected renal pelvic dilatation (Coplen, 2006) found that a threshold of 15 mm correctly discriminated obstruction in at least 80% of cases with a sensitivity of 73% and a specificity of 82%.

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Evidence Level: V

Children with unilateral multicystic kidney are at increased risk of reflux in the non-affected kidney?
In a series of 48 infants with unilateral multicystic kidney (Zerin, 1998), 9 patients (19%) had VUR into the contralateral kidney. Another series of 59 children (Karmazyn, 1997) found VUR to be the most common concurrent abnormality, detected in 15 patients (25%). Three of seven patients (42%) had VUR in a small retrospective Japanese study (Kaneko, 1995). In the largest retrospective study to date (Eckoldt, 2003), 11 of 110 (12.5%) patients were affected.
A retrospective cohort study in 75 children (Miller, 2004) found contralateral VUR in 19 cases (26.4%), 9 of which were low grade (I – II).

Ylinen E, Ala HM, Wikstrom S. Risk of renal scarring in vesicoureteral reflux detected either antenatally or during the neonatal period. Urology 2003;61:1238-42

Evidence Level: V

Children with unilateral multicystic kidney are at increased risk of reflux in the non-affected kidney?
Evidence Level: IV

What degree of postnatal renal dilatation in a kidney with pelvi-ureteric junction obstruction (PUJO) necessitates surgical correction?
In a retrospective study of 44 children with a prenatal diagnosis of PUJO (Chertin, 2002), 35 (77%) had severe dilatation of the renal pelvis by >3 cm. Despite this, pyeloplasty was delayed until the mean deterioration in renal function was 8.2%, and renal function returned to initial levels in 81% of patients 6-12 months after surgery. The authors concluded that expectant management was prudent and might spare some children unnecessary surgery. Views on surgical correction range from the extremely enthusiastic (King, 1984) to the extremely cautious (Koff, 1992), with caution generally having the greater support: “A large number of patients with pelvic dilatation are free from other symptoms” (Josephson, 1997). Degree of dilatation does not seem to be a reliable indicator of obstruction and renal damage.


Evidence Level: V

How safe are isotope scans in relation to radiation risk?
Any exposure to radiation carries some risk of somatic or genetic damage and there is no threshold or safe dose (Payne, 1975). Findings from both animal and human studies on risk at low doses are, however, inconclusive due to statistical limitations (Ron, 2003; Hall, 2000; Swartz, 1978).

Hall EJ. Radiation, the two-edged sword: cancer risks at high and low doses. Cancer J 2000;6:343-50


Swartz HM, Reichling BA. The safety of x-ray examination or radioisotope scan. JAMA 1978;239:2031-2

Evidence Level: V

Should babies with two vessels in umbilical cord or external ear abnormalities have renal ultrasound scans to exclude renal abnormality also?

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In the largest study of infants with isolated single umbilical artery (SUA) (Bourke, 1993), 8 of 112 (7.1%) infants with the condition were found on renal ultrasonography to have significant renal abnormalities, including 5 (4.5%) with VUR. The authors concluded that all infants with SUA should have a renal ultrasound scan.

A retrospective study in 52 infants with SUA (Doornebal, 2007) found abnormalities in 5 infants (10.4%) on renal ultrasound. A relative subpelvine stenosis was detected in one infant, and the remaining four had mild hydronephrosis without further consequences. The authors concluded that it was unnecessary to perform renal ultrasound in infants with SUA.

In a retrospective series of 42 patients with external ear abnormalities (Wang, 2001), renal ultrasound revealed anomalies in 12 (29%). The authors recommended that renal ultrasound should be performed in infants with isolated preauricular pits, cup ears, or any other ear anomaly accompanied by 1 or more of the following: other malformations or dysmorphic features, family history of deafness, auricular malformations or maternal history of gestational diabetes. Renal ultrasound was considered unnecessary in the absence of these conditions. Renal abnormalities are also more common in infants with isolated preauricular tags (Kohelet, 2000) and preauricular sinuses (Leung, 1992).

A study in 96 infants with minor ear anomalies (85% of which were preauricular tags) found that, of 91 (95%) undergoing renal sonography, only one infant (1.1%, 95% CI 0.03 – 5.9) had transient unilateral pyelectasia. The authors concluded that routine renal imaging was not warranted in infants with minor ear abnormalities unless accompanied by other systemic malformations (Deshpande, 2006).


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672645/


http://pediatrics.aappublications.org/content/105/5/e61.long


http://pediatrics.aappublications.org/content/108/2/e32.long

Evidence Level: IV

Children with a horseshoe, duplex, or pelvic kidney are at increased risk of other renal abnormalities?

Of pregnancies in which a fetal renal anomaly has been detected, 19.6% fail to produce a surviving child, often because of co-existing abnormalities in the urinary tract or elsewhere (Scott, 2002). A study of 560 deaths among 2,857 infants with urinary tract abnormalities between 1984 and 2000 (Scott, 2002) revealed that a renal anomaly was the cause of death in 323 (57.7%) cases. 209 deaths were caused by anomalies in other systems but with a renal anomaly present, of which 36 (54.5%) had a horseshoe kidney.

In a study of 52 children with horseshoe kidney (Cascio, 2002), more than half (52%) also had VUR or ureteropelvic junction obstruction.

In a retrospective study comparing 19 foetuses with horseshoe kidney and 20 normal controls (Cho, 2005), 15 of the 19 with horseshoe kidney had no other abnormality. However, 4 (21%) had severe complex abnormalities which in 3 cases were associated with trisomy 18. Many case reports attest to the increased risk of associated abnormalities in duplex (Cheng, 1997; Rossleih, 1996; Bellah, 1995) and in pelvic kidneys (Hill, 1994; Takeuchi, 1994; Donahoe, 1980).

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Scott JE. Fetal, perinatal, and infant death with congenital renal anomaly. Arch Dis Child 2002;87:114-7 http://adc.bmj.com/content/87/2/114.long


Evidence Level: IV

Is cephalexin the most appropriate antibiotic to be given prophylactically to infants with obstructed or refluxing kidneys?
A randomised trial in 236 patients (Garin, 2006) comparing antibiotic prophylaxis with a variety of third generation cephalosporins versus no treatment found no statistically significant differences between the two groups at one-year follow-up. A commentary on this study (Wald, 2006) points out that patients with VUR grades higher than III may produce different results, and that further research in these patients is necessary. Garin EH, Olavarria F, Nieto VG, et al. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicentre, randomized, controlled study. Pediatrics 2006;117:626-32


Evidence Level: II

Last amended October 2007
Last reviewed September 2015
This guideline has been prepared with reference to the following:


Babies whose mothers develop chickenpox from < 6 days pre-delivery up to 14 days after delivery should be given zoster immune globulin (VZIG)?

The RCOG guidelines recommend that if birth occurs within the 7-day period following the onset of the maternal rash, or if the mother develops the chickenpox rash within the 7-day period after birth, the neonate should be given VZIG. The infant should be monitored for signs of infection until 28 days after the onset of maternal infection. Australian guidelines (Heuchan, 2001) differ in that VZIG is recommended from 7 days before or up to 28 days after delivery. These Australian recommendations no longer agree with UK Department of Health advice (DoH, 2013) which states that “VZIG is not usually required for infants born more than seven days after the onset of maternal chickenpox or whose mothers develop Herpes zoster (shingles) before or after delivery, as these infants will have maternal antibody.”

Infants born to mothers with onset of chickenpox 4 days before to 2 days after delivery are at increased risk of severe or fatal varicella, despite the use of VZIG (Reynolds, 1999).

Evidence Level: V

Last amended May 2015
Last reviewed September 2015

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
Venepuncture is superior to heel prick for blood sampling in neonates?

A Cochrane systematic review of 6 trials in 478 infants (Shah, 2011) found a statistically significantly lower pain scores for venepuncture compared to heel prick. Additionally, there was less need for repeated skin puncture when venepuncture was used (NNT=3).

Shah V, Ohlsson A. Venepuncture versus heel lance for blood sampling in term neonates. Cochrane Database of Systematic Reviews 2011, Art. No.: CD001452

Evidence Level: I

Sucrose may be used for analgesia?

A double-blind trial in 304 newborns (Dilen, 2010) compared four selected 2 mL solutions (10, 20, 30% glucose, and placebo) administered orally before venepuncture. Pain was scored using a validated pain scale (the "Leuven Pain Scale"). A significantly lower average pain score was noted in the 30% glucose group (3.99) when compared with the placebo group (8.43). The average pain scores in the 20% glucose group (5.26) and the 10% glucose group (5.92) were also significantly lower than those in the placebo group.

A double-blind trial of 330 healthy term newborns (Taddio 2011) found that sucrose was more effective than liposomal lidocaine for reducing pain during venepuncture. They also found that the addition when liposomal lidocaine and sucrose were used in combination did not confer any benefits to sucrose alone. Before venipuncture, neonates received (1) 1 g of liposomal lidocaine cream topically, (2) 2 mL of 24% sucrose solution orally, or (3) sucrose and liposomal lidocaine. The facial grimacing score (0-100) was used to assess pain. Facial grimacing scores were lower in the sucrose group compared with those in the liposomal lidocaine group (mean difference: -27 [95% confidence interval (CI): -36 to -19; P < .001]) and for the sucrose plus liposomal lidocaine group compared with those in the liposomal lidocaine group (mean difference: -23 [95% CI: -31 to -14]; P < .001). The sucrose and sucrose plus liposomal lidocaine groups did not differ (mean difference: -5 [95% CI: -13 to 4]; P = .3).


Evidence Level: II

Not found an answer to your question? Contact bedsideclinicalguidelines@uhns.nhs.uk
All babies should be offered vitamin K prophylaxis?
A Cochrane Review (Puckett, 2000) of two RCTs in 385 newborns found that a single dose (1.0 mg) of intramuscular vitamin K after birth was effective in the prevention of classic HDN (Haemorrhagic Disease of the Newborn).

Puckett RM, Offringa M. Prophylactic vitamin K for vitamin K deficiency bleeding in neonates. Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD002776

Evidence Level: I

Last amended September 2007
Last reviewed September 2015
Volume targeted is more effective than pressure limited ventilation for preterm infants?

A Cochrane Review (Wheeler 2010) of 9 trials found that, compared with pressure-limited ventilation, VT ventilation significantly reduces rates of death and bronchopulmonary dysplasia, pneumothorax, hypocarbia and severe cranial ultrasound abnormalities.

A systematic review of 18 RCTs and quasi-RCTS (Peng, 2014) found that volume targeted ventilation (VTV) did not significantly (statistical) reduce the number of deaths when compared with pressure-limited ventilation (RR 0.73, 93% CI 0.51 to 1.05). The use of VTV did though result in a reduction in the incidence of bronchopulmonary dysplasia (RR 0.61, 95% CI 0.46 to 0.82) and duration of mechanical ventilation (mean difference (MD) -2.0 days, 95% CI -3.14 to -0.86).

VTV modes also resulted in reductions in intraventricular haemorrhage (IVH) (RR 0.65, 95% CI 0.42 to 0.99), grade 3/4 IVH (RR 0.55, 95% CI 0.39 to 0.79), periventricular leukomalacia (PVL) (RR 0.33, 95% CI 0.15 to 0.72), pneumothorax (RR 0.52, 95% CI 0.29 to 0.93), failure of primary mode of ventilation (RR 0.64, 95% CI 0.43 to 0.94), hypocarbia (RR 0.56, 95% CI 0.33 to 0.96), mean airway pressure (MD -0.54 cmH2O, 95% CI -1.05 to -0.02) and days of supplemental oxygen administration (MD -1.68 days, 95% CI -2.47 to -0.88).


Evidence Level: I