NEONATAL GUIDELINES 2017–19
SUPPORTING EVIDENCE

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ABSTINENCE SYNDROME
Supporting information

This guideline has been prepared with reference to the following:

Hudak ML, Tan RC. Neonatal drug withdrawal. Pediatrics 2012;129:e540-60

http://pediatrics.aappublications.org/content/129/2/e540.full

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 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).

Anon. Neonatal drug withdrawal. American Academy of Pediatrics. Committee on Drugs. Pediatrics 1998;101:1079-88
http://pediatrics.aappublications.org/content/101/6/1079.full

Coyle MG, Ferguson A, Lagasse L, et al. Diluted tincture of opium (DTO) and phenobarbitol versus DTO alone for neonatal opiate withdrawal in term infants. J Pediatr 2002;140:561-4

Ebner N, Rohrmeister K, Winklbaur B, et al. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. Drug Alcohol Depend 2007;87:131-8

Etzersdorfer P, Fischer G, Eder H, et al. Comparison of morphine and methadone maintenance in pregnant opiate addicts. NIDA Research Monograph Series, 1997;178:343

Fischer G, Jagsch R, Eder H, et al. Comparison of methadone and slow-release morphine maintenance in pregnant addicts. Addiction 1999;94:231-9

Lee TS. Slow-release morphine was not more effective than methadone in reducing neonatal abstinence syndrome. West J Med 2000;172:26
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1070715/pdf/wjm17200026.pdf

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://bnfc.nice.org.uk/drug/morphine.html

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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
  https://bnfc.nice.org.uk/drug/phenobarbital.html

Last amended May 2012
Last reviewed November 2017

ADMISSION TO NEONATAL UNIT
Supporting information

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

https://www.bapm.org/sites/default/files/files/Service_Standards%20for%20Hospitals_Final_Aug2010.pdf

Last amended August 2013
Last reviewed November 2017

ANO-RECTAL MALFORMATION
Supporting information

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-imflammatory) 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.

Kallen B, Norstedt Wikner B. Maternal hypothyroidism in early pregnancy and infant structural congenital malformations. J Thyroid Res 2014; 2014:Epub
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3972937/

Lin S, Munsie JPW, Herdt-Losavio ML et al. Maternal asthma medication use and the risk of selected birth defects. Pediatrics 2012; 129:317-324.
http://pediatrics.aappublications.org/content/129/2/e317.long

Wijers CH, van Rooij IA, Bakker MK. Anorectal malformations and pregnancy-related disorders: a registry-based case-control study in 17 European regions. BJOG 2013; 120;1066-74
http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.12235/full

Zwink N, Jenetzky E and Brenner H. Parental risk factors and anorectal malformations: systematic review and meta-analysis Orphanet Journal of Rare Diseases 2011; 6: 1-17.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121580/

Evidence Level III

Last amended November 2017
Last reviewed November 2017

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.

Kaiser AS, Ferris L., Katz R, et al. Psychological responses to prenatal NTS counseling and the uptake of invasive testing in women of advanced maternal age. Patient Educ Counsel 2004;54:45-53

Evidence Level: IV

Last amended January 2011
Last reviewed November 2017

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, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD000140 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000140.pub2/full

Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD000273 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000273.pub2/full

Henderson-Smart DJ, De Paoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD000432 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000432.pub2/full

Evidence Level: I

Last amended March 2011
Last reviewed November 2017

ARTERIAL LINE INSERTION
Supporting information

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://vuneo.org/npart1.htm

Auckland District Health Board Newborn Services Clinical Guideline 2007.
http://www.adhb.govt.nz/newborn/Guidelines/VascularCatheters/IVC_PeriphArterialLines.htm

Evidence Level: V

Last amended June 2013
Last reviewed November 2017

ARTERIAL LINE SAMPLING
Supporting information

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.

Armstrong L; Stenson B. Effect of delayed sampling on umbilical cord arterial and venous lactate and blood gases in clamped and unclamped vessels. Arch Dis Child Fetal Neonatal Ed 2006;91:F342-5
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672835/

Evidence Level: IV

Last amended January 2011
Last reviewed November 2017

BABIES BORN AT THE MARGIN OF VIABILITY
Supporting information

This guideline has been prepared with reference to the following:
Manktelow BN, Seaton SE, Field DJ et al. Population-based estimates of in-unit survival for very preterm infants. Pediatrics. 2013;131:e425-32
http://pediatrics.aappublications.org/content/131/2/e425.long (Draper Grid available separately at: http://pediatrics.aappublications.org/content/pediatrics/131/2/e425/F1.large.jpg)

Most babies born <24 weeks gestation are expected to die, but outcome improves with each additional week of gestational age?
A population-based audit of inpatient neonatal care based in the East Midlands and Yorkshire regions selected all white singleton infants born at 23+0 to 32+6 weeks' gestational age between January 1, 2008, and December 31, 2010 (Manktelow, 2013). The results (see table below) showed most babies born <24 weeks gestation are expected to die, but outcome improves with each additional week of gestational age.

	Survival rate (%)	
Gestational age	Male	Female
23	28.6	34.8
24	48.1	55.6
25	73.4	67.2
26	77.4	83.6
27	83.3	90.0
28	88.7	93.1
29	93.0	96.1
30	95.3	98.9

Manktelow BN, Seaton SE, Field DJ et al. Population-based estimates of in-unit survival for very preterm infants. Pediatrics. 2013;131:e425-32
http://pediatrics.aappublications.org/content/131/2/e425.long

Evidence Level: II

Last amended July 2017
Last reviewed November 2017

BCG IMMUNISATION
Supporting information

This guideline has been produced with reference to the following:

World Health Organisation. Tuberculosis country profiles. 2016. WTO

http://www.who.int/tb/country/data/profiles/en/

Public Health England. Reports of cases of TB to UK enhanced tuberculosis surveillance systems. 2015. Public Health England

https://www.gov.uk/government/statistics/reports-of-cases-of-tb-to-uk-enhanced-tuberculosis-surveillance-systems

Department of Health. Immunisation against infectious disease: the green book. 2014. London. Department of Health

https://www.gov.uk/government/organisations/public-health-england/series/immunisation-against-infectious-disease-the-green-book

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) 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 suppurative cases in which needle aspiration has failed, or in which sinuses have formed in previously-drained nodes (Banani, 1994; Baki, 1991).
Non-suppurative lymphadenopathy requires no treatment (Goraya, 2002).

Baki A, Oncu M, Usta S, et al. Therapy of regional lymphadenitis following BCG vaccination. Infection 1991;19:414-6

Banani SA, Alborzi A. Needle aspiration for suppurative post-BCG adenitis. Arch Dis Child 1994;71:446-7
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1030063/pdf/archdisch00571-0054.pdf

Goraya JS, Virdi VS. Bacille Calmette-Guerin lymphadenitis. Postgrad Med J 2002;78:327-9
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1742390/pdf/v078p00327.pdf

Kuyucu N, Kuyucu S, Ical B, et al. Comparison of oral erythromycin, local administration of streptomycin and placebo therapy for non-suppurative Bacillus Calmette-Guerin lymphadenitis. Pediatr Infect Dis 1998;17:524-5

Noah PK, Pande D, Johnson B, et al. Evaluation of oral erythromycin and local isoniazid instillation therapy in infants with Bacillus Calmette-Guerin lymphadenitis and abscesses. Pediatr Infect Dis J 1993;12:136-9

Evidence Level: II

Patient Information is available from:
Public Health England. Tuberculosis. 2016
https://www.gov.uk/government/collections/immunisation#tuberculosis

Last amended December 2016
Last reviewed November 2017

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BLOOD GROUP INCOMPATIBILITIES
Supporting information

This guideline has been produced with reference to the following:

NICE. Jaundice in newborn babies under 28 days. 2016. London. NICE

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

Anon. Transfusion guidelines for neonates and older children. Br J Haematol 2004;124:433–53

http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2004.04815.x/epdf

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 (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 Sciellour, 2004).

Divakaran TG, Waugh J, Clark TJ, et al. Noninvasive techniques to detect fetal anemia due to red blood cell alloimmunization: a systematic review. Obstet Gynecol 2001;98:509-17

Mari G. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. N Engl J Med 2000;342:9-14
http://www.nejm.org/doi/full/10.1056/NEJM200001063420102#t=articleTop

Oepkes D. Invasive versus non-invasive testing in red-cell alloimmunized pregnancies. Eur J Obstet Gynecol Reprod Biol 2000;92:83-9

Rijnders RJ, Christiaens GC, Bossers B, et al. Clinical applications of cell-free fetal DNA from maternal plasma. Obstet Gynecol 2004;103:157-64

Rouillac le Sciellour C, Puillandre P, Gillot R, et al. Large-scale pre-diagnosis study of fetal RHD genotyping by PCR on plasma DNA from RhD-negative pregnant women. Mol Diagn 2004;8:23-31

Saade GR. Noninvasive testing for fetal anemia. N Engl J Med 2000;342:52-3

Sikkel E, Vandenbussche FP, Oepkes D, et al. Amniotic fluid delta OD 450 values accurately predict severe fetal anemia in D-alloimmunization. Obstet Gynecol 2002;100:51-7

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).

Anon. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:297-316
http://pediatrics.aappublications.org/content/114/1/297.full
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Maurer HM, Kirkpatrick BV, McWilliams NB, et al. Phototherapy for hyperbilirubinemia of haemolytic disease of the newborn. Pediatrics 1985;75:407-12

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.

Janssens HM, de Haan MJ, van Kamp IL, et al. Outcome for children treated with fetal intravascular transfusions because of severe blood group antagonism. J Pediatr 1997;131:373-80

Stewart G, Day RE, Del Priore C, et al. Developmental outcome after intravascular intrauterine transfusion for rhesus haemolytic disease. Arch Dis Child Fetal Neonatal Ed 1994;70:F52-F53

Evidence Level: V

Last amended September 2011
Last reviewed November 2017

BLOODSPOT SCREENING
Supporting information

This guideline has been prepared with reference to the following:

Public Health England. Guidelines for Newborn Blood Spot Sampling. 2016. PHE

https://www.gov.uk/government/publications/newborn-blood-spot-screening-sampling-guidelines

Last amended January 2017
Last reviewed November 2017

BOTTLE FEEDING
Supporting information

This guideline has been prepared with reference to the following:

Public Health England. Newborn blood spot screening: sampling guidelines. 2014.

https://www.gov.uk/government/publications/newborn-blood-spot-screening-sampling-guidelines

Warren, I. Bond, C., 2014 Caring for your Baby in the Neonatal Unit. A Parent's Handbook. Matador

Dawson J, Foster J, Jacobs S, et al (2014). What is the best position for bottle feeding preterm infants? A Cochrane Review. Archives of Disease in Childhood. 2014. 99:A132

http://adc.bmj.com/content/99/Suppl_2/A132.1

Park J, Thoyre S, Knafl GJ et al. Efficacy of Semi-Elevated Side-Lying Feeding Position during Bottle Feeding of Very Preterm Infants. J Perinat Neonatal Nursing 2014. 28:69-79

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. 19:189-97

Shaker CS. Reading the Feeding (online). The ASHA Leader American-Speech-Language-Hearing Association 2013. 18:42-7

http://leader.pubs.asha.org/article.aspx?articleid=1784804

Shaker CS. Cue-based Co-regulated Feeding in the Neonatal Intensive Care Unit: Supporting Parents in learning to feed their Preterm Infant. Newborn and Infant Nursing Reviews 2013. 13 51-5

Shaker CS. Cue-based Feeding in the NICU: Using the Infant's Communication as a Guide. Neonatal Network 2013. 32:6

Sridhar S, Arguello S, Chong LH. Transition to Oral Feeding in Preterm Infants. Neo reviews 2011. 12:.3

NICE. Quality Standards programme – Neonatal specialist care. 2010. London. NICE

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

Shaker CS. Improving feeding outcomes in the NICU: Moving from Volume-Driven to Infant-Driven Feeding. Perspectives on Swallowing and Swallowing Disorders (Dysphagia) 2010. 19. 68-74

Bond C and Warren I. A guide to infant development in the new born nursery. 2010 5th Edition. Inga Warren and Cherry Bond, Winnicott Baby Unit, St. Mary's Hospital, Paddington

Bliss. The Bliss Baby Charter Standards. First edition, 2009

http://www.bliss.org.uk/the-bliss-baby-charter-guide

Department of Health. Toolkit for High Quality Neonatal Services. 2009

http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107845

Bagnall A., 2005. Feeding problems (Chapter 11). In: Jones, E., King, C. (Eds.), Feeding and Nutrition in the Preterm Infant.165-83. Elsevier

UNICEF. The Baby Friendly Initiative.

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

Last amended November 2017
Last reviewed November 2017

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BREAST MILK EXPRESSION
Supporting information

This guideline has been prepared with reference to the following:

Alekseev NP & Ilyin VI. The Mechanics of Breast Pumping: Compression Stimuli Increased Milk Ejection. Breastfeed Med. 2016;11:370-5

UNICEF. Neonatal unit guidance: implementing the standards. 2015. UNICEF

https://www.unicef.org.uk/babyfriendly/baby-friendly-resources/guidance-for-health-professionals/implementing-the-baby-friendly-standards/neonatal-guidance-document/

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.

Becker GE, Smith HA, Cooney F. Methods of milk expression for lactating women. Cochrane Database of Systematic Reviews 2015. Art. No.: CD006170
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006170.pub4/full

Evidence Level: I

Last amended July 2017
Last reviewed November 2017

BREAST MILK HANDLING AND STORAGE
Supporting information

This guideline has been prepared with reference to the following:

Paediatric Group of the British Dietetic Association. Guidelines for the Preparation and Handling of Expressed and Donor Breast Milk and Special Feeds for Infants and Children in Neonatal and Paediatric Health Care Settings. 2016

https://www.bda.uk.com/regionsgroups/groups/paediatric/sfu_guidelines

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.

Silvestre D, Miranda M, Muriach M, et al. Frozen breast milk at -20 degrees C and -80 degrees C: a longitudinal study of glutathione peroxidase activity and malondialdehyde concentration. J Hum Lactat 2010;26:35-41

Evidence Level: IV

Breast milk can be stored in the fridge for 48 hr and in the freezer for up to 3 months?
A 2008 NICE guideline advises mothers that expressed milk can be stored for:

- up to 5 days in the main part of a fridge, at 4ºC or lower
- up to 2 weeks in the freezer compartment of a fridge
- up to 6 months in a domestic freezer, at minus 18ºC or lower.

Since the publication of the NICE guidelines, two studies have concluded that breast milk can be safely refrigerated for up to 4 days.
A laboratory study (Slutzah, 2010) of fresh breast milk samples (n = 36) were divided and stored at 4°C for 0, 24, 48, 72, and 96 hours. There were no significant changes for osmolality, total and Gram-negative bacterial colony counts or concentrations of sIgA, lactoferrin, and fat. Gram-positive colony counts (2.9 to 1.6 x 10(5) colony-forming units per mL), pH (7.21 to 6.68), white blood cell counts (2.31 to 1.85 x 10(6) cells per mL), and total protein (17.5 to 16.7 g/L) declined, and free fatty acid concentrations increased (0.35 to 1.28 g/L) as storage duration increased, P < .001. Changes were minimal and the overall integrity of milk during refrigerator storage was preserved. A similar study by Bertino et al (2013) concluded that infants who receive expressed milk stored for up to 96 hours receive essentially the same supply of fatty acids and active lipases as do infants fed directly at the breast.
An earlier study by Silvestre et al. (2006) came to a different conclusion than Bertino, concluding that breast milk should not be refrigerated for a period in excess of 48 hours due to the bactericidal activity observed in their study of 19 samples.
In terms of freezing breast milk, a study by Garcia-Lane et al. (2012) concludes that “after 3 months from freezing at -20 °C, an important decrease in fat and caloric content is observed”.

Bertino E, Giribaldi M, Baro C et al. Effect of prolonged refrigeration on the lipid profile, lipase activity, and oxidative status of human milk. J Pediatr Gastroenterol Nutr. 2013;56:390-6

García-Lara NR, Escuder-Vieco D, García-Algar O et al. Effect of freezing time on macronutrients and energy content of breastmilk. Breastfeed Med. 2012 Aug;7:295-301
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411345/

NICE. Maternal and child nutrition. 2008. NICE
https://www.nice.org.uk/guidance/ph11

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Silvestre D, López MC, March L et al. Bactericidal activity of human milk: stability during storage. Br J Biomed Sci. 2006;63:59-62.

Slutzah M, Codipilly CN, Potak D et al. Refrigerator storage of expressed human milk in the neonatal intensive care unit. J Pediatr. 2010;156:26-8

Evidence Level: III

Last amended October 2016
Last reviewed: November 2017

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 (Park, 2015. The data suggested that infants fed with breast milk achieved each of five milestones earlier than formula-fed infants.

Henderson G, Anthony MY, McGuire W. Formula milk versus maternal breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD002972
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002972.pub2/full

Park J, Knafl G, Thoyre S et al. Factors associated with feeding progression in extremely preterm infants. Nursing research 2015, 64;159-167.

Evidence Level: IV

Last amended August 2015
Last reviewed November 2017

EMLA (Eutectic Mixture of Local Anaesthetics) cream is not used in neonates?
A 2017 systematic review of RCTs found no decent quality evidence either for or against the use of EMLA in neonates (Foster, 2017).
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.

Acharya AB, Bustani PC, Phillips JD, et al. Randomised controlled trial of eutectic mixture of local anaesthetics cream for venepuncture in healthy preterm infants. Arch Dis Child Fetal Neonat Ed 1998;78:F138-42
http://fn.bmj.com/content/78/2/F138.long

Foster JP, Taylor C, Spence K. Topical anaesthesia for needle-related pain in newborn infants. Cochrane Database Syst Rev. 2017
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010331.pub2/full

Evidence Level: II

Last amended November 2017
Last reviewed November 2017

CARDIAC MURMURS
Supporting information

This guideline has been prepared with reference to the following:

Knowles R, Griebsch I, Dezateux C, et al. Newborn screening for congenital heart defects: a systematic review and cost effectiveness analysis. Health Technology Assessment 2005;9

http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0017/65015/FullReport-hta9440.pdf

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%.

Ainsworth S, Wylie JP, Wren C. Prevalence and clinical significance of cardiac murmurs in neonates. Arch Dis Child Fetal Neonatal Ed 1999;88:F147-51
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720873/pdf/v080p00F43.pdf

Evidence Level: IV

Last amended September 2007
Last reviewed November 2017

CHEST DRAIN INSERTION: TRADITIONAL
Supporting information

This guideline has been prepared with reference to the following:

British Thoracic Society. Pleural disease guideline. 2010. BTS

https://www.brit-thoracic.org.uk/document-library/clinical-information/pleural-disease/pleural-disease-guidelines-2010/pleural-disease-guideline/

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).

Pacharn P, Heller DN, Kammen BF, et al. Are chest radiographs routinely necessary following thoracostomy tube removal? Pediatr Radiol 2002;32:138-42

van den Boom J, Battin M. Chest radiographs after removal of chest drains in neonates: clinical benefit or common practice? Arch Dis Child Fetal Neonatal Ed 2007;92:F46-8
http://fn.bmj.com/content/92/1/F46.long

Evidence Level: IV

Last amended August 2015
Last reviewed November 2017

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. Specialist neonatal care quality standard (see (Statement 3b). 2010. London. NICE

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

Bliss. Standard 3.2 Multidisciplinary team in The Bliss Baby Charter Standards, 2011. BAPM. 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

http://www.nna.org.uk/html/BAPM_Standards_Final_Aug2010.pdf

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 porencephal. (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 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.

Beeby, PJ, Henderson-Smart, DJ, Lacey, JL et al. Short- and long-term neurological outcomes following neonatal chest physiotherapy.J.Paediatric Child Health 1998 34: 60-2.

Flenady, P and Gray, P.H. Chest Physiotherapy for preventing morbidity in babies being extubated from mechanical ventilation. Cochrane Database of Systematic Reviews 2002, Issue 2. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000283/full

Harding, JE, Miles, FK, Becroft, DM et al. Chest physiotherapy may be associated with brain damage in extremely premature infants. J Pediatr. 1998. 132: 440-444.

Knight, DB, Bevan, CJ, Harding, JE et al. Chest physiotherapy and porencephalic brain lesions in very preterm infants. J Paediatric Child Health 2001. 37: 554-8.

Raval D, Yeh TF, Mora A, Cuevas D, Pyati S, Pildes RS. Chest Physiotherapy in preterm infants with RDS in the first 24 hours of life. J. Perinatol. 7 (4): 301-4, 1987

Roqué i Figuls M, Giné-Garriga M, Granados Rugeles C, Perrotta C. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD004873. DOI: 10.1002/14651858.CD004873.pub4. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004873.pub4/full

Evidence Level: II

Is chest physiotherapy associated with an increased risk of periventricular leukomalacia?
No evidence could be identified to suggest such a link.

Last amended September 2017
Last reviewed November 2017

CHRONIC LUNG DISEASE
Supporting information

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 dependence 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

Bancalari E, Abdenour GE, Feller R, et al. Bronchopulmonary dysplasia: clinical presentation. J Pediatr 1979;95: 819-23

Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med 2007;357:1946-55

Charafeddine L, D'Angio CT, Phelps DL. Atypical chronic lung disease patterns in neonates. Pediatrics 1999;103: 759-65

Northway WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease: bronchopulmonary dysplasia. N Engl J Med 1967;276:357-68

Panickar J, Scholefield H, Kumar Y, et al. Atypical chronic lung disease in preterm infants. J Perinat Med 2004;32:162-7

Shennan AT, Dunn MS, Ohlsson A, et al. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32

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.

Doyle L, Ehrenkranz R, Halliday H. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database of Systematic Reviews 2014. Art. No.: CD001146
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001146.pub4/pdf/standard

Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. The Cochrane Database of Systematic *Reviews* 2003, Issue 1. Art. No.: CD001144
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001144/full

Doyle L, Ehrenkranz R, Halliday H. Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants. The Cochrane Database of Systematic Reviews. 2014. Art. No.: CD001145
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001145.pub3/full

Shah SS, Ohlsson A, Halliday H, et al. Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants. The Cochrane Database of Systematic Reviews 2012. Art. No.: CD002057
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002057.pub3/full

Stark AR, Carlo WA, Tyson JE, et al. Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. N Engl J Med 2001;344:95-101
http://www.nejm.org/doi/full/10.1056/NEJM200101113440203#t=articleTop

van der Heide-Jalving M, Kamphuis PJ, van der Laan MJ, et al. Short-and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? Acta Paediatr 2003;92:827-35

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.

Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD001817
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001817.pub2/full

Stewart A, Brion LP. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD001453
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001453.pub2/full

Evidence Level: I

Last amended September 2015
Last reviewed November 2017

CMV (CYTOMEGALOVIRUS INFECTION)
Supporting information

This guideline has been prepared with reference to the following:

Shah T, Luck S, Sharland M et al. Fifteen-minute consultation: diagnosis and management of congenital CMV. Arch Dis Child Educ Pract Ed. 2016;101:232-5

http://ep.bmj.com/content/101/5/232.long

Kadambari, S, Williams, EJ, Luck, S. et al. Evidence based management guidelines for the detection and treatment of congenital CMV. Early Human Development 2011:87;723-8

European Congenital Cytomegalovirus Initiative. Rationale for treating neurologically symptomatic babies. (Recommendation 13). 2006

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. Thrombocytopaenia 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 ($P < .01$).

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 valganciclovir 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 ($P=0.003$).

Jones CA. Congenital cytomegalovirus infection. Curr Prob Pediatr Adolesc Health Care 2003;33:65-100

Kimberlin DW, Lin CY, Sanchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr 2003;143:16-25

Kimberlin DW, Acosta, EP, Sanchez, PJ, et al. Pharmacokinetic and Pharmacodynamic Assessment

of Oral Valganciclovir in the Treatment of Symptomatic Congenital Cytomegalovirus Disease. J Infect Dis 2008:197:836-45.
http://jid.oxfordjournals.org/content/197/6/836.long

Kimberlin DW, Jester PM, Sánchez P et al. Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease. New Eng J Med. 2015;372:933-43
http://www.nejm.org/doi/full/10.1056/NEJMoa1404599#t=articleTop

G. Lombardi, F. Garofili, P. Vilani et al. Oral valganciclovir treatment in newborns with symptomatic congenital cytomegalovirus infection Eur J Clin Microbiol Dis, 12 (28) (2009), pp. 1465–1470.

Oliver SE, Cloud GA, Sanchez PJ, et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. J Clin Virol 2009;46 Suppl 4:S22-6
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2805252/

Whitley R, Cloud G, Gruber W, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a Phase II study. National Institutes of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis 1997;175:1080-6
http://jid.oxfordjournals.org/content/175/5/1080.long

Evidence Level: II

Last amended April 2017
Last reviewed November 2017

COAGULOPATHY
Supporting information

This guideline has been prepared with reference to the following:

Chalmers E, Williams M, Brennand J, et al. Guideline on the management of haemophilia in the fetus and neonate. Br J Haematol 2011;154:208-15

http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2010.08545.x/full

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).

Buchanan GR. Coagulation disorders in the neonate. Pediatr Clin N Am 1986;33:203-220

Lippi G, Salvagno GL, Rugolotto S, et al. Routine coagulation tests in newborn and young infants. J Thromb Thrombolysis 2007;24:153-5

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).
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.

Amato M, Fauchere JC, Hermann U. Coagulation abnormalities in low birth weight infants with peri-intraventricular hemorrhage. Neuropediatrics 1988;19:154-7

Beverley DW, Chance GW, Inwood MJ, et al. Intraventricular haemorrhage and haemostasis defects. Arch Dis Child 1984;59:444-8
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1628492/pdf/archdisch00734-0058.pdf

Kazzi NJ, Ilagan NB, Liang KC, et al. Maternal administration of vitamin K does not improve the coagulation profile of preterm infants. Pediatrics 1989;84:1045-50

Krishnamoorthy KS, Shannon DC, DeLong GR, et al. Neurologic sequelae in the survivors of neonatal intraventricular haemorrhage. Pediatrics 1979;64:233-7

Morales WJ, Angel JL, O'Brien WF, et al. The use of antenatal vitamin K in the prevention of early neonatal intraventricular hemorrhage. Am J Obstet Gynecol 1988;159:774-9

Pomerance JJ, Teal JG, Gogolok JF, et al. Maternally administered antenatal vitamin K1: effect on neonatal prothrombin activity, partial thromboplastin time, and intraventricular hemorrhage. Obstet Gynecol 1987;70:235-41

Setzer ES, Webb IB, Wassenaar JW, et al. Platelet dysfunction and coagulopathy in intraventricular hemorrhage in the premature infant. J Pediatr 1982;100:599-605

Van de Bor M, Briet E, Van Bel F, et al. Hemostasis and periventricular-intraventricular hemorrhage of the newborn. Am J Dis Child 1986;140:1131-4

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.

Anon. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. Northern Neonatal Nursing Initiative Trial Group. Lancet 1996;348:229-32

Beverley DW, Pitts TT, Congdon PJ, et al. Prevention of intraventricular haemorrhage by fresh frozen plasma. Arch Dis Child 1985;60:710-3
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1777434/pdf/archdisch00719-0022.pdf

Contreras M, Ala FA, Greaves M, et al. Guidelines for the use of fresh frozen plasma. British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. Transfus Med 1992;2:57-63
http://www.bcshguidelines.com/documents/Use_of_fresh_frozen_plasma_1992.pdf

Hambleton G, Appleyard WJ. Controlled trial of fresh frozen plasma in asphyxiated low birthweight infants. Arch Dis Child 1973;48:31-5
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1647801/pdf/archdisch00869-0033.pdf

Hyytiainen S, Syrjala M, Fellman V, et al. Fresh frozen plasma reduces thrombin formation in newborn infants. J Thromb Haemost 2003;1:1189-94

Muntean W. Fresh frozen plasma in the pediatric age group and in congenital factor deficiency. Thromb Res 2002;107(Suppl 1):S29-32

Osborn DA, Evans NJ. Early volume expansion for prevention of morbidity and mortality in very preterm infants. Cochrane Database of Systematic Reviews 2004, Issue 2. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002055.pub2/pdf/standard

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).

Anon. Controversies concerning vitamin K and the newborn. Policy statement. American Academy of Pediatrics. Committee on Fetus and Newborn. Pediatrics 2003;112:191-2 http://pediatrics.aappublications.org/content/112/1/191.long

Hey E. Vitamin K – what, why, and when. Arch Dis Child Fetal Neonatal Ed 2003;88:F80-3 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://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002776/full

Roman E, Fear NT, Ansell P, et al. Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies. Br J Cancer 2002;86:63-9 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746550/

Evidence Level: I

Last amended July 2017
Last reviewed November 2017

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."

Johnson BA, Mussatto K, Uhing MR, et al. Variability in the preoperative management of infants with hypoplastic left heart syndrome. Pediatr Cardiol 2008;29:515-20

Evidence Level: V

Last amended July 2011
Last reviewed November 2017

CONGENITAL HYPOTONIA
Supporting information

This guideline has been prepared with reference to the following:

Dyke M and Jackson N. Joint Trust Guideline for Assessment of a Floppy Baby (Neonatal Hypotonia). 2016. James Paget University Hospitals NHS Foundation Trust and Norfolk and Norwich University Hospitals NHS Foundation Trust

http://www.nnuh.nhs.uk/publication/floppy-baby-jcg0009-v2/

Bodamer O and Miller G. Approach to the infant with hypotonia and weakness. In: UpToDate. 2016

Auckland District Health Board. Neonatal Hypotonia. 2015

http://www.adhb.govt.nz/newborn/Guidelines/Neurology/Hypotonia.htm

Lisi EC and Cohn RD. Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature. Dev Med Child Neurol. 2011;53:586-99

http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2011.03918.x/full

Children's Hospital Orange County. Neonatal Hypotonia - Clinical Approach to Floppy Baby. 2011. CHOC Children's

https://specialists.chocchildrens.org/wp-content/uploads/2011/08/Neonatal-Hypotonia.pdf

Leyenaar J, Camfield P, Camfield C. A schematic approach to hypotonia in infancy. Paediatr Child Health. 2005;10:397-400

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2722561/

van Toorn R. Clinical approach to the floppy child. CME. 2004;22:449-55

http://www.ajol.info/index.php/cme/article/viewFile/44002/27518

Last amended October 2016
Last reviewed November 2017

CONJUNCTIVITIS
Supporting information

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).

Patel PB, Diaz MC, Bennett JE, et al. Clinical features of bacterial conjunctivitis in children. Acad Emerg Med 2007;14:1-5
http://onlinelibrary.wiley.com/doi/10.1197/j.aem.2006.08.006/epdf

Evidence Level: IV

Is the topical application of breast milk an effective treatment for conjunctivitis?
The use of human milk in the treatment of ocular surface disease is documented in ancient Egyptian, Indian, Greek, Roman and Byzantine texts. Galen recommended human milk specifically for conjunctivitis (Hirschberg, 1982). Ocular application of human milk continues today in the developing world, and is recommended in widely distributed parenting guidebooks. Despite these endorsements, the antibacterial activity of topically applied breast milk has not been adequately studied.
A laboratory study using milk from 23 women found that breast milk was not an effective inhibitor of bacteria responsible for most cases of conjunctivitis, and hence was unlikely to be an effective treatment (Baynham, 2013).

Baynham JT, Moorman MA, Donnellan C et al. Antibacterial effect of human milk for common causes of paediatric conjunctivitis. Br J Ophthalmol. 2013;97:377-9
http://bjo.bmj.com/content/97/3/377.2.long

Hirschberg J, Blodi FC. trans. The history of ophthalmology. Vol 1. Antiquity . Bonn: Verlag J. P. Wayenborgh, 1982

Evidence Level: V

Last amended March 2017
Last reviewed November 2017

CONSENT
Supporting information

This guideline has been prepared with reference to the following:

Public Health England. Newborn blood spot screening: programme overview. 2013. PHE

https://www.gov.uk/guidance/newborn-blood-spot-screening-programme-overview

Last amended March 2017
Last reviewed November 2017

CPAP (CONTINUOUS POSITIVE AIRWAY PRESSURE)
Supporting information

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). Pao_2 < 50-60 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.

Carlo WA. Assisted ventilation. In: Klaus MH, Fanaroff AA (eds). Care of the high-risk neonate, 5th ed. Philadelphia, W.B. Saunders, 2001. p.282

Dani C, Bertini G, Pezzati M, et al. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. Pediatrics 2004;113:e560-3
http://pediatrics.aappublications.org/content/113/6/e560.long

De Paoli AG, Davis PG, Faber B, et al. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. The Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD002977
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002977.pub2/full

Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. New Engl J Med 2010;362:1970-9
http://www.nejm.org/doi/full/10.1056/NEJMoa0911783#t=articleTop

Halliday HL. What interventions facilitate weaning from the ventilator? A review of the evidence from systematic reviews. Paediatr Respir Rev 2004;5(Suppl A):S347-52

Kirchner L, Weninger M, Unterasinger L, et al. Is the use of early nasal CPAP associated with lower rates of chronic lung disease and retinopathy of prematurity? Nine years of experience with the Vermont Oxford Neonatal Network. J Perinat Med 2005;33:60-6

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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
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002272/full

Evidence Level: I

What pressure range should be used?
Conventionally, a nasal CPAP of 5 cm H_2O 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

Carlo WA. Assisted ventilation. In: Klaus MH, Fanaroff AA (eds). Care of the high-risk neonate, 5th ed. Philadelphia, W.B. Saunders, 2001. p.283

De Paoli AG, Davis PG, Faber B, et al. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. The Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD002977
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002977.pub2/full

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).

Jardine LA, Inglis GD, Davies MW. Strategies for the withdrawal of nasal continuous positive airway pressure (NCPAP) in preterm infants. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD006979
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006979.pub2/full

Todd DA, Wright A, Broom M, et al. Methods of weaning preterm babies <30 weeks gestation off CPAP: a multicentre randomised controlled trial. Arch Dis Child Fetal Neonat Ed 2012;97:F236-40
http://fn.bmj.com/content/97/4/F236.long

Evidence Level: I

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

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.

Boumecid H, Rakza T, Abazine A, et al. Influence of three nasal continuous positive airway pressure devices on breathing pattern in preterm infants. Arch Dis Child Fetal Neonatal Ed 2007;92:F298-300
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675435/

De Paoli AG, Morley C, Davis PG. Nasal CPAP for neonates: what do we know in 2003? Arch Dis Child Fetal Neonatal Ed 2003;88:F168-72
http://fn.bmj.com/content/88/3/F168.long

De Paoli AG, Davis PG, Faber B, et al. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. The Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD002977
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002977.pub2/full

Stefanescu BM, Murphy WP, Hansell BJ, et al. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics 2003;112:1031-8
http://pediatrics.aappublications.org/content/112/5/1031.long

Evidence Level: II

Is bubble CPAP superior to conventional CPAP?
A 2016 RCT compared CPAP failure rates between Bubble CPAP (BCPAP) and conventional ventilator derived CPAP (VCPAP) among 68 very low birthweight babies (VLBW), with moderate respiratory distress (Agarwal, 2016). The failure rates were found to be similar whether BCPAP or ventilator VCCPAP was used (14.7% vs 32.4% p=0.08). There was no difference in complication rates of intraventricular haemorrhage (24% vs 9% p=0.10) or mortality (6% vs 9% p=0.642) with either method of CPAP.
A few earlier randomised studies have compared these two approaches (Colaizy, 2004; McEvoy, 2004; Lee, 1998) and 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).

Agarwal S, Maria A, Roy MK et al. A Randomized Trial Comparing Efficacy of Bubble and Ventilator Derived Nasal CPAP in Very Low Birth Weight Neonates with Respiratory Distress. J Clin Diagn Res. 2016;10:SC09-SC12
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5072040/

Colaizy TT, McEvoy C, Crichton C, et al. Bubble vs. conventional CPAP: a prospective, randomized, pilot study. Pediatr Res 2004;55:80

Koyamaibole L, Kado J, Qovu JD, et al. An evaluation of bubble-CPAP in a neonatal unit in a developing country: effective respiratory support that can be applied by nurses. J Trop Pediatr 2006;52:249-53

Lee KS, Dunn MS, Fenwick M, et al. A comparison of underwater bubble continuous positive airway pressure with ventilator-derived continuous positive airway pressure in premature neonates ready for extubation. Biol Neonate 1998;73:69-75

McEvoy CT, Colaizy T, Crichton C, et al. Randomized trial of early bubble continuous positive airway pressure (BCPAP) versus conventional CPAP (CCPAP): effect on pulmonary function in preterm infants. Pediatr Res 2004;55:169

Evidence Level: II

Last amended September 2017
Last reviewed November 2017

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.

Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD003311
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003311.pub3/pdf/standard

Kendall GS, Kapetanakis A, Ratnavel N, et al. Passive cooling for initiation of therapeutic hypothermia in neonatal encephalopathy. Arch Dis Child Fetal Neonat Ed 2010;95:F408-12

Shah PS. Hypothermia: a systematic review and meta-analysis of clinical trials. Semin Fetal Neonat Med 2010;15:238-46

Tagin MA, Woolcott CG, Vincer MJ, et al. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. Arch Pediatr Adolesc Med 2012;166:558-66
http://archpedi.jamanetwork.com/article.aspx?articleid=1149494

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 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.

Kawano G, Iwata O, Iwata S, et al. Determinants of outcomes following acute child encephalopathy and encephalitis: pivotal effect of early and delayed cooling. Arch Dis Child 2011;96:936-41 http://adc.bmj.com/content/96/10/936.long

Evidence Level: IV

Last amended July 2013
Last reviewed November 2017

CRANIAL ULTRASOUND SCANS
Supporting information

This guideline has been prepared with reference to the following:

Ment LR, Bada HS, Barnes P, et al. Neuroimaging of the neonate: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002; 81:726-38

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).

Harris NJ, Palacio D, Ginzel A, et al. Are routine cranial ultrasounds necessary in premature infants greater than 30 weeks gestation? Am J Perinatol 2007;24:17-21

Evidence Level: IV

Last amended September 2007
Last reviewed November 2017

DEATH AND SERIOUSLY ILL BABIES
Supporting information

This guideline has been prepared with reference to the following:

Midlands Newborn Network. Integrated Comfort Care Pathway (ICCP) – Newborn. 2017

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.

Naghib S, van der Starre C, Gischler SJ, et al. Mortality in very long-stay pediatric intensive care unit patients and incidence of withdrawal of treatment. Intens Care Med 2010;36:131-6

Evidence Level: IV

Last amended July 2017
Last reviewed November 2017

DEVELOPMENTAL DYSPLASIA OF THE HIP
Supporting information

This guideline has been prepared with reference to the following:

Public Health England. Newborn and Infant Physical Examination Screening Programme Handbook 2016/17. 2016. PHE

https://www.gov.uk/government/publications/newborn-and-infant-physical-examination-programme-handbook

UK National Screening Committee. Newborn and Infant Physical Examination. Programme Statement: Ultrasound examination of the hips in screening for developmental dysplasia of the hips. 2014. Public Health England.

https://www.gov.uk/government/publications/newborn-and-infant-physical-examination-ultrasound-scan-for-hip-dysplasia

UK National Screening Committee. Newborn and infant Physical Examination. Standards and Competencies. 2008. PHE

https://www.gov.uk/government/publications/newborn-and-infant-physical-examination-screening-standards

Sewell MD, Rosendahl K, Eastwood DM. Developmental dysplasia of the hip. BMJ. 2009. 339; b4454.

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

Last amended November 2017
Last reviewed November 2017

DISCHARGE FROM NEONATAL UNIT
Supporting information

This guideline has been prepared with reference to the following:

American Academy of Pediatrics Committee on Fetus and Newborn. Hospital discharge of the high-risk neonate. Pediatrics 2008;122:1119-26 [Policy reaffirmed May 2011]

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%)].

Nehra V, Pici M, Visintainer P, et al. Indicators of compliance for developmental follow-up of infants discharged from a regional NICU. J Perinat Med 2009;37:677-81
http://edoc.hu-berlin.de/oa/degruyter/jpm.2009.135.pdf

Evidence Level: IV

Last amended January 2011
Last reviewed November 2017

DISORDERS OF SEXUAL DEVELOPMENT
Supporting information

This guideline has been prepared with reference to the following:

Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:4133-60

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

Houk CP, Hughes, IA, Ahmed SF, et al. Summary of consensus statement on intersex disorders and their management. Pediatrics 2006;118:753-7

Last amended September 2011
Last reviewed November 2017

DOWN SYNDROME
Supporting information

This guideline has been prepared with reference to the following:

Down vs. Down's?
The American National Down Syndrome Society state: “Down syndrome is named for the English physician John Langdon Down, who characterized the condition, but did not have it. An "apostrophe s" connotes ownership or possession… While Down syndrome is listed in many dictionaries with both popular spellings (with or without an apostrophe s), the preferred usage in the United States is Down syndrome. The AP Stylebook recommends using ‘Down syndrome,’ as well.”

National Down Syndrome Society. Preferred Language Guide. 2012.
http://www.ndss.org/Down-Syndrome/Preferred-Language-Guide/

Evidence level: V

Last amended July 2017
Last reviewed November 2017

ECG ABNORMALITIES
Supporting information

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.”

Calabro MP, Cerrito M, Luzza F, et al Supraventricular tachycardia in infants: epidemiology and clinical management. Curr Pharmaceut Design 2008;14:723-8

Evidence Level: V

Last amended February 2011
Last reviewed November 2017

ENVIRONMENT AND NOISE
Supporting information

This guideline has been prepared with reference to the following:

American Academy of Pediatrics, Committee on Environmental Health. Noise: a hazard for the fetus and newborn. Pediatrics 1997;100:724-7

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

Last amended September 2011
Last reviewed November 2017

EXAMINATION OF THE NEWBORN
Supporting information

This guideline has been prepared with reference to the following:

NICE. Postnatal care up to 8 weeks after birth. 2015. London.NICE

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.

Cartlidge PH. Routine discharge examination of babies: is it necessary? Arch Dis Child 1992;67:1421-2
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1793965/pdf/archdisch00631-0011.pdf

Glazener CM, Ramsay CR, Campbell MK, et al. Neonatal examination and screening trial (NEST): a randomised, controlled, switchback trial of alternative policies for low risk infants. BMJ 1999;318:627-32
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

Hayes J, Dave S, Rogers C, et al. A national survey in England of the routine examination of the newborn baby. Midwifery 2003;19:277-84

Lee TW, Skelton RE, Skene C. Routine neonatal examination: effectiveness of trainee paediatrician compared with advanced neonatal nurse practitioner. Arch Dis Child Fetal Neonatal Ed 2001;85:F100-4
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721315/pdf/v085p0F100.pdf

Moss GD, Cartlidge PH, Speidel BD, et al. Routine examination in the neonatal period. BMJ 1991;302:878-9
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1669235/pdf/bmj00121-0026.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/

Townsend J, Wolke D, Hayes J, et al. Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers. Health Technol Assess 2004;8:14
http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0005/64877/FullReport-hta8140.pdf

Wolke D, Dave S, Hayes J, et al. Routine examination of the newborn and maternal satisfaction: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2002;86:F155-60
http://fn.bmj.com/content/86/3/F155.long

Evidence Level: II

Last amended February 2017
Last reviewed November 2017

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 >/= 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 fa.ctors.

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).

Anon. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114: 297-316
http://pediatrics.aappublications.org/content/114/1/297.long

Gottvall T, Hilden JO, Selbing A. Evaluation of standard parameters to predict exchange transfusions in the erythroblastotic newborn. Acta Obstet Gynecol Scand 1994;73:300-6

Newman TB, Liljestrand P, Jeremy RJ, et al. Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more. New Engl J Med 2006;354:1889-900
http://www.nejm.org/doi/full/10.1056/NEJMoa054244#t=articleTop

Chitty HE, Ziegler N & Savioa H et al. Neonatal exchange transfusions in the 21st century: A single hospital study. Jnl Paediatrics & Child Health 2013: 49;825–832

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 UA/V route than ET via the FV and UV routes ($p < .05$; OR 2.4; 95% CI 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."

Anagnostakis D, Kamba A, Petrochilou V, et al. Risk of infection associated with umbilical vein catheterization. A prospective study in 75 newborn infants. J Pediatr 1975;86:759-65

Anon. Transfusion guidelines for neonates and older children. British Committee for Standards in Haematology. Br J Haematol 2004;124:433-53
http://www.bcshguidelines.com/documents/trasnfusion_Neonates_bjh_124_4_2004.pdf

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

Corkery JJ, Dubowitz V, Lister J, et al. Colonic perforation after exchange transfusion. BMJ 1968;4:345-9
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1912639/pdf/brmedj02109-0039.pdf

Fok TF, So LY, Leung KW, et al. Use of peripheral vessels for exchange transfusion. Arch Dis Child 1990;65:676-8
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1590202/pdf/archdisch00896-0036.pdf

Guimaraes H, Castelo L, Guimaraes J, et al. Does umbilical vein catheterization to exchange transfusion lead to portal vein thrombosis? Eur J Pediatr 1998;157:461-3

Livaditis A, Wallgren G, Faxelius G. Necrotizing enterocolitis after catheterization of the umbilical vessels. Acta Paediatr Scand 1974;63:277-82

Murray NA, Roberts IA. Neonatal transfusion practice. Arch Dis Child Fetal Neonatal Ed 2004;89:F101-7
http://fn.bmj.com/content/89/2/F101.long

Orme RL, Eades SM. Perforation of the bowel in the newborn as a complication of exchange transfusion. BMJ 1968;4:349-51
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1912604/pdf/brmedj02109-0043.pdf

Patra K, Storfer-Isser A, Siner B, et al. Adverse events associated with neonatal exchange transfusion in the 1990s. J Pediatr 2004;144:626-31

Rubaltelli FF, Zanardo V, Saia OS, et al. Umbilical vessel catheterization; the immediate risks with the venous route. Padiatr Padol 1978;13:39-43

Sayan A, Demircan M, Erikci VS, et al. Neonatal bladder rupture: an unusual complication of umbilical catheterization. Eur J Pediatr Surg 1996;6:378-9

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

Weng YH; Chiu YW. Comparison of efficacy and safety of exchange transfusion through different catheterizations: Femoral vein versus umbilical vein versus umbilical artery/vein. Pediatr Crit Care Med 2011;12:61-4

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.

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

Patra K, Storfer-Isser A, Siner B, et al. Adverse events associated with neonatal exchange transfusion in the 1990s. J Pediatr 2004;144:626-31

Evidence Level: V

Last amended September 2015
Last reviewed November 2017

EXTRAVASATION INJURIES
Supporting information

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?
A survey of 31 regional neonatal intensive care units in the UK (Wilkins, 2004) found that the prevalence of neonates who sustained an extravasation injury that caused skin necrosis was 38 per 1000.

Wilkins CE, Emmerson AJB. Extravasation injuries on regional neonatal units. Arch Dis Child Fetal Neonatal Ed. 2004;89: F274-5
http://fn.bmj.com/content/89/3/F274.full

Evidence Level: V

Is the risk of extravasation injury different when comparing centrally placed catheters with peripheral cannulae?
A 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) (Ainsworth, 2015).

Ainsworth S, McGuire W. Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. Cochrane Database Syst Rev. 2015:CD004219
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004219.pub4/full

Evidence Level: I

Last amended January 2016
Last reviewed November 2017

GASTRO-OESOPHAGEAL REFLUX
Supporting information

This guideline has been prepared with reference to the following:

NICE. Gastro-oesophageal reflux disease in children and young people: diagnosis and management : guidance. 2015. NICE. London

https://www.nice.org.uk/guidance/ng1

NASPGHAN. Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009;49:498–547

http://www.naspghan.org/files/documents/pdfs/position-papers/FINAL%20-%20JPGN%20GERD%20guideline.pdf

Does positioning have an effect on GOR?
A systematic review of RCTs (Carroll, 2002) quotes a controlled prospective study of 9 infants with GOR which found that positioning at a 60 degree elevation in an infant seat increased reflux compared with the prone position.
The “supine reversed-Trendelenburg sleeping position” was found to increase acid reflux parameters in all 10 consecutively investigated infants in a Belgian study (Bagucka, 1999).
A prospective sham-controlled trial of 51 patients found that left lateral positioning did not result in a significant improvement in symptoms other than vomiting (Loots, 2014). An earlier study of 18 preterm infants with GOR (Ewer, 1999) compared prone, left lateral and right lateral positions. The reflux index was significantly less in prone (6.3) and left lateral (11.0) positions compared to the right lateral (29.4).
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.

Bagucka B, De Schepper J, Peelman M, et al. Acid gastro-esophageal reflux in the 10 degrees-reversed-Trendelenburg-position in supine sleeping infants. Acta Paediatr Taiwan 1999;40:298-301

Carroll AE, Garrison MM, Christakis DA. A systematic review of nonpharmacological and nonsurgical therapies for gastroesophageal reflux in infants. Arch Pediatr Adolesc Med 2002;156:109-13
http://archpedi.jamanetwork.com/article.aspx?articleid=191516

Corvaglia L, Rotatori R, Ferlini M, et al. The effect of body positioning on gastroesophageal reflux in premature infants: evaluation by combined impedance and pH monitoring. J Pediatr 2007;151:591-6

Ewer AK, James ME, Tobin JM. Prone and left lateral positioning reduce gastro-oesophageal reflux in preterm infants. Arch Dis Child Fetal Neonatal Ed 1999;81:F201-5
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721012/pdf/v081p0F201.pdf

Loots C, Kritas S, van Wijk M et al. Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. J Pediatr Gastroenterol Nutr. 2014;59:237-43.

Evidence Level: I (Against infant seats and head-elevation); II (for the use of the left lateral position)

Are thickened feeds of use for GOR?
A systematic review from 2002 found no RCTs that studied whether adding feed thickeners to milk for newborn infants is effective in treating gastro-oesophageal reflux (Huang, 2002).
A 2008 systematic review 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).

Horvath A, Dziechciarz P, Szajewska H. The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta-analysis of randomized, controlled trials. Pediatrics 2008;122:e1268-77

Huang RC, Forbes DA, Davies MW. Feed thickener for newborn infants with gastro-oesophageal reflux. Cochrane database of systematic reviews. 2002.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003211/full

Evidence Level: I

Evidence Level: I (for reduced vomiting)

Is Gaviscon of use in GOR?
A systematic review of RCTs (Tighe , 2014) concluded that moderate evidence exists to indicate the Gaviscon improves symptoms of GOR in infant. A meta-analysis was not possible due to the changing formulation of Gaviscon, the diversity of study methods and heterogeneity of results.

Tighe M, Afzal N, Bevan A et al. Pharmacological treatment of children with gastro-oesophageal reflux. Cochrane database of systematic reviews. 2014.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008550.pub2/full

Evidence Level: I

Is domperidone of use in GOR?
No robust RCT evidence is available to support the use of domperidone. A 2014 systematic review of RCTs found two paediatric studies (n=80 and n=17) which found no statistically significant improvement in GOR symptoms.

Tighe M, Afzal N, Bevan A et al. Pharmacological treatment of children with gastro-oesophageal reflux. Cochrane database of systematic reviews. 2014.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008550.pub2/full

Evidence Level: I

Is ranitidine/cimetidine plus a pump inhibitor of use in relieving oesophagitis caused by GOR?
A small (n=18) prospective, double-blind study (Pfefferkorn, 2006) compared the use of proton pump inhibitors for reflux esophagitis in children with and without ranitidine. The authors concluded that there appeared to be no additional benefit to supplementation with ranitidine.

Pfefferkorn MD, Croffie JM, Gupta SK et al. Nocturnal acid breakthrough in children with reflux esophagitis taking proton pump inhibitors. J Pediatr Gastroenterol Nutr. 2006;42:160-5.

Evidence Level: III

Last amended March 2016
Last reviewed November 2017

GASTROSCHISIS
Supporting information

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.”

Holland AJ; Walker K; Badawi N. Gastroschisis: an update. Pediatr Surg Int 2010;26:871-8

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.

Department of Health. Immunisation against infectious disease: the green book. London: DH. 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147915/Green-Book-Chapter-4.pdf

Evidence Level: IV

Last amended July 2013
Last reviewed November 2017

GOLDEN HOUR (Preterm babies <28 weeks' gestation)
Supporting information

Evidence pertinent to this guideline may be found in the supporting information for the following Neonatal Guidelines:

- Resuscitation
- Hypothermia
- Ventilation
- Cannulation
- Infection

Last reviewed November 2017

HEARING SCREENING
Supporting information

This guideline has been prepared with reference to the following:

Public Health England. Newborn hearing screening: care pathways. 2015. PHE. London

https://www.gov.uk/government/publications/newborn-hearing-screening-care-pathways

U.S. Preventive Services Task Force. Universal Screening for Hearing Loss in Newborns: Recommendation Statement. Am Fam Physician. 2010; 81:185-6

http://www.aafp.org/afp/2010/0115/p185.html

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-afflicted 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 (Pimerpton and Kennedy 2012) has concluded that “exposure to Universal Newborn Hearning 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://jama.jamanetwork.com/article.aspx?articleid=186749

Pimperton, H and Kennedy, CR. The Impact of early identification of permanent childhood hearing impairment on speech and language outcomes. Arch Dis Child 2012; 97: 648-53
http://adc.bmj.com/content/97/7/648.long

Wolff R, Hommerich J, Riemsma R. Hearing screening in newborns: systematic review of accuracy, effectiveness, and effects of interventions after screening. Arch Dis Child 2010;95:130-5
http://adc.bmj.com/content/95/2/130.long

Evidence Level: III

Last amended July 2016
Last reviewed November 2017

This guideline has been prepared with reference to the following:

Department of Health. Immunisation against infectious disease: the green book. 2013. London. DoH

https://www.gov.uk/government/organisations/public-health-england/series/immunisation-against-infectious-disease-the-green-book

Mack CL, Gonzalez-Peralta RP, Gupta N et al. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr. 2012;54:838-55

http://www.sbp.com.br/fileadmin/user_upload/pdfs/NASPGHAN_Practice_Guidelines_Diagnosis_Hepatitis.pdf

Department of Health. Hepatitis B antenatal screening and newborn immunisation programme; Best practice guidance 2011. London. DoH

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_126195

Pembrey L, Newell M-L, Tovo P-A. The management of HCV infected pregnant women and their children. European paediatric HCV network. J Hepatol 2005;43:515–25

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 HB_eAg should be given HBIG in addition?

The American Academy of Pediatrics recommends that that all newborn infants with a birth weight of greater than or equal to 2000g receive hepatitis B vaccine by 24 hours of age (Committee on Infectious Diseases, 2016).

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 HB_eAG 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).

Beasley RP, Hwang LY, Lin CC, et al. Hepatitis B immune globulin (HBIG) efficacy in the interruption of perinatal transmission of hepatitis B virus carrier state: initial report of a randomised double-blind placebo-controlled trial. Lancet 1981;ii:388-93

Committee on Infectious Diseases, Committee on Fetus and Newborn. Elimination of Perinatal Hepatitis B: Providing the First Vaccine Dose Within 24 Hours of Birth. Pediatrics. 2017;140 http://pediatrics.aappublications.org/content/140/3/e20171870.long

Lee C, Gong Y, Brok J, et al. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. BMJ 2006;332:328-36

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

Polakoff S, Vandervelde EM. Immunisation of neonates at high risk of hepatitis B in England and Wales: national surveillance. BMJ 1988;297:249-53
http://www.bmj.com/content/297/6643/249.full.pdf+html

Reesink HW, Reerink-Brongers EE, Lafeber-Schut BJ, et al. Prevention of chronic HbsAG carrier state in infants of HbsAG-positive mothers by hepatitis B immunoglobulin. Lancet 1979;ii:436-8

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

Evidence Levels: I

Last amended July 2017
Last reviewed November 2017

HERPES SIMPLEX
Supporting information

This guideline has been prepared with reference to the following:

Royal College of Obstetricians and Gynaecologists & British Association for Sexual Health and HIV. Management of genital herpes in pregnancy. (Green Top Guideline No. 30). 2014. London. RCOG

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/genital-herpes/

Pinninti S & Kimberlin, D. Management of neonatal herpes simplex virus infection and exposure. Arch Dis Child Fetal Neonatal Ed 2014;99:F240-F244.

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

Kimberlin DW, Brady MT, Byington CL, et al. Guidance on Management of Asymptomatic Neonates Born to Women With Active Genital Herpes Lesions. 2013;131;e635-e646.

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.

Jones CA, Walker KS, Badawi N. Antiviral agents for treatment of herpes simplex virus infection in neonates. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD004206
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004206.pub2/full

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.

Gardella C, Huang ML, Wald A, et al. Rapid polymerase chain reaction assay to detect herpes simplex virus in the genital tract of women in labor. Obstet Gynecol 2010;115:1209-16
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034453/

Evidence Level: II

Last amended July 2015
Last reviewed November 2017

HIGH FLOW NASAL CANNULAE (HFNC) RESPIRATORY SUPPORT
Supporting information

HFNC is superior to nasal CPAP as a means of respiratory support in preterm infants?
A 2016 RCT of 564 preterm infants found that treatment failure rates were significantly higher in the HFNC group compared with the CPAP group (25.5% vs 13.3%, 95% CI, 5.8 to 18.7; p<0.001), but the rate of intubation within 72 hours was not significantly different between the two groups (15.5% and 11.5%). Inspired oxygen of 40% or higher was the most common reason for treatment failure. Furthermore, the median duration of respiratory support was longer (4 vs 3 days, p=0.005) and incidence of nasal trauma was less (8.3% vs 18.5%, p<0.001) in the HFNC infants than the CPAP group. Owing to the large difference between the groups for the primary outcome, the independent data and safety monitoring committee recommended stopping the study after recruitment of 75% of the target sample size.

Roberts CT, Owen LS, Manley BJ, et al. Nasal high-flow therapy for primary respiratory support in preterm infants. N Engl J Med 2016;375:1142–51
http://www.nejm.org/doi/full/10.1056/NEJMoa1603694

Evidence Level: II

Last amended November 2017
Last reviewed November 2017

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

Taylor G, Clayden P, Dhar J et al. British HIV Association (BHIVA) guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). HIV Medicine 2014:15:1-77

http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/BHIVA-Pregnancy-guidelines-update-2014.pdf

Taylor G, Anderson J, Clayden P, et al. British HIV Association and Children's HIV Association position statement on infant feeding in the UK 2011. HIV Medicine 2011;12:389-93

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

Cao Y, Krogstad P, Korber BT, et al. Maternal HIV-1 viral load and vertical transmission of infection: the Ariel Project for the prevention of HIV transmission from mother to infant. Nat Med 1997;3:549-52

Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173-80

Dickover RE, Garratty EM, Herman SA, et al. Identification of levels of maternal HIV-1 RNA associated with risk of perinatal transmission: effect of maternal zidovudine treatment on viral load. JAMA 1996;275:599-605

Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/mL. J Infect Dis 2001;183:539-45

Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. N Engl J Med 1999;341:385-93
http://www.nejm.org/doi/full/10.1056/NEJM199908053410601#t=articleTop

Siegfried N, van der Merwe L, Brocklehurst P, et al. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD003510
http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD003510.pub3

Thea DM, Steketee RW, Pliner V, et al. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. New York City Perinatal HIV Transmission Collaborative Study Group. AIDS 1997;11:437-44

Evidence Level: I

Should delivery be by elective caesarean section?

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.

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).

Boer K, England K, Godfried MH, et al. Mode of delivery in HIV-infected pregnant women and prevention of mother-to-child transmission: changing practices in Western Europe. HIV Medicine 2010;11:368-78
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428890/

Rowland BL, Vermillion ST, Soper DE. Scheduled cesarean delivery and the prevention of human immunodeficiency virus transmission: a survey of practicing obstetricians. Am J Obstet Gynecol 2001;185:327-31

Evidence Level: V

Should breast-feeding be avoided?

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)

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Public Health Service Task Force, 2015
https://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf

British HIV Association (BHIVA). Guidelines for the management of HIV infection in pregnant women 2012
http://www.bhiva.org/PregnantWomen2012.aspx

Chantry CJ, Morrison P, Panchula J, et al. Effects of lipolysis or heat treatment on HIV-1 provirus in breast milk. J Acquir Immune Defic Syndr 2000;24:325-9

Evidence Level: IV

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

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 96% (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).

Brown TM, Steketee RW, Abrams EJ, et al. Early diagnosis of perinatal HIV infection comparing DNA-polymerase chain reaction and plasma viral RNA amplification. Int Conf AIDS 1996 Jul 7-12 (abstract no. Tu.B.2374)

Cervia J, Kaplan B, Schuval S, et al. Virologic testing in the management of perinatal HIV exposure. AIDS Read 2003;13:39-46

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
http://www.nejm.org/doi/full/10.1056/NEJM199705083361901#t=articleTop

Evidence Level: V

Last amended September 2015
Last reviewed November 2017

HYDROPS FETALIS
Supporting information

This guideline has been prepared with reference to the following:

Derderian SC, Jeanty C, Fleck SR, Cheng LS, Peyvandi S, Moon-Grady AJ, Farrell J, Hirose S, Gonzalez J, Keller RL, MacKenzie TC. The many faces of hydrops. J Pediatr Surg. 2015;50:50-4

Turgal M, Ozyuncu O, Boyraz G, Yazicioglu A, Sinan Beksac M. Non-immune hydrops fetalis as a diagnostic and survival problems: what do we tell the parents? J Perinat Med. 2014

Santo S, Mansour S, Thilaganathan B, Homfray T, Papageorghiou A, Calvert S, et al. Prenatal diagnosis of non-immune hydrops fetalis: what do we tell the parents? Prenat Diagn 2011;31:186–95

Bellini C, Hennekam RC, Bonioli E. A diagnostic flow chart for non-immune hydrops fetalis. Am J Med Genet A 2009;149A:852–3

Ismail KM, Martin WL, Ghosh S, Whittle MJ, Kilby MD. Etiology and outcome of hydrops fetalis. J Matern Fetal Med 2001;10:175–81

Fraser SH. Non-immune hydrops: no longer an automatic death sentence. Australia and NZ Perinatal Society. Perth 1997

McCoy MC, Katz VL, Gould N, Kuller JA. Non-immune hydrops after 20 weeks' gestation: review of 10 years' experience with suggestions for management. Obstet Gynecol 1995;85:578–82

Machin GA. Hydrops revisited: literature review of 1,414 cases published in the 1980s. Am J Med Gen A 1989;34:366–90

Machin GA. Hydrops, cystic hygroma, hydrothorax, pericardial effusion and fetal ascites. In: Gilbert-Barness E, ed. Potter's pathology of the fetus and infant. St-Louis: Mosby; 1997

Last amended March 2015
Last reviewed November 2017

HYPERGLYCAEMIA
Supporting information

This guideline has been prepared with reference to the following:

NHS National Patient Safety Agency. Safety alert: safer administration of insulin. 2010. NHS

http://www.nrls.npsa.nhs.uk/alerts/?entryid45=74287
(additional note: The NPSA mandated that a training programme should be in place for all healthcare staff expected to prescribe, prepare and administer insulin. A neonatal-specific training package has been devised by Birmingham Women's NICU team, and can be made available.)

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 intra-ventricular haemorrhage of grade 3 or 4 before the 10th day of life.
Another prospective study in 252 premature infants weighing </=1500 g (Heimann, 2007) found a significant increase in mortality ($p<0.0001$) with increasing median blood glucose level and repeated (>/=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 (>/=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. Hyperglycemia is a risk factor for early death and morbidity in extremely low birth-weight infants. Pediatrics 2006;118:1811-18

Heimann K, Peschgens T, Kwiecien R, et al. Are recurrent hyperglycemic episodes and median blood glucose level a prognostic factor for increased morbidity and mortality in premature infants </=1500 g? J Perinat Med 2007;35:245-8

Kao LS, Morris BH, Lally KP, et al. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J Perinatol 2006;26:730-6
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.

Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD007453
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007453.pub3/full

Evidence Level: I

Last amended November 2017
Last amended November 2017

HYPERKALAEMIA
Supporting information

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). 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).

Ditzenberger GR, Collins SD, Binder N. Continuous insulin intravenous infusion therapy for VLBW infants. J Perinat Neonat Nurs 1999;13:70-82

Helfrich E, de Vries TW, van Roon EN. Salbutamol for hyperkalaemia in children. Acta Paediatr 2001;90:1213-6

Kemper MJ, Harps E, Hellwege HH, et al. Effective treatment of acute hyperkalaemia in childhood by short-term infusion of salbutamol. Eur J Pediatr 1996;155:495-7

Singh BS, Sadiq HF, Noguchi A, et al. Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. J Pediatr 2002;141:16-20

Evidence Level: II

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”

Bennett LN, Myers TF, Lambert GH. Cecal perforation associated with sodium polystyrene sulfonate-sorbitol enemas in a 650 gram infant with hyperkalemia. Am J Perinatol 1996;13:167-70

Grammatikopoulos T, Greenough A, Pallidis C, et al. Benefits and risks of calcium resonium therapy in hyperkalaemic preterm infants. Acta Paediatr 2003;92:118-27

Helfrich E, de Vries TW, van Roon EN. Salbutamol for hyperkalaemia in children. Acta Paediatr 2001;90:1213-6

Hu PS, Su BH, Peng CT, et al. Glucose and insulin infusion versus kayexalate for the early treatment of non-oliguric hyperkalaemia in very-low-birth-weight infants. Acta Paediatr Taiwan 1999;40:314-8

Vemgal P, Ohlsson A. Interventions for non-oliguric hyperkalaemia in preterm neonates. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD005257
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005257.pub3/full

Evidence Level: II (For no evidence of benefit of resins over glucose/insulin)
Evidence Level: V (For case report evidence of harm from resins)

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).

Ditzenberger GR, Collins SD, Binder N. Continuous insulin intravenous infusion therapy for VLBW infants. J Perinat Neonat Nurs 1999;13:70-82

Fukuda Y, Kojima T, Ono, A, et al. Factors causing hyperkalemia in premature infants. Am J Perinatol 1989;6:76-9

Gruskay J, Costarino AT, Polin RA, et al. Nonoliguric hyperkalemia in the premature infant weighing less than 1000 grams. J Pediatr 1988;113:381-6

Lorenz JM, Kleinmann LI, Markarian K. Potassium metabolism in extremely low birth weight infants in the first week of life. J Pediatr 1997;131:81-6

Matsuo Y, Hasegawa K, Doi Y, et al. Erythrocyte sodium-potassium transport in hyperkalaemic and normokalaemic infants. Eur J Pediatr 1995;154:571-6

Mildenberger E, Versmold HT. Pathogenesis and therapy of non-oliguric hyperkalaemia of the premature infant. Eur J Pediatr 2002;161:415-22

Sato K, Kondo T, Iwao H, et al. Internal potassium shift in premature infants: cause of nonoliguric hyperkalemia. J Pediatr 1995;126:109-13

Singh BS, Sadiq HF, Noguchi A, et al. Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. J Pediatr 2002;141:16-20

Stefano JL, Norman ME. Nitrogen balance in extremely low birth weight infants with nonoliguric hyperkalemia. J Pediatr 1993;123:632-5

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).

Ditzenberger GR, Collins SD, Binder N. Continuous insulin intravenous infusion therapy for VLBW infants. J Perinat Neonat Nurs 1999;13:70-82

Grammatikopoulos T, Greenough A, Pallidis C, et al. Benefits and risks of calcium resonium therapy in hyperkalaemic preterm infants. Acta Paediatr 2003;92:118-27

Singh BS, Sadiq HF, Noguchi A, et al. Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. J Pediatr 2002;141:16-20

Evidence Level: V

Last amended August 2013
Last reviewed September 2017

HYPERNATRAEMIC DEHYDRATION
Supporting information

This guideline has been prepared with reference to the following:

NICE. Intravenous fluid therapy in children and young people in hospital. 2015. NICE. London

https://www.nice.org.uk/guidance/ng29

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 >/= 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 >/ = 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.

Konetzny G, Bucher HU, Arlettaz R. Prevention of hypernatraemic dehydration in breastfed newborn infants by daily weighing. Eur J Pediatr 2009;168:815-8
http://onlinelibrary.wiley.com/doi/10.1111/apa.12820/full

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.

Boer S, Unal S, van Wouwe JP et al. Evidence Based Weighing Policy during the First Week to Prevent Neonatal Hypernatremic Dehydration while Breastfeeding. PLoS One. 2016;11:e0167313
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5172525/

Iyer NP, Srinivasan R, Evans K, et al. Impact of an early weighing policy on neonatal hypernatraemic dehydration and breast feeding. Arch Dis Child 2008;93:297-9
http://adc.bmj.com/content/93/4/297.long

Evidence Level: IV

Last amended November 2016
Last reviewed November 2017

HYPOGLYCAEMIA
Supporting information

This guideline has been prepared with reference to the following:

British Association of Perinatal Medicine. Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant - A Framework for Practice. 2017. BAPM

https://www.bapm.org/resources/identification-and-management-neonatal-hypoglycaemia-full-term-infant-%E2%80%93-framework-practice

British Association of Perinatal Medicine. Newborn Early Warning Trigger and Track (NEWTT) - A Framework for Practice. 2015. BAPM

https://www.bapm.org/resources/newborn-early-warning-trigger-track-newtt-framework-practice

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.

Bourchier D, Weston P, Heron P. Hypostop for neonatal hypoglycaemia. NZ Med J 1992;105:22

Singhal PK, Singh M, Paul VK, et al. A controlled study of sugar-fortified milk feeding for prevention of neonatal hypoglycaemia. Indian J Med Res 1991;94:342-5

World Health Organization. Hypoglycaemia of the newborn: review of the literature. Geneva: WHO, 1997. 39
http://www.who.int/maternal_child_adolescent/documents/chd_97_1/en/

Evidence Level: V

At what level can we define glucose levels as "profoundly low"?
Cornblath 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."

Cornblath M, Hawdon J, Williams A et al. Controversies Regarding Definition of Neonatal Hypoglycemia: Suggested Operational Thresholds. Pediatrics; 2000:105;1141-5

Evidence Level: V

At what level should we aim to maintain blood glucose?
Cornblath 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".

Cornblath M, Hawdon J, Williams A et al. Controversies Regarding Definition of Neonatal Hypoglycemia: Suggested Operational Thresholds. Pediatrics; 2000:105;1141-5

Last amended October 2017
Last reviewed November 2017

HYPOKALAEMIA
Supporting information

This guideline has been prepared with reference to the following:

Paediatric Formulary Committee. BNF for Children. 2017. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications

https://bnfc.nice.org.uk/

Worcester Acute Hospitals NHS trust. Neonatal Formulary

http://www.worcsformulary.nhs.uk/

Auckland District Health Board. Potassium Chloride Protocol. 2017

http://www.adhb.govt.nz/newborn/DrugProtocols/

Ainsworth SB. Neonatal Formulary: Drug Use in Pregnancy and the First Year of Life, Volume 7. Wiley & Sons, 2014

Choudhury et al. Principles of Pediatric and Neonatal Emergencies. 2011. Jaypee Brothers

Somers MJ, Traum AZ. Hypokalaemia in Children. In: UpToDate. 2014

Fly AD, Uhlin KL, Wallace JP. Major mineral concentrations in human milk do not change after maximal exercise testing. Am J Clin Nutr1998;68:345–9

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

Last amended June 2015
Last reviewed November 2017

HYPOTENSION
Supporting information

This guideline has been prepared with reference to the following:

National Association of Neonatal Nurse Practitioners. The management of hypotension in the very-low-birth-weight infant: guideline for practice. 2011. Illinois. NANNP

http://nann.org/uploads/Membership/NANNP_Pubs/Hypotension_Guideline.pdf

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

Cordero L, Timan CJ, Waters HH, et al. Mean arterial pressures during the first 24 hours of life in < or = 600-gram birth weight infants. J Perinatol 2002;22:348-53
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

Nascimento MC, Xavier CC, Goulart EM. Arterial blood pressure of term newborns during the first week of life. Braz J Med Biol Res 2002;35:905-11
http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-879X2002000800007&lng=en&nrm=iso&tlng=en

Nelson RM, Stebor AD, Groh CM, et al. Determination of accuracy in neonates for non-invasive blood pressure device using an improved algorithm. Blood Press Monit 2002;7:123-9

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?
According to a 2017 literature review, "In the premature neonate, there is no consensus regarding normal blood pressure (BP)" (St Peter, 2017). "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. Treating hypotension in the preterm infant: when and with what: a critical and systematic review. J Perinatol 2007;27:469-78

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

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

Fanaroff AA, Fanaroff JM. Short- and long-term consequences of hypotension in ELBW infants. Semin Perinatol 2006;30:151-5

Hegyi T, Carbone MT, Anwar M, et al. Blood pressure ranges in premature infants. I. The first hours of life. J Pediatr 1994;124:627-33

Hegyi T, Anwar M, Carbone MT, et al. Blood pressure ranges in premature infants. II. The first week of life. Pediatrics 1996;97:336-42

Kent AL, Meskell S, Falk MC, et al. Normative blood pressure data in non-ventilated premature neonates from 28-36 weeks gestation. Pediatr Nephrol 2009;24:141-6

Knight D. Newborn Services Clinical Guidelines: Hypotension. 2012. Auckland District Health Board. http://www.adhb.govt.nz/newborn/Guidelines/Cardiac/Hypotension.htm

St Peter D, Gandy C, Hoffman SB. Hypotension and Adverse Outcomes in Prematurity: Comparing Definitions. Neonatology. 2017;111:228-233

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).

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

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).

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

Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. J Perinatol 2003;23:473-6

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
http://fn.bmj.com/content/76/1/F43.long

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).

Sassano-Higgins S, Friedlich P, Seri I. A meta-analysis of dopamine use in hypotensive preterm infants: blood pressure and cerebral hemodynamics. J Perinatol 2011;31:647-55

Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD001242
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001242/full

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
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1763241/pdf/v088p0F450.pdf

Knight D. Newborn Services Clinical Guidelines: Hypotension. 2012. Auckland District Health Board.
http://www.adhb.govt.nz/newborn/Guidelines/Cardiac/Hypotension.htm

Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD001242
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001242/full

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 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.

Heckmann M, Trotter A, Pohlandt F, et al. Epinephrine treatment of hypotension in very low birthweight infants. Acta Paediatr 2002;91:566-70

Paradisis M, Osborn DA. Adrenaline for prevention of morbidity and mortality in preterm infants with cardiovascular compromise. The Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD003958
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003958.pub2/full

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 as 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."

Baker CF, Barks JD, Engmann C, et al. Hydrocortisone administration for the treatment of refractory hypotension in critically ill newborns. J Perinatol 2008;28:412-9

Bourchier D, Weston PJ. Randomised trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 1997;76:F174-F178
http://fn.bmj.com/content/76/3/F174.long

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

Gaissmaier RE, Pohlandt F. Single-dose dexamethasone treatment of hypotension in preterm infants. J Pediatr 1999;134:701-5

Higgins S, Friedlich P, Seri I. Hydrocortisone for hypotension and vasopressor dependence in preterm neonates: a meta-analysis. J Perinatol 2010;30:373-8

Ibrahim H, Sinha IP, Subhedar NV. Corticosteroids for treating hypotension in preterm infants. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD003662
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003662.pub4/full

Seri I, Tan R, Evans J. Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. Pediatrics 2001;107:1070-4

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

Ewer AK, Tyler W, Francis A, et al. Excessive volume expansion and neonatal death in preterm infants born at 27-28 weeks gestation. Paediatr Perinat Epidemiol 2003;17:180-6

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 (Knight, 2012). The maximum dose of adrenaline (epinephrine) is 0.5 mcg/kg/min (Knight, 2012).

Knight D. Newborn Services Clinical Guidelines: Hypotension. 2012
http://www.adhb.govt.nz/newborn/Guidelines/Cardiac/Hypotension.htm

Evidence Level: I

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.

Logan JW, O'Shea TM, Allred EN, et al. Early postnatal hypotension and developmental delay at 24 months of age among extremely low gestational age newborns. Arch Dis Child Fetal Neonat Ed 2011;96:F321-8

Evidence Level: III

Last amended September 2017
Last reviewed November 2017

HYPOTHERMIA
Supporting Information

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).

McCall EM, Alderdice F, Halliday HL, et al. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD004210
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004210.pub4/full

Doglioni N,Cavallin F, Mardegan V et al. Total body polyethylene wraps for preventing hypothermia in preterm infants: a randomized trial. Journal of paediatrics 2014: 165: 261

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 ($p = 0.004$).

Ibrahim CP, Yoxall CW. Use of self-heating gel mattresses eliminates admission hypothermia in infants born below 28 weeks gestation. Eur J Pediatr 2010;169:795-9

Evidence Level: IV

Last amended September 2015
Last reviewed November 2017

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. 2006. London. ACB

http://www.acb.org.uk/docs/default-source/guidelines/TFTguidelinefinal.pdf

Rose SR, Brown RS, Foley T, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006;117:2290-303

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 2006 (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.

Korada M, Pearce MS, Ward Platt MP, et al. Repeat testing for congenital hypothyroidism in preterm infants is unnecessary with an appropriate thyroid stimulating hormone threshold. Arch Dis Child Fetal Neonatal Ed 2008;93:F286-8
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 cchildren 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).

Kumar J, Gordillo R, Kaskel FJ, et al. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. J Pediatr 2009;154:263-6
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, 2006). 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 T_4 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.

Bakkar B, Kempers MJ, DeVijlder JJ, et al. Dynamics of the plasma concentrations of TSH, FT4 and T3 following thyroxine supplementation in congenital hypothyroidism. Clin Endocrinol 2002;57:529-37

Hrytsiuk I, Gilbert R, Logan S, et al. Starting dose of levothyroxine for the treatment of congenital hypothyroidism: a systematic review. Arch Pediatr Adolesc Med 2002;156:485-91
http://archpedi.jamanetwork.com/article.aspx?articleid=191868

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://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006972.pub2/full

Oerbeck B, Sundet K, Kase BF, et al. Congenital hypothyroidism: no adverse effects of high dose thyroxine treatment on adult memory, attention, and behaviour. Arch Dis Child 2005;90:132-7
http://adc.bmj.com/content/90/2/132.long

Rose SR, Brown RS, Foley T, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006;117:2290-303
http://pediatrics.aappublications.org/content/117/6/2290.full

Evidence Level: III

Last amended April 2011
Last reviewed November 2017

HYPOXIC ISCHAEMIC ENCEPHALOPATHY
Supporting information

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 </= 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

Biagioni E, Mercuri E, Rutherford M, et al. Combined use of electroencephalogram and magnetic resonance imaging in full-term neonates with acute encephalopathy. Pediatrics 2001;107:461-8

Blankenberg FG, Loh NN, Bracci P, et al. Sonography, CT, and MR imaging: a prospective comparison of neonates with suspected intracranial ischemia and hemorrhage. AJNR Am J Neuroradiol 2000;21:213-8
http://www.ajnr.org/content/21/1/213.long

Eken P, Toet MC, Groenendaal F, et al. Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 1995;73:F75-80
http://fn.bmj.com/content/73/2/F75.long

Hellstrom-Westas L, Rosen I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings in outcome after severe birth asphyxia in full term infants. Arch Dis Child 1995;72:F34-38
http://fn.bmj.com/content/72/1/F34.long

Jongeling BR, Badawi N, Kurinczuk JJ, et al. Cranial ultrasound as a predictor of outcome in term newborn encephalopathy. Pediatr Neurol 2002;26:37-42

Malik GK, Pandey M, Kumar R, et al. MR imaging and in vivo proton spectroscopy of the brain in neonates with hypoxic ischemic encephalopathy. Eur J Radiol 2002;43:6-13

Pressler RM, Boylan GB, Morton M, et al. Early serial EEG in hypoxic ischaemic encephalopathy. Clin Neurophysiol 2001;112:31-7

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

Toet MC, Hellstrom WL, Groenendaal F, et al. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 1999;81:F19-23
http://fn.bmj.com/content/81/1/F19.long

Evidence Level: IV

Normal body temperature (36.5 – 37.2^{o}) 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).

Jacobs SE, Berg M, Hunt R et al. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD003311
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003311.pub3/full

Kirpalani H, Barks J, Thorlund K, et al. Cooling for neonatal hypoxic ischemic encephalopathy: do we have the answer? Pediatrics 2007;120:1126-30

Perlman M, Shah P. Time to adopt cooling for neonatal hypoxic-ischemic encephalopathy: response to a previous commentary. Pediatrics 2008;121:616-8

Shah PS, Ohlsson A, Perlman M. Hypothermia to treat neonatal hypoxic ischemic encephalopathy: systematic review. Arch Pediatr Adolesc Med 2007;161:951-8
http://archpedi.jamanetwork.com/article.aspx?articleid=571322

Evidence Level: I

Last amended August 2013
Last reviewed November 2017

IMMUNISATIONS
Supporting information

This guideline has been prepared with reference to the following:

Salisbury D & Ramsay M. Immunisation against infectious disease: the green book. 2016. Public Health England. London

https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

NHS Choices. The NHS vaccination schedule. 2016. NHS

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

NHS Choices. Men B vaccine. 2015. NHS

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

British HIV Association (BHIVA). British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 Interim Review).

http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/BHIVA-Pregnancy-guidelines-update-2014.pdf

Department of Health. Immunisation against infectious disease: the green book. 2013. London. DOH

https://www.gov.uk/government/organisations/public-health-england/series/immunisation-against-infectious-disease-the-green-book

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

A 2015 narrative review concludes that “preterm infants should be vaccinated using the same schedule as term infants, with the exception of the HBV vaccine, where the full schedule needs to be repeated in infants who received their first dose when they weighed less than 2000g” (Gagneur. 2015).

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%.

Bonhoeffer J, Siegrist CA, Heath PT. Immunisation of premature infants. Arch Dis Child 2006;91:929-35

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

Gagneur A, Pinquier D & Quach C. Immunization of preterm infants. Hum Vaccin Immunother. 2015;11:2556–63
http://europepmc.org/articles/PMC4685684

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.

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).

Newman RD, Grupp PJ, Shay DK, et al. Perinatal risk factors for infant hospitalisation with viral gastroenteritis. Pediatrics 1999;103:E3

Evidence Level: III

Last amended August 2017
Last reviewed November 2017

INFECTION – LATE ONSET
Supporting Information

This guideline has been prepared with reference to the following:

Muller-Pebody B, Johnson AP, Heath PT et al. Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed 2011 96: F4-F8

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

NICE. Neonatal infection (early onset): antibiotics for prevention and treatment. 2012. London. NICE

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

Neonatal infection can be predicted by surface swabs

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).

Berger A, Witt A, Haiden N, et al. Amniotic cavity cultures, blood cultures, and surface swabs in preterm infants: useful tools for the management of early-onset sepsis? J Perinat Med 2004;32:44-52

Evans ME, Schaffner W, Federspiel CF, et al. Sensitivity, specificity, and predictive value of body surface cultures in a neonatal intensive care unit. JAMA 1988;259:248-53

Jolley AE. The value of surveillance cultures on neonatal intensive care units. J Hosp Infect 1993;25:153-9

Puri J, Revathi G, Faridi MM, et al. Role of body surface cultures in prediction of sepsis in a neonatal intensive care unit. Ann Trop Paediatr 1995;15:307-11

Van den Bruel A, Thompson MJ, Haj-Hassan T, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ 2011; 342:d3082 http://www.bmj.com/content/342/bmj.d3082.long

Evidence Level: I

Neonatal infection can be predicted by White cell count

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/mm^3, sensitivity and specificity were 79% and 5%; at a cutoff of 15,000 cells/mm^3, 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/mm^3, 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."

Baraff LJ, Bass JW, Fleischer GR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Pediatrics 1993;92:1-12

Bonsu BK, Harper MB. Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? Ann Emerg Med 2003;42:216-25

Gombos MM, Bienkowski RS, Gochman RF, et al. The absolute neutrophil count: is it the best indicator for occult bacteremia in infants? Am J Clin Pathol 1998;109:221-5

Purcell K, Fergie J. Lack of usefulness of an abnormal white blood cell count for predicting a concurrent serious bacterial infection in infants and young children hospitalized with respiratory syncytial virus lower respiratory tract infection. Pediatr Infect Dis J 2007;26:311-5

Evidence Level: III

Neonatal infection can be predicted by C-reactive protein
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 off 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.

Arnon S, Litmanovitz I, Regev R, et al. The prognostic virtue of inflammatory markers during late-onset sepsis in preterm infants. J Perinat Med 2004;32:176-80

Benitz WE, Han MY, Madan A, et al. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics 1998;102:E41
http://pediatrics.aappublications.org/content/102/4/e41.long

Clark JE, Hammal D, Spencer D, et al. Children with pneumonia: how do they present and how are they managed? Arch Dis Child 2007;92:394-8
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 003;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

Laborada G, Rego M, Jain A, et al. Diagnostic value of cytokines and C-reactive protein in the first 24 hours of neonatal sepsis. Am J Perinatol 2003;20:491-501

Manucha V, Rusia U, Sikka M, et al. Utility of haematological parameters and C-reactive protein in the detection of neonatal sepsis. J Paediatr Child Health 2002;38:459-64

Sanders S, Barnett A, Correa-Velez I, et al. Systematic review of the diagnostic accuracy of C-reactive protein to detect bacterial infection in nonhospitalized infants and children with fever. J Pediatr 2008;153:570-4

Evidence Level: III

Neonatal infection can be predicted by respiratory distress

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 septicaemia in 3.5%. The authors concluded that antibiotics should not be given routinely in such cases, in view of the low incidence of confirmed septicaemia.

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/mm^3.

Boyle RJ, Chandler BD, Stonestreet BS, et al. Early identification of sepsis in infants with respiratory distress. Pediatrics 1978;62:744-50

Dorond RD, Cook LN, Andrews BF. Incidence of sepsis in neonates with clinical respiratory distress. South Med J 1979;72:1262-4

Galanakis E, Krallis N, Levidiotou S, et al. Neonatal bacteraemia: a population-based study. Scand J Infect Dis 2002;34:598-601

Evidence Level: III

Neonatal infection can be predicted by prolonged rupture of membranes

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)

Chua S, Arulkumaran S, Sailesh KS, et al. Prelabour rupture of membranes to delivery interval related to the incidence of maternal and neonatal infection. J Obstet Gynaecol 1995;21:367-72

Seaward PG, Hannah ME, Myhr TL, et al. International Multicenter Term PROM Study: evaluation of predictors of neonatal infection in infants born to patients with premature rupture of membranes at term. Am J Obstet Gynecol 1998;179:635-9

Evidence Level: III

Neonatal infection can be predicted by discharging eyes

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).

Poschl JM, Hellstern G, Ruef P, et al. Ophthalmia neonatorum caused by group B streptococcus. Scand J Infect Dis 2002;34:921-2

Winceslaus J, Goh BT, Dunlop EM, et al. Diagnosis of ophthalmia neonatorum. BMJ 1987;295:1377-9 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1248537/pdf/bmjcred00048-0017.pdf

Evidence Level: V

Neonatal infection can be predicted by inflammation of umbilical cord
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).

Yoon BH, Romero R, Park JS, et al. The relationship among inflammatory lesions of the umbilical cord (funisitis), umbilical cord plasma interleukin 6 concentration, amniotic fluid infection, and neonatal sepsis. Am J Obstet Gynecol 2000;183:1124-9

Evidence Level: IV

Last amended August 2013
Last reviewed November 2017

INFECTION IN FIRST 72 HOURS OF LIFE
Supporting information

This guideline has been prepared with reference to the following:

Royal College of Obstetricians and Gynaecologists. Group B Streptococcal Disease, Early-onset (Green-top Guideline No. 36). 2017. RCOG

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg36/

NICE. Neonatal infection (early onset): antibiotics for prevention and treatment. NICE. London

https://www.nice.org.uk/guidance/cg149
(NB: Early-onset neonatal infection overview flowchart was updated in 2015, see: https://pathways.nice.org.uk/pathways/early-onset-neonatal-infection)

Last amended August 2017
Last reviewed November 2017

INGUINAL HERNIA
Supporting Information

This guideline has been prepared with reference to the following:

American Academy of Pediatrics. Assessment and Management of Inguinal Hernia in Infants. Pediatrics. 2012; 130:768-73

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

Last amended August 2013
Last reviewed November 2017

INHERITED METABOLIC DISORDERS (IMD)
Supporting information

This guideline has been produced with reference to the following:

British Inherited Metabolic Disorders Group. Guidelines: Emergency Protocols- Children. BIMDG

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

Treatment with L-carnitine is appropriate in the management of neonatal hyper ammonaemia, 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."

Nasser M, Javaheri H, Fedorowicz Z, et al. Carnitine supplementation for inborn errors of metabolism. Cochrane Database of Systematic Reviews 2012,Art. No.: CD006659
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006659.pub3/full

Evidence Level: I (For "no evidence")

Last amended July 2015
Last reviewed November 2017

INTRA ABDOMINAL CYSTS
Supporting information

Do many antenatally detected cysts resolve spontaneously?

A retrospective survey of 118 cases of antenatally diagnosed intra-abdominal cysts revealed that 26 cases (22%) resolved spontaneously in utero (Thakkar, 2015).

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 Hosptial, 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.

Sherwood W, Boyd P & Lakhoo K. Postnatal outcome of antenatally diagnosed intra-abdominal cysts. 2008: 24:763-5

Thakkar HS, Bradshaw C, Impey L et al. Post-natal outcomes of antenatally diagnosed intra-abdominal cysts: a 22-year single-institution series. Pediatr Surg Int. 2015;31:187-90

Evidence Level: IV

Last updated August 2017
Last reviewed November 2017

INTRAVENOUS FLUID THERAPY
Supporting information

This guideline has been prepared with reference to the following:

NICE. Intravenous fluid therapy in children and young people in hospital. 2015. London. NICE

https://www.nice.org.uk/guidance/ng29

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).

Costarino AT, Gruskay JA, Corcoran L, et al. Sodium restriction versus daily maintenance replacement in very low birth weight premature neonates: a randomized, blind therapeutic trial. J Pediatr 1992;120:99-106

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

Modi N. Management of fluid balance in the very immature neonate. Arch Dis Child Fetal Neonatal Ed 2004;89:F108-11
http://fn.bmj.com/content/89/2/F108.long

Shaffer SG, Meade VM. Sodium balance and extracellular volume regulation in very low birth weight infants. J Pediatr 1989;115:285-90

Evidence Level: II

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).

Armon K, Riordan A, Playfor S, et al. Hyponatraemia and hypokalaemia during intravenous fluid administration. Arch Dis Child 2008;93:285-7
http://adc.bmj.com/content/93/4/285.long

Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2014: CD000503
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000503.pub3/full

Modi N. Management of fluid balance in the very immature neonate. Arch Dis Child Fetal Neonatal Ed 2004;89:F108-11
http://fn.bmj.com/content/89/2/F108.long

Evidence Level: I

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

Can chronic lung disease, necrotising enterocolitis or patent ductus arteriosus (PDA) be caused by fluid overload, rather than inappropriate sodium supplementation?
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. Cochrane Database Syst Rev. 2014: CD000503
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000503.pub3/full

Lorenz JM. Fluid and electrolyte therapy and chronic lung disease. Curr Opin Pediatr 2004;16:152-6

Stephens BE, Gargus RA, Walden RV, et al. Fluid regimens in the first week of life may increase risk of patent ductus arteriosus in extremely low birth weight infants. J Perinatol 2008;28:123-8

Evidence Level: I

Should infants receiving phototherapy be given extra fluids?
A 2017 systematic review of RCTs found that Infants who received additional fluid appeared to have shorter duration of phototherapy (on average 10.70 hours shorter, participants = 218, studies = three) (Lai, 2017).
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.

Grunhagen DJ, de Boer MG, de Beaufort AJ, et al. Transepidermal water loss during halogen spotlight phototherapy in preterm infants. Pediatr Res 2002;51:402-5
http://www.nature.com/pr/journal/v51/n3/full/pr200264a.html

Hansen TW. Therapeutic approaches to neonatal jaundice: an international survey. Clin Pediatr 1996;35:309-16

Kjartansson S, Hammarlund K, Sedin G. Insensible water loss from the skin during phototherapy in term and preterm infants. Acta Paediatr 1992;81:764-8

Kjartansson S, Hammarlund K, Riesenfeld T, et al. Respiratory water loss and oxygen consumption in newborn infants during phototherapy. Acta Paediatr 1992;81:769-73

Lai NM, Ahmad Kamar A, Choo YM et al. Fluid supplementation for neonatal unconjugated hyperbilirubinaemia. Cochrane Database Syst Rev. 2017:CD011891
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011891.pub2/full

Maayan MA, Yosipovitch G, Hadad E, et al. Transepidermal water loss and skin hydration in preterm infants during phototherapy. Am J Perinatol 2001;18:393-6

Wananukul S, Praisuwanna P. Transepidermal water loss during conventional phototherapy in nonhemolytic hyperbilirubinemia term infants. J Med Assoc Thai 2001;84(Suppl 1):S46-S50

Wu PY, Hodgman JE, Kirkpatrick BV, et al. Metabolic aspects of phototherapy. Pediatrics 1985;75:427-33
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2532565/

Evidence Level: I

Last amended July 2017
Last reviewed November 2017

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.

Cormack R. & Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia 1984 39:1105–11

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, 224-52

Yentis SM & Lee DJ. Evaluation of an improved scoring system for the grading of direct laryngoscopy. Anaesthesia 1998 53 (11): 1041–1044

Evidence Level: III

Last amended September 2015
Last reviewed November 2017

INTUBATION
Supporting information

This guideline has been prepared with reference to the following:

Australian Resuscitation Council, New Zealand Resuscitation Council (2011), Tracheal Intubation and Ventilation of the Newborn Infant. ARC and NZRC Guideline 2010. Emergency Medicine Australasia, 23: 436–439

http://onlinelibrary.wiley.com/doi/10.1111/j.1742-6723.2011.01442_12.x/abstract

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.

Kempley ST, Moreiras JW, Petrone FL. Endotracheal tube length for neonatal intubation. Resuscitation 2008;77: 369-73

Luten R, Kahn N, Wears R, et al. Predicting endotracheal tube size by length in newborns. J Emerg Med 2007; 32: 343-7

Whyte KL, Levin R, Powis A. Clinical audit: optimal positioning of endotracheal tubes in neonates. Scott Med J 2007;52:25-7

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).

Carbajal R, Eble B, Anand KJ. Premedication for tracheal intubation in neonates: confusion or controversy? Semin Perinatol 2007;31:309-17

Cignacco E, Hamers JP, van Lingen RA, et al. Pain relief in ventilated preterms during endotracheal suctioning: a randomized controlled trial. Swiss Med Week 2008;138:635-45

Pereira e Silva Y, Gomez, RS, Marcatto JO, et al. Morphine versus remifentanil for intubating preterm neonates. Arch Dis Child Fetal Neonatal Ed 2007;92:F293-4
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675432/

Wyllie JP. Neonatal endotracheal intubation. Arch Dis Child Educ Pract Ed 2008;93:44-9

http://ep.bmj.com/content/93/2/44.full

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

Rogahn J. Intragastric feeding in preterm infants: a survey of frequency of tube change. J Neonatal Nurs 1998;4:31-3

Evidence Level: V

Last amended August 2013
Last reviewed November 2017

JAUNDICE
Supporting Information

This guideline has been prepared with reference to the following:

NICE. Jaundice in newborn babies under 28 days. 2016. London. NICE

https://www.nice.org.uk/guidance/qs57

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

Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. Acta Paediatr 2000;89:694-7

Manning D, Todd P, Maxwell M, et al. Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland. Arch Dis Child Fetal Neonatal Ed 2007;92:F342-6
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" (Dennery, 2001). This time period is inexact, although 14 days is commonly accepted as a cut-off point for investigation of sustained jaundice (Fenton, 1998).

Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. N Engl J Med 2001;344:581-90

Fenton TR, Gastrointestinal problems and jaundice of the newborn. In: Campbell AG, McIntosh N, (eds). Forfar and Arneil's Textbook of pediatrics, 5th ed. New York: Churchill Livingstone, 1998. p214

Evidence Level: V

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

Beutler E. Glucose-6-phosphate dehydrogenase deficiency and other enzyme abnormalities. In: Beutler E, Lichtman MA, Coller BS, et al (eds). Williams Hematology, 5th ed. New York, McGraw-Hill, 1995. p572

Evidence Level: V

What is the incidence of hereditary spherocytosis presenting with prolonged neonatal jaundice only?
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.

Delhommeau F, Cynober T, Schischmanoff PO, et al. Natural history of hereditary spherocytosis during the first year of life. Blood 2000;95:393-7
http://www.bloodjournal.org/content/95/2/393.long?sso-checked=true

Evidence Level: V

What percentage of congenital hypothyroidism is missed in the Guthrie test?
A report of the first 3 years of the UK national screening programme (Grant, 1988) recorded 493 cases in a total of 1,941,146 live births (incidence 1:3937). 4 cases were missed (0.8%), which was

similar to the North American experience (Holtzman, 1986) of 2 missed cases for every 1 million infants screened.

Grant DB, Smith I. Survey of neonatal screening for primary hypothyroidism in England, Wales, and Northern Ireland 1982-4. BMJ 1988;296:1355-8
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2545827/

Holtzman C, Slazyk WE, Cordero JF, et al. Descriptive epidemiology of missed cases of phenylketonuria and congenital hypothyroidism. Pediatrics 1986;78:553-8

Evidence Level: V

What percentage of urinary tract infection in newborns presents with jaundice only?
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.

Bilgen H, Ozek E, Unver T et al. Urinary tract infection and hyperbilirubinemia. Turk J Pediatr 2006; 48:51–5

Evidence Level: IV

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?
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. Although “free” or unbound bilirubin may provide a more accurate measure, no tests for this have been validated to date. Bhutani et al suggest using a sliding scale, based on infant weight, to indicate when intensive phototherapy should be started, but exchange transfusion is recommended when TSB >190 mL/kg.

Bhutani VK, Johnson LH. Urgent clinical need for accurate and precise bilirubin measurements in the United States to prevent kernicterus. Clin Chem 2004;50:477-80
http://www.clinchem.org/content/50/3/477.long

Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. J Pediatr 2002;140:396-403

Evidence Level: V

Can gamma-glutamyl transpeptidase (GGTP) be useful in distinguishing neonatal hepatitis (NH) from extrahepatic biliary atresia (EHBA)?
A study in 132 patients (Arora, 2001) found that serum GGTP 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.
A study in 47 infants with EHBA, 10 with NH and 130 age-matched healthy controls (Yamagiwa, 1996), noted significant differences in GGTP levels between the EHBA and NH infants at 6 weeks of age (314 +/- 232 IU/L vs 69 +/- 58 IU/L).

Arora NK, Kohli R, Gupta DK, et al. Hepatic technetium-99m-mebrofenin iminodiacetate scans and serum gamma-glutamyl transpeptidase levels interpreted in series to differentiate between extrahepatic biliary atresia and neonatal hepatitis. Acta Paediatr 2001;90:975-81

Yamagiwa I, Iwafuchi M, Obata K, et al. Pre-operative time course changes in liver function tests in biliary atresia: its usefulness in the discrimination of biliary atresia in early infancy. Acta Paediatr Jpn 1996;38:506-12

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Evidence Level: IV

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

Al-Hathlol K, Al-Madani A, Al-Saif S, et al. Ursodeoxycholic acid therapy for intractable total parenteral nutrition-associated cholestasis in surgical very low birth weight infants. Singapore Med J 2006;47:147-51

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”.

Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. Acta Paediatr 2000;89:694-7

Evidence Level: IV

Last amended March 2016
Last reviewed November 2017

KANGAROO CARE
Supporting information

This guideline has been prepared with reference to the following:

Ludington-Hoe SM. Evidence-based review of physiologic effects of kangaroo care Curr Women's Health Rev 2011;7:243-253

Kangaroo Care (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"

Cong X, Ludington-Hoe SM, Walsh S. Randomized crossover trial of kangaroo care to reduce biobehavioral pain responses in preterm infants: a pilot study. Biol Res Nurs 2011;13:204-16

Johnston C,Campbell-Yeo M, Fernandes A et al. Skin-to-skin care for procedural pain in neonates. Cochrane database of systematic reviews 2014. CD008435
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008435.pub2/full

Pillai Riddell RR, Racine NM, Turcotte K, et al. Non-pharmacological management of infant and young child procedural pain. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD006275
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006275.pub2/pdf/standard

Evidence Level: I

KC can help to reduce mortality in premature or low birth weight infants?
A 2016 systematic review of RCTs found that when compared with conventional neonatal care, KC was found to reduce mortality of low birth weight infants at discharge or at 40 to 41 weeks' postmenstrual age and at latest follow-up [risk reduction 0.60, 95% confidence interval 0.39 to 0.92] (Conde-Agudelo, 2016).
A 2010 systematic review of randomised and observational studies (all from low or middle-income countries—Colombia, Ethiopia, Ecuador, Ethiopia, Indonesia, Bangladesh, India, Mexico and South Africa) found that KMC substantially reduces neonatal mortality amongst preterm babies (birth weight <2000 g) in hospital, and is highly effective in reducing severe morbidity, particularly from infection (Lawn, 2010).

Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev. 2016;23;(8):CD002771
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002771.pub4/full

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Lawn JE, Mwansa-Kambafwile J, Horta BL et al. 'Kangaroo mother care' to prevent neonatal deaths due to preterm birth complications. Int J Epidemiol. 2010 Apr;39 Suppl 1:i144-54
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2845870/

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:

UNICEF. Baby Friendly Health Initiative
https://www.unicef.org.uk/babyfriendly/

Evidence Level: V

Last amended March 2017
Last reviewed November 2017

LIVER DYSFUNCTION IN PRETERM INFANTS
Supporting information

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.

Costa S, Maggio L, Sindico P, et al. Preterm small for gestational age infants are not at higher risk for parenteral nutrition-associated cholestasis. J Pediatr 2010;156:575-9

Evidence Level: IV

Last amended July 2011
Last reviewed November 2017

LONG LINE INSERTION (PERIPHERALLY SITED)
Supporting information

This guideline has been prepared with reference to the following:

British Association of Perinatal Medicine. Use of Central Venous Catheters in Neonates - A Framework for Practice. 2015. BAPM

https://www.bapm.org/resources/use-central-venous-catheters-neonates-framework-practice

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).

Anon. Central venous access in children. Lancet 1991;338:1301-2

Boros SJ, Thompson TR, Reynolds JW, et al. Reduced thrombus formation with silicone elastomere (silastic) umbilical artery catheters. Pediatrics 1975;56:981-6

Goutail-Flaud MF, Sfez M, Berg A, et al. Central venous catheter-related complications in newborns and infants: a 587-case survey. J Pediatr Surg 1991;26:645-50

Wheeler RA, Griffiths DM, Burge DM. Retrograde Tunnel: A Method for the Fixation of Long-Term Pediatric Central Venous Catheters. JPEN J Parenteral Enteral Nutr 1991;15:114-5

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).

Anon. Central venous access in children. Lancet 1991;338:1301-2

Hausdorf G, Bitzan M, Commentz J, et al. Intra-atrial malpositions of silastic catheters in newborns. Crit Care Med 1987;15:308-9

Soong WJ, Hsieh KS, Tiu CM, et al. Central venous silastic catheters in newborns and children: localization by sonography and radiology. Zhonghua Yi Xue Za Zhi (Taipei) 1991;48:97-102

De Carvalho, OPS, Da Luz, GPM, Peterlini, MA. Placement of peripherally inserted central catheters in children guided by ultrasound: a prospective randomized, and controlled trial. 2012; 13:282-7.

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).

Anon. Central venous access in children. Lancet 1991;338:1301-2

Grisoni ER, Mehta SK, Connors AF. Thrombosis and infection complicating central venous catheterization in neonates. J Pediatr Surg 1986;21:772-6

Jardine LA, Inglis GD, Davies MW. Prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with central venous catheters. The Cochrane Database of Systematic Reviews 2008, Issue 1. CD006179
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006179.pub2/full

Klein JF, Shahrivar F. Use of percutaneous silastic central venous catheters in neonates and the management of infectious complications. Am J Perinatol 1992;9:261-4

Moller JC, Reiss I, Schaible T. Vascular access in neonates and infants: indications, routes, techniques and devices, complications. Intensive Care World 1995;12:48-53

Mulloy RH, Jadavji T, Russell ML. Tunneled central venous catheter sepsis: risk factors in a pediatric hospital. JPEN J Parenteral Enteral Nutr 1991;15:460-3

Puntis JW, Holden CE, Smallman S, et al. Staff training: a key factor in reducing intravascular catheter sepsis. Arch Dis Child 1990;65:335-7
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1792884/pdf/archdisch00652-0071.pdf

Evidence Level: V

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.

Anon. Central venous access in children. Lancet 1991;338:1301-2

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
http://fn.bmj.com/content/95/4/F252.full

Durand M, Ramanathan R, Martinelli B, et al. Prospective evaluation of percutaneous central venous silastic catheters in newborn infants with birth weights of 510 to 3,920 grams. Pediatrics 1986;78:245-50

Moller JC, Reiss I, Schaible T. Vascular access in neonates and infants: indications, routes, techniques and devices, complications. Intensive Care World 1995;12:48-53

Mulloy RH, Jadavji T, Russell ML. Tunneled central venous catheter sepsis: risk factors in a pediatric hospital. JPEN J Parenteral Enteral Nutr 1991;15:460-3

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

Puntis JW, Holden CE, Smallman S, et al. Staff training: a key factor in reducing intravascular catheter sepsis. Arch Dis Child 1991;66:335-7
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1792884/pdf/archdisch00652-0071.pdf

Rand T, Kohlhauser C, Popow C, et al. Sonographic detection of internal jugular vein thrombosis after central venous catheterization in the newborn period. Pediatr Radiol 1994;24:577-80

Randolph AG, Cook DJ, Gonzales CA, et al. Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials. BMJ 1998;316:969-75
http://www.bmj.com/content/316/7136/969.long

Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. The Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD002772
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002772.pub3/full

Sherman MP, Vitale DE, McLaughlin GW, et al. Percutaneous and surgical placement of fine silicone elastomer central catheters in high-risk newborns. JPEN J Parenteral Enteral Nutr 1983;7:75-8

Soong WJ, Jeng MJ, Hwang B. The evaluation of percutaneous central venous catheters: a convenient technique in pediatric patients. Intensive Care Med 1995;21:759-65

Evidence Level: V

Last amended August 2017
Last reviewed November 2017

MEDIUM-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (MCADD)
Supporting information

This guideline has been prepared with reference to the following:

British Inherited Metabolic Disease Group. Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD). 2016. BIMDG

http://www.bimdg.org.uk/store/guidelines/ER-MCFAO-v4_340405_09092016.pdf

NHS Newborn Blood Spot Screening Programme. The MCADD programme. 2012.

http://newbornbloodspot.screening.nhs.uk/mcadd

Last amended August 2017
Last reviewed November 2017

METABOLIC BONE DISEASE
Supporting information

Which biochemical marker should be used to identify metabolic disease in preterm infants?
None of the evaluated metabolites (Ca, PO_4, 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 PO_4. 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 PO_4 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 PO_4 <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.

Backstrom MC, Kouri T, Kuusela AL et al. Bone isoenzyme of serum alkaline phosphatase and serum inorganic phosphate in metabolic bone disease of prematurity. Acta Paediatrica. 2000; 89: 867-73

Catache M, Leone CR. Role of plasma and urinary calcium and phosphorus measurements in early detection of phosphorus deficiency in very low birthweight infants. Acta Paediatr. 2003;92:76-80

Figueras-Aloy J, Álvarez-Domínguez E, Pérez-Fernández JM et al. Metabolic bone disease and bone mineral density in very preterm infants. J Pediatr. 2014 Mar;164:499-504
http://www.sciencedirect.com/science/article/pii/S0022347613013851

Hung YL1, Chen PC, Jeng SF et al. Serial measurements of serum alkaline phosphatase for early prediction of osteopaenia in preterm infants. J Paediatr Child Health. 2011;47(3):134-9.

Visser F1, Sprij AJ, Brus F. The validity of biochemical markers in metabolic bone disease in preterm infants: a systematic review. Acta Paediatr. 2012 Jun;101:562-8

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 PO4 at >0.4 mmol/L (in spot urinary specimens) by means of an individual supplementation with Ca and/or PO4 resulting in a slight surplus supply showed the highest bone mineral accretion measured by single-photon absorption densitometry. Hence, an individualized Ca and PO_4 supplementation in preterm infants aiming for a slight excess of the actual need, guided by urinary Ca and PO_4 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 PO_4 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 PO_4 threshold may be lowered in premature infants. Infants between 26 and 31 weeks were found to have a renal PO_4 threshold in the range of normal serum PO_4 values (2 mmol/L) but Hellstern et al have shown that extremely preterm infants (23-25 weeks) had a much lower renal PO_4 threshold, leading to urinary PO_4 excretion even in the presence of low PO_4 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 PO_4 deficiency homeostasis (PPV 0.92 and 0.83) defined as 24 h urinary concentrations <1 mmol/l Ca or PO_4. As urinary ratios depend heavily on type of feed as mentioned in the guideline, standard reference ranges are less useful.

Hellstern G, Poschl J, Linderkamp O. Renal phosphate handling of premature infants of 23–25 weeks gestational age. Ped Nephr 2003; 18: 756–8.

Mihatsch W1, Trotter A, Pohlandt F. Calcium and phosphor intake in preterm infants: sensitivity and specifity of 6-hour urine samples to detect deficiency. Klin Padiatr. 2012 Mar;224:61-5
Pohlandt F. Prevention of postnatal bone demineralization in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus. Pediatr Res 1994;35:125–129

Trotter A, Pohlandt F. Calcium and phosphorus retention in extremely preterm infants supplemented individually. Acta Paediatr 2002;91:1–4

Evidence Level: III

Which method of monitoring urine mineral excretion should be used- urinary Ca or PO_4 concentrations or Ca/creatinine(Cr) or PO_4 /creatinine ratios?

It is unclear whether the Ca/Cr and PO_4/Cr ratios are superior to the simple urinary Ca and PO_4 concentrations. Aladangady et al reported a reference range for urinary Ca/Cr and UPO_4/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/ PO_4 excretion is not the primary target as simple urinary Ca and PO_4 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 PO_4 but the results did not allow for identifying superiority of either method on the decision to supplement. PO_4 is not bound in the plasma like Ca and so the percent tubular reabsorption of PO_4 (TRP) is the best guide to adequacy of PO_4 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 PO_4. Similarly, if PO_4 intake is low, there is breakdown of bone and hence release of Ca leading to hypercalcaemia and calciuria. TRP can be calculated using the formula:
%TRP = 1 − Urine PO_4/Urine creatinine× Plasma creatinine/Plasma phosphate× 100.

Aladangady N, Coen PG, White MP et al. Urinary excretion of calcium and phosphate in preterm infants. Pediatric Nephrology. 2004; 19: 1225-31

Boehm G, Wiener M, Schmidt C et al. Usefulness of short-term urine collection in the nutritional monitoring of low birthweight infants. Acta Paediatr 1998;87:339–343

Payne RB. Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretations. Ann Clin Biochem 1998; 35: 201–6

Pohlandt F. Prevention of postnatal bone demineralization in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus. Pediatr Res 1994;35:125–129

Pohlandt F, Mihatsch WA. Reference values for urinary calcium and phosphorus to prevent osteopenia of prematurity. Pediatr Nephrol 2004;19:1192–1193

Staub E, Wiedmer N, Staub LP et al. Monitoring of urinary calcium and phosphorus excretion in preterm infants: comparison of 2 methods. J Pediatr Gastroenterol Nutr. 2014 Apr;58(4):404-8

Trotter A, Stoll M, Leititis JU et al. Circadian variations of urinary electrolyte concentrations in preterm and term infants. J Pediatr 1996;128:253–256

Trotter A, Pohlandt F. Calcium and phosphorus retention in extremely preterm infants supplemented individually. Acta Paediatr 2002;91:1–4

Evidence Level: III

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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.

Carrascosa A, Gussiny_eM, Yeste D. Bone mass, osteopenia and osteoporosis. In: Argente J, Carrascosa A, Gracia R, Rodr_ıguez-Hierro F, eds. Treaty of pediatric and adolescent Endocrinology. 2nd ed. Barcelona, Spain: Doyma; 2000. p. 1353-82. (in Spanish)

ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr 2010;50:85-91

Rigo J, De Curtis M, Pieltain C et al. Bone mineral metabolism in the micropremie. Clin Perinatol 2000;27:147-70

Rigo J, Pieltain C, Salle B, Senterre J. Enteral calcium, phosphate and vitamin D requirements and bone mineralization in preterm infants. Acta Paediatr 2007;96:969-74

Evidence Level: IV

Last amended February 2015
Last reviews November 2017

MULTI-DRUG RESISTANT ORGANISM COLONISATION (MRSA, ESBL ETC.)
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.

Lepelletier D, Corvec S, Caillon J, et al. Eradication of methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit: which measures for which success? Am J Infect Control 2009;37:195-200

van Rijen M, Bonten M, Wenzel R, et al. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD006216
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006216.pub2/full

Evidence Level: I

Last amended October 2012
Last reviewed November 2017

NASOGASTRIC TUBE – ADMINISTRATION OF FEED, FLUID OR MEDICATION
Supporting information

Evidence pertinent to this guideline may be found in the supporting information for the following Neonatal Guideline:

- Nasogastric tube insertion

NASOGASTRIC TUBE INSERTION
Supporting information

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

Rogahn J. Intragastric feeding in preterm infants: a survey of frequency of tube change. J Neonatal Nurs 1998;4:31-3

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).

McCullough S, Halton T, Mowbray D, et al. Lingual sucrose reduces the pain response to nasogastric tube insertion: a randomised clinical trial. Ach Dis Child Fetal Neonatal Ed 2008;93:F100-3
http://fn.bmj.com/content/93/2/F100.long

Evidence Level: II

Last amended June 2008
Last reviewed November 2017

NECROTISING ENTEROCOLITIS (NEC)
Supporting information

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."

Najaf TA, Vachharajani NA, Warner BW, et al. Interval between clinical presentation of necrotizing enterocolitis and bowel perforation in neonates. Pediatr Surg Int 2010;26:607-9

Evidence Level: IV

How effective are probiotics at preventing NEC in high risk babies?
In 2016, the largest RCT to date of a probiotic intervention found no evidence of benefit and does not support routine use of probiotics for preterm infants (Costeloe, 2016). 654 babies were allocated to receive probiotic and 661 to receive placebo over 37 months. There was no evidence of benefit for NEC Bell stage ≥ 2: 9.4% vs. 10.0% [adjusted RR 0.93, 95% CI 0.68 to 1.27]; and death: 8.3% vs. 8.5% [adjusted RR 0.93, 95% CI 0.67 to 1.30]}.
A systematic review of observational studies agreed with the earlier review by ALFaleh, concluding that probiotic supplementation reduces the risk of NEC and mortality in preterm infants. This review included 12 studies with 10,800 premature neonates (5,144 receiving prophylactic probiotics and 5,656 controls) and found a significantly decreased incidence of NEC (risk ratio, RR = 0.55, 95% CI 0.39 to 0.78) and mortality (RR = 0.72, 95% CI, 0.61-0.85).
In a meta-analysis of RCTs, enteral probiotics supplementation was found to significantly reduce the incidence of severe NEC (stage II or more) (typical relative risk (RR) 0.43, 95% confidence interval (CI) 0.33 to 0.56; 20 studies, 5529 infants) and mortality (typical RR 0.65, 95% CI 0.52 to 0.81; 17 studies, 5112 infants) (AlHaleh, 2014). The included trials reported no systemic infection with the supplemental probiotics organism. Probiotics preparations containing either lactobacillus alone or in combination with bifidobacterium were found to be effective.

AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2014:CD005496
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005496.pub4/full

Costeloe K, Bowler U, Brocklehurst P et al. A randomised controlled trial of the probiotic Bifidobacterium breve BBG-001 in preterm babies to prevent sepsis, necrotising enterocolitis and death: the Probiotics in Preterm infantS (PiPS) trial. Health Technol Assess. 2016;20:1-194
https://www.journalslibrary.nihr.ac.uk/hta/hta20660#/abstract

Olsen R, Greisen G, Schrøder M et al. Prophylactic Probiotics for Preterm Infants: A Systematic Review and Meta-Analysis of Observational Studies. Neonatology. 2016;109:105-12
https://www.karger.com/Article/FullText/441274

Evidence Level: I

Last amended December 2016
Last reviewed November 2017

NITRIC OXIDE
Supporting information

This guideline has been prepared with reference to the following:

Macrae DJ, Field D, Mercier JC, et al. Inhaled nitric oxide therapy in neonates and children: reaching a European consensus. Intens Care Med 2004;30:372-80

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.

Bizzarro M, Gross I, Barbosa F. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database of Systematic Reviews 2014, Art. No.: CD005055
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005055.pub3/full

Evidence Level: I

Last amended May 2015
Last reviewed November 2017

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 2015 systematic review of RCTs found that when compared with controls NNS resulted in improved pain reactivity (Standard mean difference [SMD] -1.20, 95% CI -2.01 to -0.38) and improved immediate pain regulation (SMD -0.90; 95% CI -1.54 to -0.25) (Pillai Riddell, 2015).
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

Pillai Riddell RR, Racine NM, Gennis HG et al. Non-pharmacological management of infant and young child procedural pain. Cochrane Database Syst Rev. 2015
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006275.pub3/full

Evidence Level: I

Last amended November 2017
Last reviewed November 2017

OESOPHAGEAL ATRESIA
Supporting information

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

- Intravenous Fluid Therapy (Bedside Clinical Guidelines)
- Vitamin K (Bedside Clinical Guidelines)

Last reviewed November 2017

OXYGEN ON DISCHARGE
Supporting information

This guideline has been prepared with reference to the following:

Balfour-Lynn IM, Field DJ, Gringras P, et al. BTS Guidelines for home oxygen in children. Thorax 2009;64 Suppl 2/(ii1-26)

https://www.brit-thoracic.org.uk/document-library/clinical-information/oxygen/home-oxygen-(children)/home-oxygen-in-children-guideline/

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.

Bajaj L, Turner CG, Bothner J. A randomized trial of home oxygen therapy from the emergency department for acute bronchiolitis. Pediatrics 2006;117:633-40

Evidence Level: II

Last amended May 2011
Last reviewed November 2017

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)?

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. However, an earlier 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%."

A retrospective chart review (Tlucek, 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 (BWs) 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.

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).

Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. New Engl J Med 2010;362:1959-69
http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=articleTop

Chen ML, Guo L, Smith LE, et al. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. Pediatrics 2010;125:e1483-92
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4016714/

Manja V, Lakshminrusimha S, Cook D. Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis. JAMA paediatrics. 2015:169;332-40

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

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Stenson BJ, Tarnow-Mordi, WO, Darlow, BA et al. Oxygen saturation and outcomes in preterm infants N Engl J Med 2013 368:2094-2104.
http://www.nejm.org/doi/full/10.1056/NEJMoa1302298#t=articleTop

Tlucek PS, Corff KE, Bright BC, et al. Effect of decreasing target oxygen saturation on retinopathy of prematurity. J Am Assoc Pediatr Ophthalmol Strabismus 2010;14:406-11

Evidence Level: I

Last amended September 2015
Last reviewed November 2017

This guideline has been prepared with reference to the following:

Anand K. Assessment of neonatal pain. In Post T (Ed.) UpToDate. Retrieved 1/5/2015. 2014. Waltham, MA.

Anand K. Prevention and treatment of neonatal pain. In Post T (Ed.) UpToDate. Retrieved 1/5/2015. 2014. Waltham, MA.

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.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”

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.pdf+html

Chambers CT, Taddio A, Uman LS, et al. Psychological interventions for reducing pain and distress during routine childhood immunizations: a systematic review. Clin Ther 2009;31(Suppl 2):S77-S103)

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

Johnston C,Campbell-Yeo M, Fernandes A et al. Skin-to-skin care for procedural pain in neonates. Cochrane database of systematic reviews 2014. CD008435
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008435.pub2/full

Shah PS, Herbozo C & Aliwalas LL. Breastfeeding or breast milk for procedural pain in neonates. Cochrane Database of Systematic Reviews 2012. Art. No.: CD004950
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004950.pub3/pdf/standard

Stevens B, Yamada J, Lee G et al. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database of Systematic Reviews 2013. Art. No.: CD001069
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001069.pub4/pdf

Thyr M, Sundholm A, Teeland L, et al. Oral glucose as an analgesic to reduce infant distress following immunization at the age of 3, 5 and 12 months. Acta Paediatr 2007; 96:233-6

Evidence Level: I

Last amended September 2015
Last reviewed November 2017

PALIVIZUMAB
Supporting information

This guideline has been prepared with reference to the following:

Committee on infectious diseases and bronchiolitis - Guidelines committee. Policy statement: updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134;415-20.

Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. Health Technology Assessment 2011;15:1-124 https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0014983/

Last amended November 2017
Last reviewed November 2017

PARENTERAL NUTRITION
Supporting information

This guideline has been prepared with reference to the following:

British Association of Perinatal Medicine. The Provision of Parenteral Nutrition within Neonatal Services: A Framework for Practice. 2016. BAPM

http://bapm.org/publications/documents/guidelines/Parenteral%20Nutrition%20April%202016.pdf

Ben XM. Nutritional management of newborn infants: practical guidelines. World J Gastroenterol 2008;14:6133-9

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2761573/

Parenteral Nutrition Guidelines Working Group. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). Journal of Pediatric Gastroenterology and Nutrition. 2005:41;S1-87

http://www.rch.org.au/uploadedFiles/Main/Content/rchcpg/hospital_clinical_guideline_index/ESPGHAN%20Guidelines_Paediatric_Parenteral_Nutrition_2005.pdf

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. Subsequent studies have additionally identified the male gender (Yan, 2017) as well as necrotising enterocolitis and fluconazole prophylaxis as risk factors (Lee, 2016)

Hsieh MH, Pai W, Tseng HI, et al. Parenteral nutrition-associated cholestasis in premature babies: risk factors and predictors. Pediatr Neonatol 2009;50:202-7

Lee HH, Jung JM, Nam SH et al. Risk factor analysis of parenteral nutrition-associated cholestasis in extremely low birth weight infants. Acta Paediatr. 2016;105:e313-9

Yan W, Hong L, Wang Y et al. Retrospective Dual-Center Study of Parenteral Nutrition-Associated Cholestasis in Premature Neonates: 15 Years' Experience. Nutr Clin Pract. 2017;32:07-413

Evidence Level: IV

Last amended November 2017
Last reviewed November 2017

PATENT DUCTUS ARTERIOSUS
Supporting information

Does ibuprofen have advantages over indometacin?

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 indometacin 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), indometacin 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) that a "wait and see" approach may result in more spontaneous closures and avoid potential adverse effects of treatment.

Aranda JV, Ronald T. Systematic review: intravenous ibuprofen in preterm newborns. Semin Perinatol 2006;30: 114-20

Erdeve O, Yurttutan S, Altug N, et al. Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2012;97:(F279-83)
http://fn.bmj.com/content/97/4/F279.long

Fakhraee SH, Badiee Z, Mojtahedzadeh S, et al. Comparison of oral ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. Zhongguo Dang Dai Er Ke Za Zhi 2007;9:399-403

Lago P, Bettiol T, Salvadori S, et al. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. Eur J Pediatr 2002;161:202-7

Nemerofsky SL, Parravicini E, Bateman D, et al. The ductus arteriosus rarely requires treatment in infants > 1000 grams. Am J Perinatol 2008;25:661-6

Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2015. Art. No.: CD003481
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003481.pub6/full

Patel J, Roberts I, Azzopardi D, et al. Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatr Res 2000;47:36-42

Su BH, Lin HC, Chiu HY, et al. Comparison of ibuprofen and indometacin for early-targeted treatment of patent ductus arteriosus in extremely premature infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2008;93:F94-9
http://fn.bmj.com/content/93/2/F94.long

Supapannachart S, Limrungsikul A, Khowsathit P. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomized trial at Ramathibodi Hospital. J Med Assoc Thai 2002;85(Suppl 4):S1252-8

Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000;343:674-81
http://www.nejm.org/doi/full/10.1056/NEJM200009073431001#t=articleTop

Van Overmeire B, Follens I, Hartmann S, et al. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child Fetal Neonatal Ed 1997;76:F179-84
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720646/pdf/v076p0F179.pdf

Evidence Level: I

In premature infants with patent ductus arteriosus (PDA), does early treatment with indometacin 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 indometacin 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 indometacin 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 indometacin 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 indometacin 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 indometacin 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 6.5% reopened. The mean cumulative dose of indometacin was 0.35 mg/kg.
A multicentre, randomised controlled trial in 105 infants (Jegatheesan, 2008) found that increasing indometacin 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 indometacin. 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).

Dumas de la Roque E, Fayon M, Babre F, et al. Minimal effective dose of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Biol Neonate 2002;81:91-4

Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD000174
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000174.pub2/full

Herrera C, Holberton J, Davis P. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD003480
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003480.pub3/full

Jegatheesan P, Ianus V, Buchh B, et al. Increased indomethacin dosing for persistent patent ductus arteriosus in preterm infants: a multicenter, randomized, controlled trial. J Pediatr 2008;153:183-9

Quinn D, Cooper B, Clyman RI. Factors associated with permanent closure of the ductus arteriosus: a role for prolonged indomethacin therapy. Pediatrics 2002;110:e10
http://pediatrics.aappublications.org/content/110/1/e10.long

Tammela O, Ojala R, Iivainen T, et al. Short versus prolonged indomethacin therapy for patent ductus arteriosus in preterm infants. J Pediatr 1999;134:552-7

van Overmeire B. Patent ductus arteriosus: how aggressive should we be? Neonatology 2007;91:318
http://www.curoservice.com/health_professionals/22nd_international_workshop/pdf/vanovermeire.pdf

van Overmeire B, van de Broek H, van Laer P, et al. Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. J Pediatr 2001;138:205-11

van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000;343:674-81
http://www.nejm.org/doi/full/10.1056/NEJM200009073431001#t=articleTop

van Overmeire B, Follens I, Hartmann S, et al. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child Fetal Neonatal Ed 1997;76:F179-84
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 indometacin treatment, however, has found no such association (Bellander, 2003). 32 infants given indometacin 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 indometacin 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)

Bellander M, Ley D, Polberger S, et al. Tolerance to early human milk feeding is not compromised by indomethacin in preterm infants with persistent ductus arteriosus. Acta Paediatr 2003;92:1074-8

Kelleher J, Salas A, Bhat R et al. Prophylactic indomethacin and intestinal perforation in extremely low birth weight infants. Pediatrics 2014:134:e1369.

Evidence Level: IV

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

Kumar RK, Yu VY. Prolonged low-dose indomethacin therapy for patent ductus arteriosus in very low birthweight infants. J Paediatr Child Health 1997;33:38-41

Evidence Level: IV

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).

Pizzuti A, Parodi E, Abbondi P, et al. Cardiac tamponade and successful pericardiocentesis in an extremely low birth weight neonate with percutaneously inserted central venous line: a case report. Cases J 2010;3:1757-1626
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821304/

Evidence Level: V

Last amended February 2011
Last reviewed November 2017

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)
Supporting information

This guideline has been prepared with reference to the following:

Children's Acute Transport Service (CATS). CATS clinical guideline: persistent pulmonary hypertension (PPHN). 2016

http://site.cats.nhs.uk/wp-content/uploads/2016/01/cats_pphn_2015.pdf

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.

Tanaka Y, Hayashi T, Kitajima H, et al. Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. Pediatrics 2007;119:1159-64

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
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005588.pub2/full

Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Cochrane Database of Systematic Reviews 2011, Art. No.: CD005494
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005494.pub3/full

Evidence Level: V

Last amended August 2017
Last reviewed November 2017

POLYCYTHAEMIA
Supporting information

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

British Committee for Standards in Haematology et al. Guidelines on transfusion for fetuses, neonates and older children. Br J Haematol. 2016;175:784-828

http://onlinelibrary.wiley.com/doi/10.1111/bjh.14233/full

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 polycythaemic newborn: a systematic review. Arch Dis Child Fetal Neonatal Ed 2006;91:F2-6
http://fn.bmj.com/content/91/1/F2.long

Özek E, Soll R, Schimmel MS. Partial exchange transfusion to prevent neurodevelopmental disability in infants with polycythemia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD005089
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005089.pub2/full

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 polycythaemia. Arch Dis Child Fetal Neonatal Ed 2006;91:F7-F10
http://fn.bmj.com/content/91/1/F7.long

Evidence Level: II

Last amended August 2017
Last reviewed November 2017

POSITIONING
Supporting information

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.

Hutchison BL, Stewart AW, De Chalain TB, et al. A randomized controlled trial of positioning treatments in infants with positional head shape deformities. Acta Paediatr 2010;99:1556-60 http://onlinelibrary.wiley.com/doi/10.1111/j.1651-2227.2010.01872.x/full

Evidence Level: I

In small or preterm babies, is there any benefit from monitoring SpO2 in car seats ("Infant Care Seat Challenge") before discharging from neonatal unit to prevent breathing difficulties during car travel?
In 2016 the Canadian Pediatric Society reviewed the evidence and concluded that due to inconsistency among Infant Care Seat Challenge (ICSC) test results and the lack of evidence that failing an ICSC is associated with either mortality risk or an adverse neurodevelopmental outcome, the Canadian Paediatric Society cannot recommend administering this test routinely as part of the discharge protocol for preterm infants (Narvey, 2016). Their decision not to recommend routine ICSC testing before discharge for preterm infants was based on evidence from case control studies (DeGrazia 2007, Davis 2014, Schutzman 2013).

DeGrazia M. Stability of the infant car seat challenge and risk factors for oxygen desaturation events. J Obstet Gynecol Neonatal Nurs 2007;36:300-7

Davis NL, Gregory ML, Rhein LM. Test-retest reliability of the infant car-seat challenge. J Perinatol 2014;34:54-8

Narvey MR; Canadian Paediatric Society, Fetus and Newborn Committee. Assessment of cardiorespiratory stability using the infant car seat challenge before discharge in preterm infants (<37 weeks' gestational age). Paediatr Child Health. 2016;21:155-62 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933079/

Schutzman DL, Salvador A, Janeczko M, et al. A comparison of the infant car seat challenge and the polysomnogram at the time of hospital discharge. Arch Dis Child Fetal Neonatal Ed 2013;98:F411-5 http://fn.bmj.com/content/98/5/F411.long

Evidence Level: IV

Last amended March 2017
Last reviewed November 2017

POST HAEMORRHAGIC VENTRICULAR DILATION
Supporting information

This guideline has been prepared with reference to the following:

Whitelaw A, Lee-Kelland R. Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage. Cochrane Database Syst Rev. 2017;4:CD000216
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000216.pub2/full

A multicentre randomised controlled trial of low versus high threshold treatment in preterm infants with progressive posthaemorrhagic ventricular dilatation (ongoing study)
http://www.isrctn.com/ISRCTN43171322

Last amended November 2017
Last reviewed November 2017

PROSTGLANDIN INFUSION
Supporting information

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. BNF
https://bnfc.nice.org.uk/treatment-summary/drugs-affecting-the-ductus-arteriosus.html

Madar RJ, Donaldson, TJD, Hunter S. Prostglandins in congenital heart disease – potential for confusion. Cardiol Young 1995; 5: 202-3.

Evidence Level: V

Last amended September 2011
Last reviewed November 2017

PULMONARY HAEMORRHAGE
Supporting information

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.

Aziz A, Ohlsson A. Surfactant for pulmonary hemorrhage in neonates. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD005254
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005254.pub3/full

Bland RD. Edema formation in the newborn lung. Clin Perinatol, 1982;9:593-611

Greenough A, Roberton NR. Acute respiratory disease in the newborn. In: Rennie JM, Roberton NR (eds). Textbook of neonatology, 3rd ed. Edinburgh: Churchill Livingstone, 1999. p552

Pandit PB, O'Brien K, Asztalos E, et al. Outcome following pulmonary haemorrhage in very low birthweight neonates treated with surfactant. Arch Dis Child Fetal Neonatal Ed 1999;81:F40-4
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720955/pdf/v081p00F40.pdf

Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 1998, Issue 2. Art. No.: CD001079
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001079.pub2/full

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).

Al Kharfy TM. High-frequency ventilation in the management of very-low-birth-weight infants with pulmonary hemorrhage. Am J Perinatol 2004;21:19-26

Bhandari V, Gagnon C, Rosenkrantz T, et al. Pulmonary hemorrhage in neonates of early and late gestation. J Perinat Med 1999;369-75

Dearborn DG, Smith PG, Dahms BB, et al. Clinical profile of 30 infants with acute pulmonary hemorrhage in Cleveland. Pediatrics 2002;110:627-37

Ko, SY, Chang YS, Park WS. Massive pulmonary hemorrhage in newborn infants successfully treated with high frequency oscillatory ventilation. J Korean Med Sci 1998;13:495-9
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3054512/pdf/9811178.pdf

Pappas MD, Sarnaik AP, Meert KL, et al. Idiopathic pulmonary hemorrhage in infancy: clinical features and management with high frequency ventilation. Chest 1996;110:553-5
http://journal.publications.chestnet.org/data/Journals/CHEST/21735/553.pdf

Trompeter R, Yu VY, Aynsley-Green A, Roberton NR. Massive pulmonary haemorrhage in the newborn infant. Arch Dis Child 1975;50:123-7
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1544401/pdf/archdisch00844-0047.pdf

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).

Kaneko M, Watanabe J, Ueno E. Surfactant lavage and replacement in meconium aspiration syndrome with pulmonary hemorrhage. J Perinat Med 2001;29:351-6

Mikawa K, Maekawa N, Nishina K, et al. Improvement of gas exchange following endobronchial instillation of an exogenous surfactant in an infant with respiratory failure by postoperative pulmonary haemorrhage. Intensive Care Med 1994;20:58-60

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

Raju TN, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy: a metaanalysis. J Pediatr 1993;123:603-10

Evidence Level: IV

Last amended October 2012
Last updated November 2017

RECTAL WASHOUT
Supporting information

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 Hirschprung's disease and that this should be the "initial approach in the care of the child".

Coran AG, Teitelbaum DH. Recent advances in the management of Hirschsprung's disease. Am J Surg. 2000;180:382–7.

Evidence Level: IV

Last amended August 2013
Last reviewed November 2017

RECYCLING OF STOMA LOSSES VIA A MUCOUS FISTULA
Supporting information

What evidence is there that this approach is beneficial?

A retrospective study of 92 neonates with necrotizing enterocolitis necessitating surgery for the formation of stoma with mucous fistula found that those in the refeeding group showed less bowel ends size discrepancy than those in the non-refeeding group (25% vs. 53% p=0.034) and less postoperative anastomotic leakage (3% vs 20%, p=0.029) [Lau, 2016]. Fewer refeeding group patients developed parenteral nutrition related cholestasis (42% vs 73%, p=0.045) and required shorter parenteral nutrition support (47days vs 135days, p=0.002). The mean peak bilirubin level was higher in the non-refeeding group (155 µmol/L vs 275µmol/L, p<0.001). No major complication was associated with refeeding. The authors of the study concluded that "Mucous fistula refeeding is safe and can decrease risk of anastomotic complication and parental nutrition related cholestasis. It provides both diagnostic and therapeutic value preoperatively and its use should be advocated".

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.

Haddock CA, Stanger JD, Albersheim SG, et al. Mucous fistula refeeding in neonates with enterostomies. J Pediatr Surg. 2015 :50:779-82

Lau EC, Fung AC, Wong KK et al. Beneficial effects of mucous fistula refeeding in necrotizing enterocolitis neonates with enterostomies. J Pediatr Surg. 2016;51:1914-16

Evidence Level: IV

Last amended April 2017
Last reviewed November 2017

RENAL FAILURE
Supporting information

This guideline has been prepared with reference to the following:

Selewski DT, Charlton JR, Jetton JG et al. Neonatal Acute Kidney Injury. Pediatrics. 2015;136:e463-73

http://pediatrics.aappublications.org/content/136/2/e463.long

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.

Chevalier RL, Campbell F, Brenbridge AN. Prognostic factors in neonatal acute renal failure. Pediatrics 1984; 74: 265-72

Wedekin M, Ehrich JH, Offner G, et al. Aetiology and outcome of acute and chronic renal failure in infants. Nephrol Dial Transplant 2008;23:1575-80
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.
https://bnf.nice.org.uk/treatment-summary/fluids-and-electrolytes.html

Gouyon, JB, Guignard, JP. Management of renal failure in newborns. Pediatric Nephrology 2000: 14: 1037-1044.

Evidence Level: V

Last amended August 2017
Last reviewed November 2017

RESUSCITATION
Supporting information

This guideline has been prepared with reference to the following:

Wylliea J, Bruinenberg J, Roehr C et al. European Resuscitation Council Guidelines for Resuscitation 2015 Section 7. Resuscitation and support of transition of babies at birth. Resuscitation. 2015:95;249-63

https://cprguidelines.eu/

Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics 2010;126: e1400-13

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

Anon. Ethical guidelines on resuscitation of newborns: FIGO Committee for the Ethical Aspects of Human Reproduction and Women's Health. Int J Gynecol Obstet 2006;94:169-71

http://www.glowm.com/pdf/English%20Ethical%20Issues%20in%20Obstetrics%20and%20Gynecology.pdf (see page 114)

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.

Gibbs J, Newson T, Williams J, et al. Naloxone hazard in infant of opioid abuser. Lancet. 1989;2:159–60

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)

Ezaki S, Suzuki K, Kurishima C, et al. Resuscitation of preterm infants with reduced oxygen results in less oxidative stress than resuscitation with 100% oxygen. J Clin Biochem Nutr 2009;44:111-8 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2613494/

Guay J, Lachapelle J. No evidence for superiority of air or oxygen for neonatal resuscitation: a meta-analysis. Can J Anaesth 2011;58:1075-82

Kapadia V, Chalak L, Sparks J et al. Resuscitation of preterm neonates with limited versus high oxygen strategy. Pediatrics 2013:132: e1488.
http://pediatrics.aappublications.org/content/early/2013/11/06/peds.2013-0978.full.pdf+html

Rabi Y, Rabi D, Yee W. Room air resuscitation of the depressed newborn: a systematic review and metaanalysis. Resuscitation 2007;72:353–63

Saugstad OD, Ramji S, Soll RF, et al. Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. Neonatology 2008;94:176-82

Evidence Level: I

Last amended October 2015
Last reviewed November 2017

RETINOPATHY OF PREMATURITY (ROP)
Supporting information

This guideline has been prepared with reference to the following:

American Academy of Pediatrics (Section on Ophthalmology), American Association for Pediatric Ophthalmology and Strabismus, American Academy of Ophthalmology. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2013;131:189-195

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.

O'Sullivan A, O'Connor M, Brosnahan D, et al. Sweeten, soother and swaddle for retinopathy of prematurity screening: a randomised placebo controlled trial. Arch Dis Child Fetal Neonat Ed 2010;95:F419-22
http://fn.bmj.com/content/95/6/F419.long

Sun X, Lemyre B, Barrowman N, et al. Pain management during eye examinations for retinopathy of prematurity in preterm infants: a systematic review. Acta Paediatr 2010;99:329-34

Evidence Level: I

Last amended August 2013
Last reviewed November 2017

SEIZURES
Supporting information

How efficacious and safe is levetiracetam for the treatment of neonatal seizures?
Levetiracetam has been available for treating seizures in adults since 2006, however until recently there has been very little evidence regarding its use in neonates (Khan, 2011). Following preliminary studies into the pharmacokinetics of using levetiracetam in neonates (Merhar, 2011; Sharpe, 2011). A small cohort study involving 23 neonates with electroencephalographically confirmed seizures found that levetiracetam was associated with no respiratory or cardiovascular adverse effects and was associated with a greater than 50% seizure reduction in 35% (8 of 23), including seizure termination in 7 (Abend, 2011). Another small study of 22 patients found that levetiracetam was associated with 19 of 22 patients (86%) demonstrating immediate seizure cessation at 1 hour (Khan, 2011). Seven of 22 patients (32%) achieved complete seizure cessation after administration of the loading dose, 14 (64%) achieved seizure cessation by 24 hours, 19 (86%) by 48 hours, and all 22 (100%) by 72 hours. No serious side effects were evident.

Abend NS, Gutierrez-Colina AM, Monk HM et al. Levetiracetam for treatment of neonatal seizures. J Child Neurol. 2011;26:465-70
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3082578/

Khan O, Chang E, Cipriani C et al. Use of intravenous levetiracetam for management of acute seizures in neonates. Pediatr Neurol. 2011;44:265-9

Merhar SL, Schibler KR, Sherwin CM et al. Pharmacokinetics of levetiracetam in neonates with seizures. J Pediatr. 2011;159:152-4
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3789844/

Sharpe CM, Capparelli EV, Mower A et al. A seven-day study of the pharmacokinetics of intravenous levetiracetam in neonates: marked changes in pharmacokinetics occur during the first week of life. Pediatr Res. 2012;72:43-9

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 only 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).
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).

Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004218
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004218.pub2/full

Boylan GB, Rennie JM, Pressler RM, et al. Phenobarbitone, neonatal seizures, and video-EEG. Arch Dis Child Fetal Neonatal Ed 2002;86:F165-70
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721395/pdf/v086p0F165.pdf

Brod SA, Ment LR, Ehrenkranz RA, et al. Predictors of success for drug discontinuation following neonatal seizures. Pediatr Neurol 1988;4:13-7

Gal P. Anticonvulsant therapy after neonatal seizures: how long should it be continued? 1. A case for early discontinuation of anticonvulsants. Pharmacotherapy 1985;5:268-73

Hellstrom WL, Blennow G, Lindroth M, et al. Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period. Arch Dis Child Fetal Neonatal Ed 1995;72:F97-101 http://fn.bmj.com/content/72/2/F97.long

Jeannet PY, Roulet E, Maeder IM, et al. Home and hospital treatment of acute seizures in children with nasal midazolam. Eur J Paediatr Neurol 1999;3:73-7 http://archpedi.jamanetwork.com/article.aspx?articleid=383593

Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 1999;341:485-9 http://www.nejm.org/doi/full/10.1056/NEJM199908123410704#t=articleTop

Rennie JM. Seizures in the newborn. In: Rennie JM, Roberton NR (eds). Textbook of neonatology, 3rd ed . Edinburgh, Churchill Livingstone, 1999. p1219

Rennie JM., Boylan GB. Neonatal seizures and their treatment. Curr Opin Neurol 2003;16:177-81

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

Sheth RD, Buckley DJ, Gutierrez, AR, et al. Midazolam in the treatment of refractory neonatal seizures. Clin Neuropharmacol 1996;19:165-70

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

Evidence Level: IV

Last amended November 2017
Last reviewed November 2017

SKIN BIOPSY FOR INBORN ERRORS OF METABOLISM
Supporting information

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).

Chakrapani A, Cleary MA, Wrait JE. Detection of inborn errors of metabolism in the newborn. Arch Dis Child Fetal Neonatal Ed 2001;84:F205–F21
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721249/pdf/v084p0F205.pdf

Evidence Level: V

Last amended July 2011
Last reviewed November 2017

SKIN CARE
Supporting information

This guideline has been prepared with reference to the following:

Blume-Peytavi U, Cork MJ, Faergemann J, et al. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. J Europ Acad Dermatol Venereol 2009;23:751-9

Lund CH, Kuller J, Raines DA, et al. Neonatal skin care: Evidence-based clinical practice guideline, 3rd ed. Washington DC: AWHONN, 2013

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.

Quinn D, Newton N, Piecuch R. Effect of less frequent bathing on premature infant skin. J Obstet Gynecol Neonatal Nurs 2005;34:741-6

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).

Conner JM, Soll R, Edwards WH. Topical ointment for preventing infection in preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD001150
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001150.pub2/full

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 November 2017

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.

Johnson KJ, Cress GA, Connolly NW et al. Neonatal laboratory blood sampling: comparison of results from arterial catheters with those from an automated capillary device. Neonatal network, 2000; 19: 27-34.

McLain B, Evans J, Dear P. Comparison of capillary and arterial blood gas measurements in neonates. Arch Dis Child. 1988;63:743-747
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1590118/pdf/archdisch00904-0051.pdf

Evidence Level: IV

Last amended July 2013
Last reviewed November 2017

SUDDEN COLLAPSE IN FIRST WEEK OF LIFE
Supporting information

This guideline has been prepared with reference to the following:

British Association of Perinatal Medicine. Guidelines for the investigation of newborn infants who suffer a sudden and unexpected postnatal collapse in the first week of life. 2011. London: BAPM

https://www.bapm.org/sites/default/files/files/SUPC_Booklet.pdf

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.

Pejovic NJ and Herlenius E. Unexpected collapse of healthy newborn infants: risk factors, supervision and hypothermia treatment. Acta Pediatrica 2013; 102: 680-8.

Evidence Level: IV

Last Updated August 2013
Last reviewed November 2017

SUPRAVENTRICULAR TACHYCARDIA
Supporting information

How strong is the evidence base for the use of antiarrythmics in neonates?
Infants with supraventricular tachycardia are typically treated with antiarrhythmic medications, but there is limited evidence to guide management. Current practices are based on poor quality evidence such as survey data, small clinical trials, and retrospective studies involving few (<300) infants (Chu, 2015).

Chu PY, Hill KD, Clark RH et al. Treatment of supraventricular tachycardia in infants: Analysis of a large multicenter database. Early Hum Dev. 2015;91:345-50
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4433846/

Evidence level IV

Last amended July 2017
Last reviewed November 2017

SURFACTANT REPLACEMENT THERAPY
Supporting information

This guideline has been prepared with reference to the following:

Sweet DG, Carnielli, V, Greisen G et al. European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update. Neonatology 2013; 103:353–368

http://www.curoservice.com/health_professionals/management_nRDS/RDS_EU_guidelines_Neonat2013.pdf

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<.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).

Jobe AH, Mitchell BR, Gunkel JH. Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant on preterm infants. Am J Obstet Gynecol 1993;168:508-13

Kari MA, Hallman M, Eronen M, et al. Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: a randomized placebo-controlled multicenter study. Pediatrics 1994;93:730-6

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.

Ardell S, Pfister R, Soll R. Animal derived surfactant extract versus protein free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. The Cochrane Database of Systematic Reviews 2015, Art. No.: CD000144
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000144.pub2/full

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

Ainsworth SB. Surfactant therapy for respiratory distress syndrome in premature neonates: a comparative review. Am J Respir Med 2002;1:417-33

Hentsche R, Jorch G. Acute side effects of surfactant treatment. J Perinat Med 2002;30:143-8

Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. J Paediatr Child Health 2002;38:597-600

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)
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000511/full

Stevens TP, Harrington EW, Blennow M, et al. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003063
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003063.pub3/full

Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD001456
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001456.pub2/full

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.

Anon. Early versus delayed neonatal administration of a synthetic surfactant – the judgment of OSIRIS. Lancet 1992;340:1363-9

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
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000141.pub2/full

Evidence Level: I

Last amended July 2015
Last reviewed November 2017

SYPHILIS
Supporting information

This guideline has been prepared with reference to the following:

British Association for Sexual Health and HIV – BASHH. UK National Guidelines on the Management of Syphilis. Int J STD AIDS. 2016;27:421-46

https://www.bashhguidelines.org/media/1053/syphilis-2015.pdf

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).

Doroshenko A, Sherrard J, Pollard AJ. Syphilis in pregnancy and the neonatal period. Int J STD AIDS 2006; 17: 221–8

Evidence Level: V

Last amended February 2017
Last reviewed November 2017

THROMBOCYTOPENIA
Supporting information

This guideline has been prepared with reference to the following:

New HV, Berryman J, Bolton-Maggs PH et al. Guidelines on transfusion for fetuses, neonates and older children. Br J Haematol. 2016;175:784-828

http://onlinelibrary.wiley.com/doi/10.1111/bjh.14233/full

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-Marin, 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 Kamphuis et al. (2014) of 6 prospective studies found 59,425 newborns screened for severe thrombocytopenia, of which 89 (0.15%) tested positive.

Ferrer-Marin F, Liu ZJ, Gutti R, et al. Neonatal thrombocytopenia and megakaryocytopoiesis. Semin Hematol 2010;47:281-8
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2934854/

Kamphuis M, Paridaans N, Porcelijn L et al. Incidence and consequences of neonatal alloimmune thrombocytopenia: a systematic review. Pediatrics 2014, 133:715-721
http://pediatrics.aappublications.org/content/early/2014/02/25/peds.2013-3320.full.pdf+html

Knight M, Pierce M, Allen D, et al. The incidence and outcomes of fetomaternal alloimmune thrombocytopenia: a UK national study using three data sources. Br J Haematol 2011;152:460-8
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2010.08540.x/full

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).

Sola-Visner M, Saxonhouse MA, Brown RE. Neonatal thrombocytopenia: what we do and don't know. Early Hum Develop 2008;84:499-506

Evidence Level: V

Last amended November 2016
Last reviewed November 2017

TRANSCUTANEOUS CO_2 AND O_2
Supporting information

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 (Hejilsesn, 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 (PC02 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.

Hejlesen OK, Cichosz SL, Vangsgaard S, et al. Clinical implications of a quality assessment of transcutaneous CO2 monitoring in preterm infants in neonatal intensive care. Studies Health Technol Informat 2009;150:490-4

Sandberg KL, Brynjarsson H, Hjalmarson O. Transcutaneous blood gas monitoring during neonatal intensive care. Acta Paediatr 2011; 100:676-9.

Evidence Level: IV

Last amended August 2013
Last reviewed November 2017

TRANSFUSION OF RED BLOOD CELLS
Supporting information

This guideline has been prepared with reference to the following:

New HV, Berryman J, Bolton-Maggs PH et al. Guidelines on transfusion for fetuses, neonates and older children. Br J Haematol. 2016;175:784-828

http://onlinelibrary.wiley.com/doi/10.1111/bjh.14233/full

Norfolk D. 10.2: Neonatal transfusion in Handbook of Transfusion Medicine 5th ed. 2014. 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) reported no differences in mesenteric blood flow in babies. One of review trials reported on mortality and described no differences between the two arms.

Kasat K, Hendricks-Munoz KD, Mally PV. Neonatal red blood cell transfusions: searching for better guidelines. Blood Transfusion 2011;9:86-94
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 systematic review of randomized controlled trials. Br. J Haematol; 158:370-85
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09180.x/full

Evidence Level: V

Last amended November 2016
Last reviewed November 2017

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).

Mori R, Fujimura M, Shiraishi J, et al. Duration of inter-facility neonatal transport and neonatal mortality: systematic review and cohort study. Pediatr Int 2007;49:452-8

Evidence Level: III

Last amended September 2007
Last reviewed November 2017

TUBERCULOSIS
(INVESTIGATION AND MANAGEMENT FOLLOWING EXPOSURE IN PREGNANCY)
Supporting information

This guideline has been prepared with reference to the following:

NICE. Tuberculosis: guidance. 2016. NICE. London

https://www.nice.org.uk/guidance/ng33

Last amended March 2017
Last reviewed November 2017

UMBILICAL ARTERY CATHETERISATION & REMOVAL
Supporting information

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.

Inglis GT, Jardine LA, Davies W. Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD004697
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004697.pub3/full

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).
A 2015 study compared Wright's formula with the Dunn Method and found that the former was significantly more accurate in measuring the correct insertion length for term, low birth weight and very low birth weight newborns (success rate 83% vs 61% [p<0.05]) (Min, 2015).

Min SR, Lee HS. Comparison of Wright's formula and the Dunn method for measuring the umbilical arterial catheter insertion length. Pediatr Neonatol. 2015;56:120-5
http://www.sciencedirect.com/science/article/pii/S1875957214001363?via%3Dihub

Wright IM, Owers M, Wagner M. The umbilical arterial catheter: a formula for improved positioning in the very low birth weight infant. Pediatr Crit Care Med 2008;9:498-501

Evidence Level: II

Last amended November 2017
Last reviewed November 2017

UMBILICAL VENOUS CATHETERISATION & REMOVAL
Supporting information

Are alcohol swabs useful for disinfection of the skin?

A 2016 systematic review of 3 RCTs (855 patients) found that chlorhexidine dressing/alcohol skin cleansing reduced catheter colonisation (risk ratio [RR] 0.62, 95% CI 0.45 to 0.86; number needed to treat for an additional beneficial outcome 11, 95% CI 7 to 33), but made no significant difference in major outcomes like sepsis (RR 1.06, 95% CI 0.75 to 1.52) and catheter-related blood stream infection (RR 1.18, 95% CI 0.53 to 2.65; 95% CI −0.02 to 0.03) compared to polyurethane dressing/povidone-iodine cleansing. Chlorhexidine dressing/alcohol cleansing posed a substantial risk of contact dermatitis in preterm infants (RR 43.06, 95% CI 2.61 to 710.44; number needed to treat for an additional harmful outcome 17, 95% CI 13 to 33).

Lai NM, Taylor JE, Tan K et al. Antimicrobial dressings for the prevention of catheter-related infections in newborn infants with central venous catheters. Cochrane Database Syst Rev. 2016 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011082.pub2/full

Evidence Level: I

Last amended September 2017
Last reviewed November 2017

UPPER LIMB INJURIES
Supporting information

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.

Backe B, Magnussen EB, Johansen OJ, et al. Obstetric brachial plexus palsy: a birth injury not explained by the known risk factors. Acta Obstet Gynecol Scand 2008;87:1027-32

Evidence Level: IV

Last amended March 2011
Last reviewed November 2017

URINARY TRACT ABNORMALITIES ON ANTENATAL SCAN
Supporting information

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).

Dinneen MD, Duffy PG. Posterior urethral valves. Br J Urol 1996;78:275-81

Gonzales ET. Alternatives in the management of posterior urethral valves. Urol Clin N Am 1990;17:335-42

Nguyen TH, Thorup JM, Larsen T. Vesico-amniotic shunt-therapy in fetal obstructive uropathy. Ugeskr Laeger 1996;158:5463-4

Quintero RA, Shukla AR, Homsy YL, et al. Successful in utero endoscopic ablation of posterior urethral valves: a new dimension in fetal urology. Urology 2000;55:774

Ropacka M, Markwitz W, Nycz P, et al. Intrauterine therapy of obstructive uropathy: case report. Ginekol Pol 2001;72:153-9

Shimada K, Hosokawa S, Tohda A, et al. Follow-up of children after fetal treatment for obstructive uropathy. Int J Urol 1998;5:312-6

Thomas DF, Gordon AC. Management of prenatally diagnosed uropathies. Arch Dis Child Fetal Neonatal Ed 1989;64:58-63
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1590073/pdf/archdisch00902-0062.pdf

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%.

Anderson NG, Wright S, Abbott GD, et al. Fetal renal pelvic dilatation: poor predictor of familial vesicoureteral reflux. Pediatr Nephrol 2003; 18:902-5

Coplen DE, Austin PF, Yan Y, et al. The magnitude of fetal renal pelvic dilatation can identify obstructive postnatal hydronephrosis, and direct postnatal evaluation and management. J Urol 2006;176:724-7

Phan V, Traubici J, Hershenfield B, et al. Vesicoureteral reflux in infants with isolated antenatal hydronephrosis. Pediatr Nephrol 2003;18:1224-8

Scott JE, Renwick M. Antenatal renal pelvic measurements: what do they mean? BJU Int 2001;87:376-80
http://onlinelibrary.wiley.com/doi/10.1046/j.1464-410x.2001.00069.x/full

Evidence Level: V

Babies with VUR diagnosed as a result of antenatal scans have an increased risk of renal scarring?

A small study comparing 21 neonates with antenatally detected VUR and 30 with postnatally detected VUR (Ylinen, 2003) found new scarring only in the latter group, and associated with VUR grades 4 and 5. The authors concluded that the risk of acquired renal scarring was significantly higher if dilating VUR was not detected antenatally.

A retrospective review of 202 patients (Chen, 2003) compared 146 presenting with UTI with 56 who had been diagnosed antenatally and found no significant differences between the two, including risk of scarring.

However, VUR diagnosed antenatally tends to be of a higher grade, which may predispose towards increased risk of scarring when combined with infection in postnatal life (Gordon, 1990).

A study in 64 children (Taskinen, 2005) found that renal scars after a first episode of pyelonephritis were generally caused by the infection itself, rather than being associated with abnormalities of the urinary tract.

A retrospective follow-up study of 53 children with prenatally detected VUR (Penido, 2006) found a significant correlation between severe reflux and renal damage scars (RR=3.4, 95% CI 1.4-8.0, p=0.002).

Chen JJ, Pugach J, West D, et al. Infant vesicoureteral reflux: a comparison between patients presenting with a prenatal diagnosis and those presenting with a urinary tract infection. Urology 2003;61:442-6

Gordon AC, Thomas DF, Arthur RJ, et al. Prenatally diagnosed reflux: a follow up study. Br J Urol 1990;65:407-12

Penido SJ, Oliveira EA, Diniz JS, et al. Clinical course of prenatally detected primary vesicoureteral reflux. Pediatr Nephrol 2006;21:86-91

Taskinen S, Ronnholm K. Post-pyelonephritic renal scars are not associated with vesicoureteral reflux in children. J Urol 2005;173:1345-8

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?

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).

Eckoldt F, Woderich R, Wolke S, et al. Follow-up of unilateral multicystic kidney dysplasia after prenatal diagnosis. J Matern Fetal Neonatal Med 2003;14:177-86

Kaneko K, Suzuki Y, Fukuda Y, et al. Abnormal contralateral kidney in unilateral multicystic dysplastic kidney disease. Pediatr Radiol 1995;25:275-7

Karmazyn B, Zerin JM. Lower urinary tract abnormalities in children with multicystic dysplastic kidney. Radiology 1997;203:223-6

Miller DC, Rumohr JA, Dunn RL, et al. What is the fate of the refluxing contralateral kidney in children with multicystic dysplastic kidney? J Urol 2004;172:1630-4

Zerin JM, Leiser J. The impact of vesicoureteral reflux on contralateral renal length in infants with multicystic dysplastic kidney. Pediatr Radiol 1998;28:683-6

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.

Chertin B, Rolle U, Farkas A, et al. Does delaying pyeloplasty affect renal function in children with a prenatal diagnosis of pelvi-ureteric junction obstruction? BJU Int 2002;90:72-5
http://onlinelibrary.wiley.com/doi/10.1046/j.1464-410X.2002.02829.x/full

Josephson S. Postnatal management of antenatally suspected pelviureteric junction obstruction: decision factors. In: O’Donnell B, Koff SA (eds). Pediatric urology. 3rd ed. Oxford, Butterworth-Heinemann, 1997. p392-5

King LR, Coughlin PW, Bloch EC, et al. The case for immediate pyeloplasty in the neonate with ureteropelvic junction obstruction. J Urol 1984;132:725-8

Koff SA, Campbell K. Nonoperative management of unilateral neonatal hydronephrosis. J Urol 1992;148:525-31

Evidence Level: IV

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

Payne JT, Loken MK. A survey of the benefits and risks in the practice of radiology. CRC Crit Rev Clin Radiol Nucl Med 1975;6:425-39

Ron E. Cancer risks from medical radiation. Health Phys 2003;85:47-59

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?

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.
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).

Bourke WG, Clarke TA, Mathews TG, et al. Isolated single umbilical artery: the case for routine renal screening. Arch Dis Child 1993;68:600-01
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1029313/pdf/archdisch00549-0072.pdf

Deshpande SA, Watson H. Renal ultrasonography not required in babies with isolated minor ear anomalies. Arch Dis Child Fetal Neonatal Ed 2006;91:F29-30
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672645/

Doornebal N, de Vries TW, Bos AF. Screening infants with an isolated single umbilical artery for renal anomalies: Nonsense? Early Hum Dev 2007;83:567-70

Wang RY, Earl DL, Ruder RO, et al. Syndromic ear anomalies and renal ultrasounds. Pediatrics 2001;108:E32
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; Rossleigh, 1996; Bellah, 1995) and in pelvic kidneys (Hill, 1994; Takeuchi, 1994; Donahoe, 1980).

Bellah RD, Long FR, Canning DA. Ureterocele eversion with vesicoureteral reflux in duplex kidneys: findings at voiding cystourethrography. Am J Roentgenol 1995;165:409-13

Cascio S, Sweeney B, Granata C, et al. Vesicoureteral reflux and ureteropelvic junction obstruction in children with horseshoe kidney: treatment and outcome. J Urol 2002;167:2566-8

Cheng SW, Sheih CP, Liao YJ, et al. Ultrasonic demonstration of ectopic urethral ureter in duplex kidney: report of two cases. Acta Paediatr Sin 1997;38:149-51

Cho JY, Lee YH, Toi A, et al. Prenatal diagnosis of horseshoe kidney by measurement of the renal pelvic angle. Ultrasound Obstet Gynecol 2005;25:554-8

Donahoe PK, Hendren WH. Pelvic kidney in infants and children: experience with 16 cases. J Pediatr Surg 1980;15:486-95

Hill LM, Grzybek P, Mills A, et al. Antenatal diagnosis of fetal pelvic kidneys. Obstet Gynecol 1994;83:333-6
http://onlinelibrary.wiley.com/doi/10.1046/j.1469-0705.1995.05060391.x/epdf

Rossleigh MA. Neonatal diagnosis with Tc-99m dimercaptosuccinic acid of intra-uterine reflux nephropathy in duplex kidneys. Clin Nucl Med 1996;21:897

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

Takeuchi T, Hara H, Nakashima Y, et al. Pelvic kidney: three case reports – reconstructive surgery for associated urinary tract abnormalities. Nishinihon J Urol 1994;56:61-6

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

Garin EH, Olavarria F, Garcia N et al. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 2006;117:626-32.

Wald ER. Vesicoureteral reflux: the role of antibiotic prophylaxis. Pediatrics 2006;117:919-22

Evidence Level: II

Last amended October 2007
Last reviewed November 2017

VARICELLA
Supporting information

This guideline has been prepared with reference to the following:

Public Health England. Guidance on viral rash in pregnancy. 2016. London. PHE

https://www.gov.uk/government/publications/viral-rash-in-pregnancy

Royal College of Obstetricians and Gynaecologists. Chickenpox in pregnancy. Guideline No. 13. 2015. London. RCOG

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg13/

Public Health England. Varicella, from Immunisation against infectious disease - 'The Green Book'. 2015. London. PHE

https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34

HPA Rash Guidance Working Group. Guidance on Viral Rash in Pregnancy: Investigation, Diagnosis and Management of Viral Rash Illness, or Exposure to Viral Rash Illness, in Pregnancy. 2011. Health Protection Agency

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/322688/Viral_rash_in_pregnancy_guidance.pdf

Public Health England. Chicken Box, Chapter 6 from Immunoglobulin Handbook. 2008.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/337630/Immunoglobulin_handbook_General_Information_July_2014.pdf

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 chicken pox 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).

Royal College of Obstetricians and Gynaecologists. Chickenpox in pregnancy. Guideline No. 13. 2015. London. RCOG
https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg13/

Department of Health.. Immunisation against infectious disease. London: DoH, 2013.
https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34

Heuchan AM, Isaacs D. The management of varicella-zoster virus exposure and infection in pregnancy and the newborn period. Australasian Subgroup in Paediatric Infectious Diseases of the Australasian Society for Infectious Diseases. Med J Aust 2001;174:288-92

Reynolds L, Struik S, Nadel S. Neonatal varicella: varicella zoster immunoglobulin (VZIG) does not prevent disease. Arch Dis Child Fetal Neonatal Ed 1999;81:F69-F70

Evidence Level: V

Last amended May 2017
Last reviewed November 2017

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VENEPUNCTURE
Supporting information

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
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001452.pub4/full

Evidence Level: I

Sucrose may be used for analgesia?
A 2016 systematic review of 9 RCTs found high-quality evidence for the use of 2 mL 24% sucrose prior to venepuncture (Stevens, 2016). Premature Infant Pain Profile (PIPP) during venepuncture was reduced by a weighted mean difference of 2.79 (95% confidence interval [CI] 3.76 to 1.83).
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 it did 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).

Dilen B, Elseviers M. Oral glucose solution as pain relief in newborns: results of a clinical trial. Birth 2010;37:98-105

Stevens B, Yamada J, Ohlsson A et al. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev. 2016
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001069.pub5/full

Taddio A, Shah V, Stephens D et al. Effects of liposomal lidocaine and sucrose alone and in combination for venepuncture pain in newborns. Pediatrics 2011; 127: 940-7
http://pediatrics.aappublications.org/content/127/4/e940.long

Evidence Level: I

Last amended November 2017
Last reviewed November 2017

VENTILATION (CONVENTIONAL)
Supporting information

Synchronised mechanical ventilation is superior to conventional ventilation?
A Cochrane systematic review of 22 studies (Greenough, 2016) found that synchronised mechanical ventilation was associated with a reduction in the risk of air leak (RR 0.69, 95% CI 0.51 to 0.93) and a shorter duration of ventilation (weighted mean difference -38.3 hrs, 95% CI -53.9 to -22.7), compared to conventional ventilation.

Greenough A, Rossor T, Sundaresan et al. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database Syst Rev. 2016, No.: CD000456
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000456.pub5/full

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." A 2017 Cochrane review similarly concluded that there was insufficient evidence to support the use of Clonidine as a sedative in the mechanical ventilation of newborns (Romantsik, 2017).

Bellù R, de Waal KA, Zanini R. Opioids for neonates receiving mechanical ventilation. Cochrane Database Syst Rev. 2008, No.: CD004212
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004212.pub3/full

Romantsik O, Calevo MG, Norman E et al. Clonidine for sedation and analgesia for neonates receiving mechanical ventilation. Cochrane Database Syst Rev. 2017: CD012468
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012468.pub2/full

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 Syst Rev. 2010, No.: CD000139
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000139.pub2/full

Evidence Level: I

Last amended September 2017
Last reviewed November 2017

VENTILATION: HIGH FREQUENCY OSCILLATORY VENTILATION
Supporting information

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).

Ben Jaballah N, Khaldi A, Mnif K, et al. High-frequency oscillatory ventilation in pediatric patients with acute respiratory failure. Pediatr Crit Care Med 2006;7:362-7

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

Clark RH, Gerstmann DR, Null DM, et al. Pulmonary interstitial emphysema treated by high-frequency oscillatory ventilation. Crit Care Med 1986;14:926-30

Cools, F, Askie, LM, Asselin, JM et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. Lancet, 06 2010; 375: 2082-91

Delemos RA, Coalson JJ, Gerstmann DR, et al. Ventilatory management of infant baboons with hyaline membrane disease: the use of high frequency ventilation. Pediatr Res 1987;21:594-602

Greenough A, Roberton NR. Acute respiratory disease in the newborn. In: Rennie JM, Roberton NR, eds. Textbook of neonatology, 3rd ed. Edinburgh, Churchill Livingstone, 1999. p559

Henderson-Smart DJ, De Paoli AG, Clark RH, et al. High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD002974
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002974.pub2/full

Kohelet C, Perlman M, Kirpalani H, et al. High-frequency oscillation in the rescue of infants with persistent pulmonary hypertension. Crit Care Med 1988;16:510-6

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

Soll RF. The clinical impact of high frequency ventilation: review of the Cochrane meta-analyses. J Perinatol 2006;26(Suppl 1):S38-S42

Vierzig A, Gunther M, Kribs A, et al. Clinical experiences with high-frequency oscillatory ventilation in newborns with severe respiratory distress syndrome. Crit Care Med 1994;22(9 Suppl):S83-S87

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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, F IO(2), OI, and P AO(2) – Pa O(2) (P </= 0.01). The authors also identified a need for RCTs to confirm the perceived benefits of HFOV vs conventional ventilation.

Ben Jaballah N, Mnif K, Khaldi A, et al. High-frequency oscillatory ventilation in term and near-term infants with acute respiratory failure: early rescue use. Am J Perinatol 2006;23:403-11

De Paoli A, Clark R & Bhuta T. High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term. The Cochrane Database of Systematic Reviews 2009. Art. No.: CD002974
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002974.pub2/full

Bhuta T, Henderson-Smart DJ. Rescue high frequency oscillatory ventilation vs conventional ventilation for pulmonary dysfunction in preterm infants. The Cochrane Database of Systematic Reviews 1998, Issue 2. Art. No.: CD000438
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000438/full

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

Courtney SE, Durand DJ, Asselin JM, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 2002;347:643-52
http://www.nejm.org/doi/full/10.1056/NEJMoa012750#t=articleTop

Johnson AH, Peacock JL, Greenough A, et al. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med 2002;347:633-42
http://www.nejm.org/doi/full/10.1056/NEJMoa020432#t=articleTop

Rojas MA, Lozano JM, Rojas et al. Randomized, multicentre trial of conventional ventilation versus high-frequency oscillatory ventilation for the early management of respiratory failure in term or near-term infants in Colombia. Journal of Perinatology 2005;25:720-4.

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

Evidence Level: I

What should the starting settings be when commencing HFOV?
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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.

Battin M. Newborn services clinical guidelines: High frequency ventilation (HFV). 2001 http://www.adhb.govt.nz/newborn/guidelines/respiratory/hfov/hfov.htm

Chan V, Greenough A. Determinants of oxygenation during high frequency oscillation. Eur J Pediatr 1993;152:350-3

Froese AB, Butler PO, Fletcher WA, et al. High-frequency oscillatory ventilation in premature infants with respiratory failure: a preliminary report. Anesth Analg 1987;66:814-24

Greenough A, Roberton NR. Acute respiratory disease in the newborn. In: Rennie JM, Roberton NR, eds. Textbook of neonatology, 3rd ed. Edinburgh, Churchill Livingstone, 1999. p569

Hoskyns EW, Milner AD, Hopkin IE. Combined conventional ventilation with high frequency oscillation in neonates. Eur J Pediatr 1991;150:357-61

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).

Greenough A, Roberton NR. Acute respiratory disease in the newborn. In: Rennie JM, Roberton NR, eds. Textbook of neonatology, 3rd ed. Edinburgh, Churchill Livingstone, 1999. p569

Cools F, Offringa M & Askie L. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. The Cochrane Database of Systematic Reviews 2014. Art. No.: CD000104
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000104.pub4/epdf

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
- 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

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- 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 http://www.adhb.govt.nz/newborn/guidelines/respiratory/hfov/hfov.htm

Mehta NM, Arnold JH. Mechanical ventilation in children with acute respiratory failure. Curr Opin Crit Care 2004;10:7-12

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.

Courtney SE, Durand DJ, Asselin JM, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 2002;347:643-52 http://www.nejm.org/doi/full/10.1056/NEJMoa012750#t=articleTop

Seller L, Mullahoo K, Liben S, et al. Weaning to extubation directly from high-frequency oscillatory ventilation in an infant with cystic lung disease and persistent air leak: a strategy for lung protection. Respir Care 2001;46:263-6

Evidence Level: V

Last amended September 2015
Last reviewed November 2017

VENTILATION: SYNCHRONOUS POSITIVE PRESSURE (SIPPV)
Supporting information

Is SIPPV superior to conventional mechanical ventilation (CMV)?
A 2016 systematic review of 22 RCTs found that when compared to conventional mechanical ventilation (CMV), synchronised mechanical ventilation, delivered as high-frequency positive pressure ventilation (HFPPV) reduced the risk of air leak (relative risk [RR] for pneumothorax was 0.69, 95% confidence interval [CI] 0.51 to 0.93) and triggered ventilation was associated with a shorter duration of ventilation (mean difference [MD] −38.3 hours, 95% CI −53.90 to −22.69) (Greenough, 2016). Compared to high-frequency oscillation, however, certain triggered modes of ventilation resulted in a greater risk of moderate to severe chronic lung disease (RR 1.33, 95% CI 1.07 to 1.65) and a longer duration of ventilation (MD 1.89 days, 95% CI 1.04 to 2.74).

Greenough A, Rossor TE, Sundaresan A et al. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database Syst Rev. 2016
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000456.pub3/full

Evidence Level: I

Last amended January 2017
Last reviewed November 2017

VENTILATION: VOLUME GUARANTEE/TARGETED TIDAL VOLUME
Supporting information

Volume targeted is more effective than pressure limited ventilation for preterm infants?

A systematic review of 20 RCTs (Klingenberg, 2017) found that use of volume targeted ventilation (VTV) resulted in a reduction in death or bronchopulmonary dysplasia at 36 weeks' gestation (RR 0.73, 95% CI 0.59 to 0.89), rates of pneumothorax (RR 0.52, 95% CI 0.31 to 0.87), mean days of mechanical ventilation (MD -1.35 days, 95% CI -1.83 to -0.86), rates of hypocarbia (RR 0.49, 95% CI 0.33 to 0.72), rates of grade 3 or 4 intraventricular haemorrhage (RR 0.53, 95% CI 0.37 to 0.77) and the combined outcome of periventricular leukomalacia with or without grade 3 or 4 intraventricular haemorrhage (RR 0.47, 95% CI 0.27 to 0.80). No statistical difference was found for death before hospital discharge (RR 0.75, 95% CI 0.53 to 1.07).VTV modes were not associated with any increased adverse outcomes.

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).

Klingenberg C, Wheeler KI, McCallion N et al. Volume-targeted versus pressure-limited ventilation in neonates. Cochrane Database Syst Rev. 2017
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003666.pub4/full

Peng W, Zhu H, Shi H et al. Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Arc dis childhood. Fetal & neonatal ed, 2014:99;F158.

Evidence Level: I

Last amended September 2017
Last reviewed November 2017

VITAMIN K PROPHYLAXIS IN NEWBORNS
Supporting information

All babies should be offered vitamin K prophylaxis?
A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends that all newborn infants should receive vitamin K prophylaxis (Mihatsch, 2016).
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).

Mihatsch WA, Braegger C, Bronsky J et al. Prevention of Vitamin K Deficiency Bleeding in Newborn Infants: A Position Paper by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2016;63:123-9
http://www.zora.uzh.ch/id/eprint/134095/1/MihatschWA_2016.pdf

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
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002776/full

Evidence Level: I

Last amended March 2017
Last reviewed November 2017