Protecting the premature brain: current evidence-based strategies for minimising perinatal brain injury in preterm infants

Charlotte L Lea,[1,2] Adam Smith-Collins,[1,2] Karen Luyt[1,2]

[1]Department of Neonatal Neuroscience, St Michael's Hospital, Bristol, UK
[2]School of Clinical Sciences, University of Bristol, Bristol, UK

Correspondence to
Dr Charlotte L Lea, Department of Neonatal Neuroscience, St Michael's Hospital, Office G2, Southwell Street, Bristol BS2 8EG, UK; charlotte.lea@bristol.ac.uk

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ABSTRACT

Improving neurodevelopmental outcome for preterm infants is an important challenge for neonatal medicine. The disruption of normal brain growth and neurological development is a significant consequence of preterm birth and can result in physical and cognitive impairments. While advances in neonatal medicine have led to progressively better survival rates for preterm infants, there has only been a modest improvement in the proportion of surviving infants without neurological impairment, and no change in the proportion with severe disability. The overall number of children with neurodisability due to prematurity is increasing. Trials investigating novel therapies are underway and many have promising early results; however, in the interim, current treatments and management strategies that have proven benefit for neurodevelopment or reduction in neonatal brain injury are often underutilised. We collate the evidence for the efficacy of such interventions, recommended by guidelines or supported by large meta-analysis or randomised control trials. We address controversies that have hindered uptake and problems with translating research into practice. We then look to the future of preterm neuroprotective care.

INTRODUCTION

Survival rates for preterm babies are increasing[1]; however, severe neurological impairment remains a significant consequence of preterm birth.[2 3] Research continues into potential treatments for reducing both the risk of initial brain injury and subsequent neurodevelopmental problems[4]; however, in the interim, these can be reduced by optimising currently approved and recommended practices.

Methods

Medline, Web of Science, the Cochrane database, national and international guidelines were searched for meta-analyses and randomised control trials (RCTs) of interventions affecting neurodevelopment and/or intraventricular haemorrhage (IVH) in preterm infants. We reviewed compliance using the National Neonatal Audit Programme (NNAP)[5]—an audit of nearly all UK neonatal units and the UK Vermont Oxford Network (VON) database,[6] which covers 25% of UK very low birthweight deliveries.

ANTENATAL INTERVENTIONS

Neural development and brain growth are fundamentally affected by the in utero environment.[7] Reducing antenatal risk, including rates of preterm labour, is important, but beyond the scope of this review. Following onset of preterm labour, neuroprotective interventions can be implemented.

Antenatal transfer for anticipated preterm delivery

Mortality for extremely preterm infants (22–26 weeks) is reduced in centres offering the highest level of intensive care (tertiary centres), compared with less specialist centres (OR 0.73 (95% CI 0.59 to 0.9)),[8] supporting the recommendation that care is centralised.[9] Transport of these infants during the first 48 hours is, however, associated with increased rates of severe IVH,[10] and babies born in tertiary centres have significantly better morbidity-free survival than infants transferred there after birth (OR 1.92 (95% CI 1.02 to 3.6)).[8] Despite guidance, only 56% of births in England at 22–26 weeks occurred in tertiary centres in 2006.[8] While the difference in morbidity is likely multifactorial,[10] the findings emphasise the importance of coordinated neonatal and obstetric network strategies for safe antenatal centralisation.

Antenatal steroids

Antenatal steroid therapy is one of the most important advances in perinatal care and has played a significant role in improving survival rates.[11] The delay in translating research on the benefits of antenatal steroids into clinical practice was a main driver for the establishment of the Cochrane Collaboration,[12] and consequently antenatal steroids are recommended for all women with threatened preterm delivery before 34 weeks gestation.[13] Despite this, only 54% of mothers in low-income and middle-income countries are offered them,[14] while 85% of eligible deliveries received one or more doses of antenatal steroids in the UK.[15] Notably, only 67% of liveborn infants at 23 weeks were treated, and 25% of units had rates of 25% or lower.[16]

Incidence of IVH and white matter damage are reduced following antenatal steroids[11 17] (table 1). This is secondary to vasoconstriction of cerebral vessels and anti-inflammatory effects, as well as increased cardiovascular stability related to reduced respiratory compromise.[18]

Meta-analysis shows lower rates of developmental delay and cerebral palsy (CP) and higher cognitive ability in children who received antenatal steroids compared with those who did not.[11] Outcome was improved after a single course, even if preterm delivery was arrested.[25] Evidence demonstrates benefits to the neonate with minimal risks to the mother, following delivery within

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7 days of a single complete course of corticosteroids.[11] This includes cases where tocolysis has been used to delay delivery for treatment, even in the presence of chorioamnionitis.[26]

A RCT is currently comparing outcomes following betamethasone versus dexmethasone,[27] since both are used with differing evidence as to which is safest and best.[28–30] Likewise, the evidence for repeating treatment if delivery has not occurred within 7 days is mixed. Meta-analysis revealed that infants exposed to multiple steroid courses have lower risk of early respiratory morbidity, but tend to have reduced birth weight and head circumference.[31] Current guidance advises against multiple courses, although a single additional rescue course may be appropriate when the first was before 26 weeks gestation.[28]

Magnesium sulfate

Magnesium sulfate ($MgSO_4$), a drug widely used in obstetrics,[32] was recognised as a potential neuroprotectant when data revealed a reduced incidence of IVH in babies whose mothers had received it.[33] Subsequently, a decrease in the incidence of CP was presented[34] and animal models and clinical trials have since corroborated these findings.[19] $MgSO_4$ acts as a non-competitive inhibitor at N-methyl-D-aspartate channels, blocking excess glutamate release, reducing excitotoxicity and consequently oligodendroglial progenitor cell death,[35] as well as modulating the effects of proinflammatory cytokines which are known to correlate with neurological outcome.[36] In addition, due to $MgSO_4$'s vasoactive properties, further benefit may result from stabilisation of blood pressure[37] and cerebral arterial perfusion.[38]

The overall risk of CP, the risk of severe and moderate CP and the incidence of gross motor dysfunction[19] (table 1) are reduced following antenatal $MgSO_4$. Until now, no neurodevelopmental advantage has been seen in later childhood[39 40]; however, individual studies are underpowered to show this. As with many interventions, the lack of proven benefit to composite outcome in older children should not negate the positive early effects.[41]

$MgSO_4$ for neuroprotection prior delivery at <30 weeks is recommended internationally[42–44] with consideration in deliveries <34 weeks also advocated in some regions.[13] Uptake has, however, been suboptimal. Only 38% of eligible UK infants <30 weeks registered on VON received antenatal $MgSO_4$ in the UK in 2014 and in 25% of units the rate was less than 16.8%.[16] From a very recent NNAP report,[45] estimated uptake is similar (36%), although data reporting were incomplete. Concerns about hypotonia and respiratory depression at birth, consequent to $MgSO_4$'s blockade of calcium into cells, are commonplace, but have not been demonstrated in large cohort studies or in the meta-analysis.[46 47] Furthermore, since $MgSO_4$ has anti-inflammatory effects, there have been concerns that it may increase sepsis. Although significant neuroprotective effects were not identified in the setting of chorioamnionitis,[48] there is no evidence that infection risks are increased.[15] The potential benefits of $MgSO_4$ for preterm deliveries 30–34 weeks are being studied, to provide clearer evidence at these higher gestations.[49]

The MagNET trial[50] reported an increase in fetal death in mothers following $MgSO_4$ versus the control group. This concerning difference was only significant when $MgSO_4$ was used at high doses and was not seen in meta-analysis.[19] Cumulative high doses of $MgSO_4$ (>50 g) are associated with IVH and increased mortality[51 52] making clear guidance on dosing crucial. Developing this is impeded by the variability in evidence.[19 35 53] Differing dosing schedules, trial inclusion criteria and mixed intent (obstetric vs fetal neuroprotective) complicate interpretation.[53] A blinded RCT is underway with a view to obtaining more conclusive evidence[54] since previous investigation found a lack of data comparing different regimens.[53] Currently, 4 g loading dose over 20–30 min followed by an infusion of 1 g/hour until birth or for a maximum of 24 hours is endorsed in the UK.[13 55]

Management of preterm prelabour rupture of membranes to reduce chorioamnionitis and early-onset infection

Chorioamnionitis and infections within the first 72 hours of life (early-onset sepsis (EOS)) contribute to adverse neurodevelopmental outcome[56 57] (table 2). Cerebral hypoperfusion, capillary thrombosis and increased permeability of the blood–brain barrier—allowing direct passage of microbial products and proinflammatory cytokines into the cerebral tissue have been suggested to cause fetal brain injury.[58] Several key biomarkers have been identified as targets for future treatments to promote normal neurological development in the presence of antenatal infection[57]; however, prevention of chorioamnionitis following preterm prelabour rupture of membranes (PPROM) is currently the mainstay of recommendations. Prophylactic antibiotics and consideration of immediate delivery after 34 weeks are advocated in the UK[59]; however, both are controversial.

Antibiotics following PPROM (without chorioamnionitis) lead to prolongation of pregnancy, reduction in neonatal

Table 1 Impact on rates of adverse neurodevelopmental outcome for specified interventions

Intervention	Outcome affected	Risk adjustment
Antenatal steroids	IVH (all grades)	RR 0.54 (0.43–0.69)[11]
	Developmental delay (3 years)	RR 0.49 (0.24–1.00)[11]
	CP (all severities 2–6 years)	RR 0.60 (0.34–1.03)[11]
Magnesium sulfate in labour	CP (all severities 12–24 months)	RR 0.68 (0.54–0.87)[19]
	CP (severe and moderate 12–24 months)	RR 0.64 (0.44–0.92)[19]
	Gross motor dysfunction (18–24 months)	RR 0.61 (0.44–0.85)[19]
Deferred cord clamping	IVH (all grades)	RR 0.59 (0.41–0.85)[20]
	Gross motor dysfunction (18–22 months)	OR 0.32 (0.10–0.90)[21]
Caffeine	CP (all severities 12–22 months)	AOR 0.58 (0.390.87)[22]
	Cognitive delay (18–22 months)	AOR 0.81 (0.66–0.99)[22]
Prophylactic indomethacin	IVH (Grades 3 and 4)	RR 0.66 (0.53–0.82)[23]
	Ventriculomegaly, PVL or other white matter echo-abnormalities	RR 0.80 (0.65–0.97)[23]
Volume ventilation	PVL and IVH (Grades 3 and 4)	RR 0.48 (0.28–0.84)[24]

AOR, adjusted OR; CP, cerebral palsy; IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia; RR, relative risk.

Table 2 Impact of acute morbidities on adverse neurodevelopmental outcome

Acute morbidity	Neurodevelopmental outcome	Risk adjustment
		EOS—OR 1.7 (0.84–3.45)[56]
Infection	CP (all types—5 years)	LOS—OR 1.71 (1.14–2.56)[56]
		EOS+LOS—OR 2.33 (1.02–5.33)[56]
NEC	Neurological impairment (18–22 months)	AOR—1.7 (1.2, 2.4)[60]
	Diparetic CP (after surgical NEC +bacteraemia—24 months)	OR—8.4 (1.9–39)[61]

AOR, adjusted OR; CP, cerebral palsy; EOS, early-onset sepsis; LOS, late-onset sepsis; NEC, necrotising enterocolitis.

infection (relative risk (RR) 0.67, 95% CI 0.52 to 0.85)[62] and fewer abnormal cranial ultrasound scans (RR 0.81, 95% CI 0.68 to 0.98).[62] At school age, however, there was no difference in functional, behavioural or attainment outcomes[63] but increased levels of functional impairment were seen in children of mothers who had received erythromycin following spontaneous onset of preterm labour with intact membranes[64] making correct diagnosis essential.

Timing of delivery following PPROM, without evidence of infection or fetal compromise, is also complex. Delayed delivery increases the risk of chorioamnionitis[65]; however, this needs to be balanced against the risks of preterm birth. Meta-analysis concluded that there was insufficient evidence to advocate either, in part since protocols were not comparable with current best practice.[66] Recent RCTs[67 68] have reported no difference in the incidence of neonatal sepsis,[67 68] morbidity or mortality,[67] but increases in preterm complications were seen making recommendation for immediate delivery contentious.[67]

POSTNATAL INTERVENTIONS

Following delivery, physiological instability and systemic inflammation predispose the preterm brain to IVH and white matter damage.[69] Careful consideration and minimisation of these can protect the premature brain.

Deferred cord clamping

Deferred cord clamping (DCC) in preterm infants leads to reduction in mortality and multisystem morbidity, including all grades of IVH.[20 70 71] Recent studies[21] have shown improved motor function at 18–22 months (table 1), whereas previously, no difference in developmental outcome had been recognised.[20] Several mechanisms for the positive effects are hypothesised,[72] including increased blood volume and oxygenation, prevention of iron deficiency anaemia and the transfer of stem and progenitor cells with extensive proliferative capacity, which may contribute to repairing tissues and promoting immunocompetence.[21] Although DCC is recommended when the infant is born in good condition without the need for resuscitation,[13 73] immediate clamping often predominates.[42]

Hesitancy arises from the lack of consensus on optimal timing for DCC and theorised risks such as potential volume overload, polycythaemia, jaundice and interruption of collection of blood for cord blood banking.[20 42 74] Concerns about delayed resuscitation, thermal care and technical difficulties are being addressed through the development and trialling of new equipment to allow transition to be assisted closer to the mother with the cord intact.[75 76] Studies have shown DCC to be feasible, safe and to have significant benefit to preterm infants, with no detriment from the risks above.[20 77]

Caffeine for apnoea of prematurity

Recurrent apnoeas are common in preterm infants and are potentially harmful.[78] In RCT, treatment with caffeine in the first 10 days decreased the incidence of CP and cognitive impairment at 18–21 months in low birthweight at-risk infants.[22] This effect was only partially explained by the reduction in bronchopulmonary dysplasia, a comorbidity that is independently associated with adverse neurodevelopmental outcome.[22 79] Caffeine has been shown to be safer than other methylxanthines and is recommended as a treatment for preterm infants.[78]

Opinion varies as to when to start caffeine. It is hypothesised that starting caffeine early, prior to the period of greatest vulnerability to white matter injury, may be beneficial[80]; however, the only significant benefit seen from this has been the incidence of a persistent ductus arteriosus (PDA).[81] Subsequent studies have shown a reduction in death, bronchopulmonary dysplasia and PDA for infants given caffeine in the first 3 days of life compared with those who received it later[82 83] and a RCT is currently recruiting to investigate prophylactic versus therapeutic caffeine further.[84]

Notably, the neuroprotective effect of caffeine was not significant at 5 years due to reduced statistical power.[85] Increased incidence of cerebellar haemorrhage on MRI has been reported following high-dose caffeine[80]; however, there is extensive evidence that caffeine is safe at standard doses and has lasting multisystem benefits for preterm infants.[78]

Indomethacin prophylaxis for PDA

Closure of the ductus arteriosus is delayed in up to 80% of infants born at <25 weeks[86] and as many as 70% <28 weeks.[86] PDA can be associated with IVH and abnormalities of cerebral perfusion as well as cardiac and pulmonary complications.[86] Optimal management is a topic of great debate—while overall prevalence is high, one-third resolve without intervention and not all of those that persist become clinically significant.[87 88] Trials investigating early versus late treatment of infants with known PDA (targeted treatment) have not shown any difference in mortality or cranial ultrasound abnormalities, leading authors to hypothesise that detriment occurs before the PDA becomes clinically significant.[89] Additionally, targeting treatment depends on access to echocardiographic expertise, which is not universal. Both the timing of intervention and the need to treat at all are contested.[88]

Indomethacin prophylaxis significantly reduces the incidence of severe IVH and leads to a borderline significant reduction in ventriculomegaly, periventricular leukomalacia (PVL) or other white matter echo-abnormalities[23] (table 1). There was no difference in mortality, necrotising enterocolitis (NEC) or other complications.[23] Fewer infants required surgical ligation following prophylaxis,[23] hence were not exposed to the risks of cardiac surgery, which include detriment to neurodevelopment.[90] In addition to closing, and therefore reducing the haemodynamic consequences of, the PDA, it is postulated that indomethacin may have a direct effect on the brain. It reduces prostaglandin synthesis and the cerebral vascular hyperaemic response as well as promoting the maturation of the basement membrane and basal lamina making the brain less vulnerable to hypoxic, hypercapnic and hypertensive insults.[91] Prophylaxis based on risk criteria has shown the effect of prophylactic

indomethacin is more significant in infants at higher risk of IVH.[92 93]

Practice is varied, with limited uptake despite convincing neonatal results.[94] Indomethacin can be difficult to source, with supply limiting both clinical use and research and[89] no difference in developmental outcome at 18–36 months was seen in meta-analysis.[23] There are concerns this may be due to detriment caused to infants without a PDA or those in whom it would close spontaneously.[89 95]

There is, however, no evidence of harm, and a significant reduction in cognitive disability at 4–5 years[96] and better language development in boys at 8 years[97] have since been reported following prophylactic indomethacin. The harms of potentially unnecessary intervention in some need to be balanced against the benefit for others, yet the current cumulative evidence is that prophylactic indomethacin is safe and pertains to short-term neonatal advantages which are linked with improved neurodevelopmental outcome.[23]

Volume-targeted ventilation to prevent hypocarbia

Although antenatal steroids and surfactant have significantly reduced rates of mechanical ventilation, 69% of VON-registered UK infants <1500 g were ventilated in 2014.[16] This can lead to hypocarbia, causing changes in cerebral blood flow and perfusion pressure, predisposing to PVL.[24] Meta-analysis revealed a statistically significant reduction in hypocarbia in patients receiving volume-targeted ventilation compared with pressure-limited ventilation.[24] This translated into a reduction in the combined outcome of PVL or grade 3–4 IVH[24] (table 1). Although current data are underpowered to determine impact on long-term neurodevelopment, these short-term benefits in reducing detectable brain injury, the mechanistic validity and the lack of demonstrable harm provide a strong basis for using volume-targeted ventilation modes, when mechanical ventilation is required.[24]

Risk is theoretically reduced further through end tidal or transcutaneous capnography, through earlier detection and therefore earlier correction of hypocarbia; however, there is currently insufficient evidence to recommend or refute this.[98 99]

PREVENTING CAUSATIVE MORBIDITIES

Late-onset sepsis (LOS), NEC and poor nutritional status are associated with adverse neurodevelopmental outcomes for preterm infants (table 2).[56 100 101] A detailed exploration of the relative importance of different strategies to reduce their incidence is complex and beyond the scope of this review, since there are no consensus recommendations and trials are ongoing; however, some key interventions are briefly highlighted.

Late-onset sepsis

Approximately 21–36% of very low birthweight preterm infants have LOS.[56 100 102] Neurodevelopmental impairment is increased following clinical infection as well as culture-positive sepsis and meningitis when compared with infants without suspected sepsis[103] and the risk is increased further in infants who have experienced both EOS and LOS as a 'double hit'.[56]

Standardised care 'bundles' for central lines—setting and enforcing standards for insertion, maintenance and timely removal decrease infections by up to 67%.[104] Implementation of such a bundle resulted in improved cognitive outcome at 2 years in one report.[105] Antimicrobial stewardship, limited postnatal steroid use, early enteral feeding with breast milk and meticulous hand hygiene are important and cost-effective strategies for reducing the burden of LOS.[104] Preliminary data also suggest bovine lactoferrin supplementation alone and in combination with probiotics may reduce LOS with a large study now recruiting.[106] Immune replacement therapy is being investigated,[104 107] and prophylactic fluconazole in at-risk populations has been shown to reduce invasive candidiasis.[104]

Necrotising enterocolitis

NEC is associated with structural brain injury[61 108] and poor neurodevelopmental outcome (table 2).[60 61 108] NEC requiring surgery is associated with worse outcomes than NEC treated with antibiotics and withholding feeds,[109] and the duration of NEC is proportional to neurodisability.[61] It may be that the systemic inflammatory response associated with NEC results directly in brain injury[61]; however, the causality is unproven and NEC could be a surrogate marker of other predisposing factors such as abdominal surgery, sepsis, organ immaturity or susceptibility to infection.[61] Detailed discussion of strategies to reduce NEC rates, which may provide neuroprotective benefit,[110] is beyond the scope of this review, but the use of probiotics,[111] lactoferrin,[112] promotion of breast milk,[113 114] avoidance of bovine origin products[114] and preventing infection are all likely to be beneficial.[115]

EMERGING STRATEGIES

Melatonin,[116] erythropoietin[117] and stem cell therapies[118] have all shown neuroprotective potential in early studies and research is ongoing into these and other interventions. First-week protein and energy intakes are associated with 18-month developmental outcomes,[119] and meta-analysis has shown that increasing early enteral nutrition may reduce neurodevelopmental impairment.[120] Preterm infants fed with predominantly breast milk had higher deep nuclear grey matter volume at term corrected age,[121] improved developmental scores at 18 months[122] as well as higher IQ and academic achievement at 7 years,[121] although this has not been seen in all studies.[123] Research is ongoing into optimal nutritional regimens; however, it is hypothesised the benefits of early nutrition and breast milk, including fortification, outweigh the risks.[124]

Interventions to ameliorate neurological sequelae following an initial brain injury are also being researched. An RCT comparing drainage, irrigation and fibrinolytic therapy with conventional management after severe IVH with posthaemorrhagic ventricular dilatation reported a reduction in the incidence of death, severe cognitive disability and physical disability at 2 years in the intervention group.[125] School-age follow-up results will be published shortly. Developmental intervention in infants at risk of disability may also improve outcomes; however, due to the heterogeneity of trials, more research is required for determining what type of intervention is most beneficial.[126]

SUMMARY AND CONCLUSIONS

We present a review of interventions that are known to reduce the incidence of preterm brain injury and/or improve neurodevelopmental outcome. Although recommended, translation of this—like much other— research into practice is far from complete. While research is ongoing into new therapies and the relative importance and interplay of current strategies, broader awareness of available measures and their effective application may lead to improvement in neurodevelopmental outcome for the current cohort of premature infants.

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REFERENCES

1 Costeloe KL, Hennessy EM, Haider S, *et al*. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ* 2012;345:e7976.
2 Moore T, Hennessy EM, Myles J, *et al*. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ* 2012;345:e7961.
3 van Haastert IC, Groenendaal F, Uiterwaal CS, *et al*. Decreasing incidence and severity of cerebral palsy in prematurely born children. *J Pediatr* 2011;159:86–91.e1.
4 Degos V, Loron G, Mantz J, *et al*. Neuroprotective strategies for the neonatal brain. *Anesth Analg* 2008;106:1670–80.
5 http://www.rcpch.ac.uk/improving-child-health/quality-improvement-and-clinical-audit/national-neonatal-audit-programme-nn-3. 2016.
6 https://public.vtoxford.org. 2016.
7 Rees S, Inder T. Fetal and neonatal origins of altered brain development. *Early Hum Dev* 2005;81:753–61.
8 Marlow N, Bennett C, Draper ES, *et al*. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F181–8.
9 Department of Health. *Report of Department of Health Expert Working Group on neonatal intensive care services*. London: Department of Health, 2003.
10 Mohamed MA, Aly H. Transport of premature infants is associated with increased risk for intraventricular haemorrhage. *Arch Dis Child Fetal Neonatal Ed* 2010;95:F403–7.
11 Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2006;(3):CD004454.
12 Dickersin K, Manheimer E. The Cochrane Collaboration: evaluation of health care and services using systematic reviews of the results of randomized controlled trials. *Clin Obstet Gynecol* 1998;41:315–31.
13 Preterm labour and birth. NICE guidelines (NG25), 2015.
14 Vogel JP, Souza JP, Gülmezoglu AM, *et al*. Use of antenatal corticosteroids and tocolytic drugs in preterm births in 29 countries: an analysis of the WHO Multicountry Survey on Maternal and Newborn Health. *Lancet* 2014;384:1869–77.
15 Royal College of Paediatrics and Child Health. National Neonatal Audit Programme 2015 Annual Report on 2014 data, 2015.
16 Vermont Oxford Network. *Database of very low birth weight infants born in 2014*. Burlington, VT: Vermont Oxford Network.
17 O'Shea TM, Doyle LW. Perinatal glucocorticoid therapy and neurodevelopmental outcome: an epidemiologic perspective. *Semin Neonatol* 2001;6:293–307.
18 Schwab M, Roedel M, Anwar MA, *et al*. Effects of betamethasone administration to the fetal sheep in late gestation on fetal cerebral blood flow. *J Physiol* 2000;528:619–32.
19 Doyle LW, Crowther CA, Middleton P, *et al*. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* 2009;(1):CD004661.
20 Rabe H, Diaz-Rossello JL, Duley L, *et al*. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2012;(8):CD003248.
21 Mercer JS, Erickson-Owens DA, Vohr BR, *et al*. Effects of placental transfusion on neonatal and 18 month outcomes in preterm infants: a randomized controlled trial. *J Pediatr* 2016;168:50–5.e1.
22 Schmidt B, Roberts RS, Davis P, *et al*. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;357:1893–902.
23 Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev* 2010;(7):CD000174.
24 Wheeler KI, Klingenberg C, Morley CJ, *et al*. Volume-targeted versus pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Neonatology* 2011;100:219-27.
25 Sotiriadis A, Tsiami A, Papatheodorou S, *et al*. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. *Obstet Gynecol* 2015;125:1385–96.
26 Been JV, Degraeuwe PL, Kramer BW, *et al*. Antenatal steroids and neonatal outcome after chorioamnionitis: a meta-analysis. *BJOG* 2011;118:113–22.
27 Crowther CA, Harding JE, Middleton PF, *et al*. Australasian randomised trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID): study protocol. *BMC Pregnancy Childbirth* 2013;13:104.
28 Roberts D. *Antenatal Corticosteroids to reduce Neonatal Morbidity and Mortality*. Green—top Guideline No. 7. Royal College of Obstetricians and Gynaecologists, 2010.
29 Baud O, Foix-L'Helias L, Kaminski M, *et al*. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. *N Engl J Med* 1999;341:1190–6.
30 Brownfoot FC, Crowther CA, Middleton P. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2008;(4):CD006764.
31 Crowther CA, McKinlay CJD, Middleton P, *et al*. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *Cochrane Database Syst Rev* 2015;(7):CD003935.
32 Bennett P, Edwards D. Use of magnesium sulphate in obstetrics. *Lancet* 1997;350:1491–1.
33 Kuban KCK, Leviton A, Pagano M, *et al*. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. *J Child Neurol* 1992;7:70–6.
34 Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics* 1995;95:263–9.
35 Chang E. Preterm birth and the role of neuroprotection. *BMJ* 2015;350:g6661.
36 Suzuki-Kakisaka H, Sugimoto J, Tetarbe M, *et al*. Magnesium sulfate increases intracellular magnesium reducing inflammatory cytokine release in neonates. *Am J Reprod Immunol* 2013;70:213–20.
37 Rantonen TH, Grönlund JU, Jalonen JO, *et al*. Comparison of the effects of antenatal magnesium sulphate and ritodrine exposure on circulatory adaptation in preterm infants. *Clin Physiol Funct Imaging* 2002;22:13–17.
38 Macdonald RL, Curry DJ, Aihara Y, *et al*. Magnesium and experimental vasospasm. *J Neurosurg* 2004;100:106–10.
39 Doyle LW, Anderson PJ, Haslam R, *et al*. School-age outcomes of very preterm infants after antenatal treatment with magnesium sulfate vs placebo. *JAMA* 2014;312:1105–13.
40 Chollat C, Enser M, Houivet E, *et al*. School-age outcomes following a randomized controlled trial of magnesium sulfate for neuroprotection of preterm infants. *J Pediatr* 2014;165:398–400.e3.
41 Marlow N. Is survival and neurodevelopmental impairment at 2 years of age the gold standard outcome for neonatal studies? *Arch Dis Child Fetal Neonatal Ed* 2015;100:F82–4.
42 American College of Obstetricians and Gynecologists Committee on Obstetric, Practice, Society for Maternal-Fetal Medicine. Committee Opinion No. 455: magnesium sulfate before anticipated preterm birth for neuroprotection. *Obstet Gynecol* 2010;115:669–71.
43 The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel. *Antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus, infant and child: National clinical practice guidelines.* Adelaide: The University of Adelaide, 2010. (www.adelaide.edu.au/arch)
44 Royal College of Obstetricians and Gynaecologists. Magnesium sulphate to prevent cerebral palsy following preterm birth: Scientific impact paper no. 29, 2011.
45 The Royal College of Paediatrics and Child Health. NNAP 2016 Dataset Audit Measures, 2016. http://www.rcpch.ac.uk/system/files/protected/page/2016 audit measures.v.1.pdf
46 Weisz DE, Shivananda S, Asztalos E, *et al*. Intrapartum magnesium sulfate and need for intensive delivery room resuscitation. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F59–65.
47 De Jesus LC, Sood BG, Shankaran S, *et al*. Antenatal magnesium sulfate exposure and acute cardiorespiratory events in preterm infants. *Am J Obstet Gynecol* 2015;212:94.e1–7.
48 Kamyar M, Manuck TA, Stoddard GJ, *et al*. Magnesium sulfate, chorioamnionitis, and neurodevelopment after preterm birth. *BJOG* 2016;123:1161–6.
49 Crowther CA, Middleton PF, Wilkinson D, *et al*., MAGENTA Study Group. Magnesium sulphate at 30 to 34 weeks' gestational age: neuroprotection trial (MAGENTA)—study protocol. *BMC Pregnancy Childbirth* 2013;13:91.
50 Mittendorf R, Covert R, Boman J, *et al*. Is tocolytic magnesium sulphate associated with increased total paediatric mortality? *Lancet* 1997;350:1517–18.
51 Mittendorf R, Dammann O, Lee KS. Brain lesions in newborns exposed to high-dose magnesium sulfate during preterm labor. *J Perinatol* 2006;26:57–63.
52 Ohhashi M, Yoshitomi T, Sumiyoshi K, *et al*. Magnesium sulphate and perinatal mortality and morbidity in very-low-birthweight infants born between 24 and 32 weeks of gestation in Japan. *Eur J Obstet Gynecol Reprod Biol* 2016;201:140–5.
53 Bain E, Middleton P, Crowther CA. Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth. *Cochrane Database Syst Rev* 2012;(2):CD009302.
54 Huusom LD, Brok J, Hegaard HK, *et al*. Does antenatal magnesium sulfate prevent cerebral palsy in preterm infants? The final trial? *Acta Obstet Gynecol Scand* 2012;91:1346–7.
55 Oddie S, Tuffnell DJ, McGuire W. Antenatal magnesium sulfate: neuro-protection for preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F553–57.
56 Mitha A, Foix-L'Helias L, Arnaud C, *et al*. Neonatal infection and 5-year neurodevelopmental outcome of very preterm infants. *Pediatrics* 2013;132:E372–80.
57 Cordeiro CN, Tsimis M, Burd I. Infections and brain development. *Obstet Gynecol Surv* 2015;70:644–55.

58 Spinillo A, Iacobone AD, Calvino IG, *et al*. The role of the placenta in feto-neonatal infections. *Early Hum Dev* 2014;90(Suppl 1):S7–9.
59 Preterm Prelabour Rupture of Membranes Green-top Guideline No 44. Royal College of Obstetrics and Gynaecology, 2006 (minor corrections 2010).
60 Wadhawan R, Oh W, Hintz SR, *et al*. Neurodevelopmental outcomes of extremely low birth weight infants with spontaneous intestinal perforation or surgical necrotizing enterocolitis. *J Perinatol* 2014;34:64–70.
61 Martin CR, Dammann O, Allred EN, *et al*. Neurodevelopment of extremely preterm infants who had necrotizing enterocolitis with or without late bacteremia. *J Pediatr* 2010;157:751–6.
62 Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. *Cochrane Database Syst Rev* 2013;(12):CD001058.
63 Kenyon S, Pike K, Jones DR, *et al*. Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. *Lancet* 2008;372:1310–18.
64 Kenyon S, Pike K, Jones DR, *et al*. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet* 2008;372:1319–27.
65 Hannah ME, Ohlsson A, Farine D, *et al*. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. TERMPROM Study Group. *N Engl J Med* 1996;334:1005–10.
66 Buchanan SL, Crowther CA, Levett KM, *et al*. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. *Cochrane Database Syst Rev* 2010;(3):CD004735.
67 Morris JM, Roberts CL, Bowen JR, *et al*. Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. *Lancet* 2016;387:444–52.
68 van der Ham DP, Vijgen SMC, Nijhuis JG, *et al*. Induction of labor versus expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks: a randomized controlled trial. *PLoS Med* 2012;9: e1001208.
69 Distefano G, Praticò AD. Actualities on molecular pathogenesis and repairing processes of cerebral damage in perinatal hypoxic-ischemic encephalopathy. *Ital J Pediatr* 2010;36:63.
70 Backes CH, Rivera BK, Haque U, *et al*. Placental transfusion strategies in very preterm neonates: a systematic review and meta-analysis. *Obstet Gynecol* 2014;124:47–56.
71 Brocato B, Holliday N, Whitehurst RM Jr, *et al*. Delayed cord clamping in preterm neonates: a review of benefits and risks. *Obstet Gynecol Surv* 2016;71:39–42.
72 Lawton C, Acosta S, Watson N, *et al*. Enhancing endogenous stem cells in the newborn via delayed umbilical cord clamping. *Neural Regen Res* 2015;10:1359–62.
73 Perlman JM, Wyllie J, Kattwinkel J, *et al*. Neonatal resuscitation: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Pediatrics* 2010;126: E1319–44.
74 Allan DS, Scrivens N, Lawless T, *et al*. Delayed clamping of the umbilical cord after delivery and implications for public cord blood banking. *Transfusion* 2016;56:662–5.
75 Pushpa-Rajah A, Bradshaw L, Dorling J, *et al*. Cord pilot trial—immediate versus deferred cord clamping for very preterm birth (before 32 weeks gestation): study protocol for a randomized controlled trial. *Trials* 2014;15:258.
76 Thomas MR, Yoxall CW, Weeks AD, *et al*. Providing newborn resuscitation at the mother's bedside: assessing the safety, usability and acceptability of a mobile trolley. *BMC Pediatr* 2014;14:135.
77 McAdams RM. Time to implement delayed cord clamping. *Obstet Gynecol* 2014;123:549–52.
78 Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst Rev* 2010;(12):CD000140.
79 Vohr BR, Wright LL, Dusick AM, *et al*. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216–26.
80 McPherson C, Neil JJ, Tjoeng TH, *et al*. A pilot randomized trial of high-dose caffeine therapy in preterm infants. *Pediatr Res* 2015;78:198–204.
81 Henderson-Smart DJ, De Paoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. *Cochrane Database Syst Rev* 2010;(12):CD000432.
82 Dobson NR, Patel RM, Smith PB, *et al*. Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. *J Pediatr* 2014;164:992–8.e3.
83 Patel RM, Leong T, Carlton DP, *et al*. Early caffeine therapy and clinical outcomes in extremely preterm infants. *J Perinatol* 2013;33:134–40.
84 Prophylactic Versus Therapeutic Caffeine for Apnea of Prematurity: Mansoura University Children Hospital. http://www.clinicaltrials.gov NCT0267758485.
85 Schmidt B, Anderson PJ, Doyle LW, *et al*. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012;307:275–82.
86 Heuchan AM, Clyman RI. Managing the patent ductus arteriosus: current treatment options. *Arch Dis Child Fetal Neonat Ed* 2014;99:F431–6.
87 Hamrick SEG, Hansmann G. Patent ductus arteriosus of the preterm infant. *Pediatrics* 2010;125:1020–30.
88 Evans N. Preterm patent ductus arteriosus: a continuing conundrum for the neonatologist? *Semin Fetal Neonatal Med* 2015;20:272–7.
89 Kluckow M, Jeffery M, Gill A, *et al*. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F99–104.
90 Weisz DE, More K, McNamara PJ, *et al*. PDA ligation and health outcomes: a meta-analysis. *Pediatrics* 2014;133:e1024–46.
91 Ballabh P. Pathogenesis and prevention of intraventricular hemorrhage. *Clin Perinatol* 2014;41:47–67.
92 Luque MJ, Tapia JL, Villarroel L, *et al*. A risk prediction model for severe intraventricular hemorrhage in very low birth weight infants and the effect of prophylactic indomethacin. *J Perinatol* 2014;34:43–8.
93 Early Prophylactic Indomethacin Administration To Infants >28weeks Without Optimal Antenatal Steroid Exposure Markedly Reduces the Subsequent Development of Severe Intraventricular Hemorrhage. PAS Meeting 2014; 2014; Vancouver, B.C.
94 Slaughter JL, Reagan PB, Bapat RV, *et al*. Nonsteroidal anti-inflammatory administration and patent ductus arteriosus ligation, a survey of practice preferences at US children's hospitals. *Eur J Pediatr* 2016;175:775–83.
95 DeMauro SB, Schmidt B, Roberts RS. Why would a sane clinician not prescribe prophylactic indomethacin? *Acta Paediatr* 2011;100:636–6.
96 Ment LR, Vohr B, Allan W, *et al*. Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2000;105:485–91.
97 Ment LR, Vohr BR, Makuch RW, *et al*. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* 2004;145:832–4.
98 Bruschettini M, Romantsik O, Zappettini S, *et al*. Transcutaneous carbon dioxide monitoring for the prevention of neonatal morbidity and mortality. *Cochrane Database Syst Rev* 2016;(2):CD011494.
99 Molloy EJ, Deakins K. Are carbon dioxide detectors useful in neonates? *Arch Dis Child Fetal Neonatal Ed* 2006;91:F295–8.
100 Adams-Chapman I. Long-term impact of infection on the preterm neonate. *Semin Perinatol* 2012;36:462–70.
101 Rand KM, Austin NC, Inder TE, *et al*. Neonatal infection and later neurodevelopmental risk in the very preterm infant. *J Pediatr* 2016;170:97–104.
102 Hentges CR, Silveira RC, Procianoy RS, *et al*. Association of late-onset neonatal sepsis with late neurodevelopment in the first two years of life of preterm infants with very low birth weight. *J Pediatr (Rio J)* 2014;90:50–7.
103 Stoll BJ, Hansen NI, Adams-Chapman I, *et al*. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;292:2357–65.
104 Shane AL, Stoll BJ. Neonatal sepsis: progress towards improved outcomes. *J Infect* 2014;68(Suppl 1):S24–32.
105 Davis J, Odd D, Jary S, *et al*. The impact of a sepsis quality improvement project on neurodisability rates in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F562–F4.
106 Enteral Lactoferrin in Neonates. https://www.npeu.ox.ac.uk/elfin
107 Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F257–63.
108 Shah DK, Doyle LW, Anderson PJ, *et al*. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J Pediatr* 2008;153:170–5.
109 Hintz SR, Kendrick DE, Stoll BJ, *et al*. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. *Pediatrics* 2005;115:696–703.
110 Lee JS, Polin RA. Treatment and prevention of necrotizing enterocolitis. *Semin Neonatol* 2003;8:449–59.
111 Embleton ND, Zalewski S, Berrington JE. Probiotics for prevention of necrotizing enterocolitis and sepsis in preterm infants. *Curr Opin Infect Dis* 2016;29:256–61.
112 Pammi M, Abrams SA. Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev* 2015;(2):CD007137.
113 Sisk PM, Lovelady CA, Dillard RG, *et al*. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *J Perinatol* 2007;27:428–33.
114 Battersby C, Longford N, Mandalia, *et al*. Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012–13: a whole-population surveillance study. *Lancet Gastroenterol Herpetol* 2016;2:43–51.
115 Lin HC, Su BH, Chen AC, *et al*. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005;115:1–4.
116 Biran V, Phan Duy A, Decobert F, *et al*. Is melatonin ready to be used in preterm infants as a neuroprotectant? *Dev Med Child Neurol* 2014;56: 717–23.

117 Zhang J, Wang Q, Xiang H, *et al*. Neuroprotection with erythropoietin in preterm and/or low birth weight infants. *J Clin Neurosci* 2014;21:1283–7.
118 Mitsialis SA, Kourembanas S. Stem cell-based therapies for the newborn lung and brain: possibilities and challenges. *Semin Perinatol* 2016;40:138–51.
119 Stephens BE, Walden RV, Gargus RA, *et al*. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics* 2009;123:1337–43.
120 Chan SHT, Johnson MJ, Leaf AA, *et al*. Nutrition and neurodevelopmental outcomes in preterm infants: a systematic review. *Acta Paediatr* 2016;105:587–99.
121 Belfort MB, Anderson PJ, Nowak PJ, *et al*. Breast milk feeding, brain development, and neurocognitive outcomes: a 7-year longitudinal study in infants born at less than 30 weeks' gestation. *J Paediatr* 2016:133–9.
122 Vohr BR, Poindexter BB, Dusick AM, *et al*. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics* 2006;118:E115–23.
123 Jacobi-Polishook T, Collins CT, Sullivan TR, *et al*. Human milk intake in preterm infants and neurodevelopment at 18 months corrected age. *Pediatr Res* 2016;80:486–92.
124 Su BH. Optimizing nutrition in preterm infants. *Pediatr Neonatol* 2014;55:5–13.
125 Whitelaw A, Jary S, Kmita G, *et al*. Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. *Pediatrics* 2010;125:E852–58.
126 Spittle A, Orton J, Anderson P, *et al*. Early developmental intervention programmes post-hospital discharge to prevent motor and cognitive impairments in preterm infants. *Cochrane Database Syst Rev* 2012;(12):CD005495.

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Charlotte L Lea, Adam Smith-Collins and Karen Luyt

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Notes