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Management of Bronchopulmonary Dysplasia in Infants

Guidelines for Corticosteroid Use

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Abstract

Bronchopulmonary dysplasia (BPD) is a common cause of morbidity and mortality in preterm neonates and at present its management is unclear. Over the past three decades there has been a growing use of corticosteroids in the postnatal period; first for the treatment and then, more recently, for the prevention of BPD. The first published use of corticosteroids to treat neonatal lung disease was in 1956; however, it was only in the 1980s and 1990s that their use in neonates became commonplace. Concerns about their long-term neurodevelopmental consequences arose in the late 1990s when follow-up of randomised controlled trials indicated an increased risk of cerebral palsy after postnatal dexamethasone exposure.

Dexamethasone has been the most frequently used corticosteroid in neonatal units, although others, including hydrocortisone, prednisolone and methylprednisolone, have been studied, as have inhaled corticosteroids. Systematic reviews indicate that systemic corticosteroids improve respiratory function in the short term and expedite extubation in preterm neonates. However, there is a high risk of hypertension, hyperglycaemia and gastrointestinal complications in corticosteroid-treated neonates and, if administered in the first 4 days of life, an association with long-term neurodevelopmental delay.

There should be emphasis on prevention of BPD by reducing the risk factors associated with its development. There is no role for use of corticosteroids in the first 4 days of life as the high risk of long-term adverse effects outweighs any likely short-term benefits. Corticosteroid use should be limited to exceptional clinical circumstances, such as a ventilator-dependent infant after the second week of life who cannot be weaned from ventilation and whose condition is worsening. If used, they should be prescribed at the lowest effective dose for the shortest possible time. Further randomised trials of low-dose corticosteroids given after the first week of life are warranted and should assess both short- and long-term outcomes.

1. Defining the Problem

The choice of whether to use postnatal corticosteroids to treat bronchopulmonary dysplasia (BPD) or not is currently one of the most difficult decisions in neonatal practice. The prevalence of BPD is high, ranging from 3% to 43% in different centres, and the condition is a significant cause of mortality, morbidity and prolonged hospitalisation.[1] The impact of an effective prevention or treatment would be immense.[2] Corticosteroids, most frequently systemic dexamethasone, have been used to treat neonates with BPD for over 20 years. Initially, the adverse effects were considered minor and reversible; however, it has become increasingly recognised that severe long-term consequences may result from their use.[3] It is the neurodevelopmental adverse effects of corticosteroids that have caused the greatest concern, leading to a marked decrease in the number of preterm neonates receiving corticosteroids over the past 4 years.[4] At present, there is no definitive treatment for BPD and the correct management of a ventilator- and oxygen-dependent neonate is unclear.

Corticosteroids improve short-term respiratory function, allowing a reduction in supplemental oxygen requirements and earlier extubation that should reduce the incidence and severity of BPD.[5] However, these short-term gains may not outweigh the long-term costs of adverse effects on the CNS. Is there any place for corticosteroids in the management of BPD? If so, what drug should be given and at what dose? When should they be given, by what route and for how long? For many of these questions the answers are unclear and, as recruitment to recent clinical trials has been understandably poor, many of these questions will not be answered by randomised controlled trials in the foreseeable future. Therefore, this article reviews the current literature and proposes guidelines for postnatal corticosteroid use based upon the available evidence.

2. What is Bronchopulmonary Dysplasia (BPD)?

Preterm neonates have structurally underdeveloped lungs, surfactant deficiency that decreases lung compliance and reduced respiratory drive, which means that many extremely premature neonates require respiratory support after birth. Most infants recover and do not need respiratory support or supplemental oxygen at 28 days. However, a significant proportion develop BPD, also called chronic lung disease, which has been defined in terms of prolonged oxygen dependency, initially as oxygen requirement at and beyond 28 days of age.[6] As a result of advances in perinatal care, very preterm neonates now survive and this definition of BPD is less predictive of clinical outcome.[7,8] A new definition of oxygen dependency beyond 36 weeks' corrected gestational age was proposed in 1988[7] and adopted in 2001.[9] Recently, a more precise definition of 'oxygen dependency' has been suggested that involves withdrawing administered oxygen from neonates for 1 hour.[10] Neonates >36 weeks' corrected gestational age who require >30% oxygen or who desaturate to <88% when in room air

are considered to have BPD. This definition has yet to gain widespread acceptance.

BPD was first described by Northway et al.[11] in 1967 as a sequela of mechanical ventilation of neonates with immature lungs. These first babies with BPD had severe alveolar septal fibrosis, airway thickening and squamous metaplasia as a consequence of barotrauma and volutrauma of poorly compliant, surfactant-deficient lungs. By the early 1990s it was recognised that the pathology of BPD was heterogeneous.[12] Some babies had similar histological appearances to those seen by Northway et al.,[11] while others had arrested development of the terminal airspaces and their vascular supply. This appearance has become known as 'new BPD',[13] which clinically resembles Wilson-Mikity syndrome (first described in 1960).[14]

It became clear that with advances in neonatal care, the use of mechanical ventilation strategies with lower pressures and higher ventilation rates together with the gradual introduction of surfactant therapy, the histopathology of BPD was changing from one of lung scarring to one of lung maldevelopment.[8,15] The babies in the 1990s with BPD had lower gestational ages than those seen in the late 1960s, giving rise to the theory that these babies had an arrest in alveolar development.[13] Some developed 'new BPD' without needing prior oxygen or respiratory support.

3. Pathogenesis of BPD

There are a number of risk factors for development of BPD (table I). The best predictors of BPD are prematurity and low birthweight. The prevalence of BPD in neonates with birthweights ≥1500g is 5%, which rises to 85% for those <700g.[16] Mechanical ventilation causes stretching of the immature airspaces releasing proinflammatory cytokines.[17] There is recruitment and migration of inflammatory cells with resulting interstitial lung damage. The exposure of immature respiratory epithelium to oxygen, often at high concentration, results in damage to lung parenchyma by producing free radicals in the epithelial cells.[18] Preterm neonates have an underdeveloped antioxidant system and are, therefore, prone to oxidative damage.[19,20]

Table I. Risk factors for development of bronchopulmonary dysplasia

Prematurity/low birth weight
Mechanical ventilation
barotrauma
volutrauma
Oxidative stress
Pulmonary oedema
persistent ductus arteriosus
excess fluid administration
Infection
antenatal: chorioamnionitis
postnatal: pneumonia, tracheal colonisation
Non-infectious inflammation
Adrenal insufficiency

Pulmonary oedema is often present in preterm babies as a result of factors that increase pulmonary blood flow, such as persistent ductus arteriosus (PDA), excess fluid administration or insufficient diuresis.[21] Pulmonary congestion causes reduced lung compliance, necessitating increased respiratory support, and may activate the inflammatory cascade.[22] Preterm lungs also have increased vascular permeability as a result of activation of the kallikrein-kinin system[23] and those who are ventilated have increased lung microvascular filtration pressure because of increased pulmonary vascular smooth muscle, which results in interstitial lung oedema.[24]

The association of inflammation caused by infection and subsequent development of BPD has been well studied.[25] Antenatal exposure to infection, specifically chorioamnionitis, can initiate acute lung injury associated with systemic release of proinflammatory cytokines. Postnatal respiratory infection, either overt pneumonia or the low-grade infection associated with airway colonisation, is associated with a marked increase in the risk of BPD, particularly if PDA is also present.[26]

Given the central role of inflammation in development of BPD it is not surprising that corticosteroids, which have been used as anti-inflammatory drugs for decades, should have been used for its

treatment and prevention. However, there is another rationale for their use since babies who develop BPD have insufficient endogenous cortisol production.[27] In a small study of extremely low birthweight neonates, those who developed BPD had lower cortisol levels, but elevated cortisol precursors, indicating a decreased capacity to synthesise cortisol.[27] This adrenal insufficiency may not be clinically evident during the neonatal period; however, during periods of physiological stress it may have adverse effects on clinical outcome and pulmonary development.[28]

4. History of Corticosteroid Use in Neonatal Lung Disease

The use of corticosteroids, specifically cortisone, to treat neonatal lung disease was first reported in 1956;[29] however, no trials evaluating their effectiveness and safety were published until the early 1970s.[30,31] The use of antenatal corticosteroids for maturation of the pulmonary surfactant system in lambs was reported in 1968[32] and a randomised controlled trial in 1972 demonstrated that they improved clinical outcomes in preterm neonates.[33] Two trials using corticosteroids in the postnatal period to treat preterm neonates with respiratory distress syndrome were published in 1972.[30,31] These trials, one with hydrocortisone and the other with prednisolone, demonstrated no clinical benefits and at follow-up it was found that the corticosteroid-treated neonates had an increased risk of severe intraventricular haemorrhage and neurodevelopmental problems.[31,34,35]

Concerns about serious adverse effects precluded further investigation of postnatal corticosteroids until the early 1980s, when two trials were published reporting the use of dexamethasone 0.5 mg/kg/day to treat ventilator-dependent neonates with BPD.[36,37] Both studies demonstrated that dexamethasone improved respiratory function and allowed earlier extubation, but neither demonstrated any improvement in survival. Few adverse effects of dexamethasone were reported in these studies, which led to reassurance about safety and a gradual increase in its use. A retrospective study on the outcomes of neonates with a birthweight <750g found that use of dexamethasone increased from 43% of babies born in 1990–2 to 84% of those born in 1993–5, indicating that postnatal corticosteroid use had almost become routine.[38]

In 1998, a large multicentre follow-up study demonstrated a significant increase in neurodevelopmental problems in those neonates treated with a 4-week course of dexamethasone started within 12 hours of birth.[3] At 2 years corrected age, 25 of the 63 surviving corticosteroid-treated children had abnormal neurodevelopmental examinations compared with 12 of the 70 surviving controls. More specifically, the risk of diplegic cerebral palsy was increased 2-fold in treated infants.[3] This study and others that followed led to a reappraisal of the use of postnatal dexamethasone.

5. Corticosteroids: Molecular Modes of Action

There are several mechanisms by which corticosteroids exert their clinical effects. The best understood mechanism of action involves changing expression of a number of genes by either direct or indirect mechanisms after binding glucocorticoid receptors within the cytosol of target cells.[39] Inactive glucocorticoid receptors are retained in the cytosol by binding to a heat shock protein (hsp90) and several components of the mitogen-activated protein (MAP) kinase intracellular signalling pathway, including Src. Corticosteroid-binding causes release of the glucocorticoid receptors from this protein complex allowing their migration into the nucleus. Dimers of active glucocorticoid receptors can then bind to specific sequences in the promoter regions of a large number of genes directly affecting their transcription.[40] Monomers of active glucocorticoid receptors can indirectly alter gene expression by binding transcription factors, preventing interaction with their DNA recognition sequences, and by reducing the half-life of certain messenger RNAs.[41]

Distinct from these genomic actions, corticosteroids have other rapid effects not involving changes in gene expression. Several mechanisms behind

these rapid non-genomic effects have been described. Corticosteroids can directly affect cell membranes as their basic structure is the sterol ring and, like other sterols such as cholesterol, they can be incorporated into and alter physical characteristics of animal cell membranes. This affects activities of membrane-associated proteins, including calcium and sodium ion channels, thereby altering cellular metabolic pathways dependent on these ions.[42] The presence of membrane-bound glucocorticoid receptors has been demonstrated in a range of cells including neurons and white blood cells. These mediate their effects through secondary messenger systems such as cyclic adenosine monophosphate and calcium, although their clinical relevance has yet to be determined. The binding of corticosteroids to cytosolic glucocorticoid receptors can also have rapid effects on cellular metabolism caused by release and activation of heat shock proteins and members of the MAP kinase system.[43]

This complexity of action contributes to the different clinical profiles seen for each corticosteroid. For example, methylprednisolone has only slightly greater potency than prednisolone but has more than three times the non-genomic potency.[44] The fluorinated corticosteroids, dexamethasone and betamethasone, are those used most frequently in the perinatal period and they differ only in conformation of the methyl group on carbon 16 of the sterol ring (α in dexamethasone and β in betamethasone) [figure 1]. They have similar potencies as measured by their genomic effects (approximately six times that of prednisolone); however, they have considerable differences in their non-genomic effects.[44] Dexamethasone has a non-genomic potency greater than five times that of prednisolone, whereas betamethasone has a non-genomic potency significantly less than prednisolone.[44] The relative differences in genomic and non-genomic potencies influences clinical effects, both wanted and adverse, of each corticosteroid. The

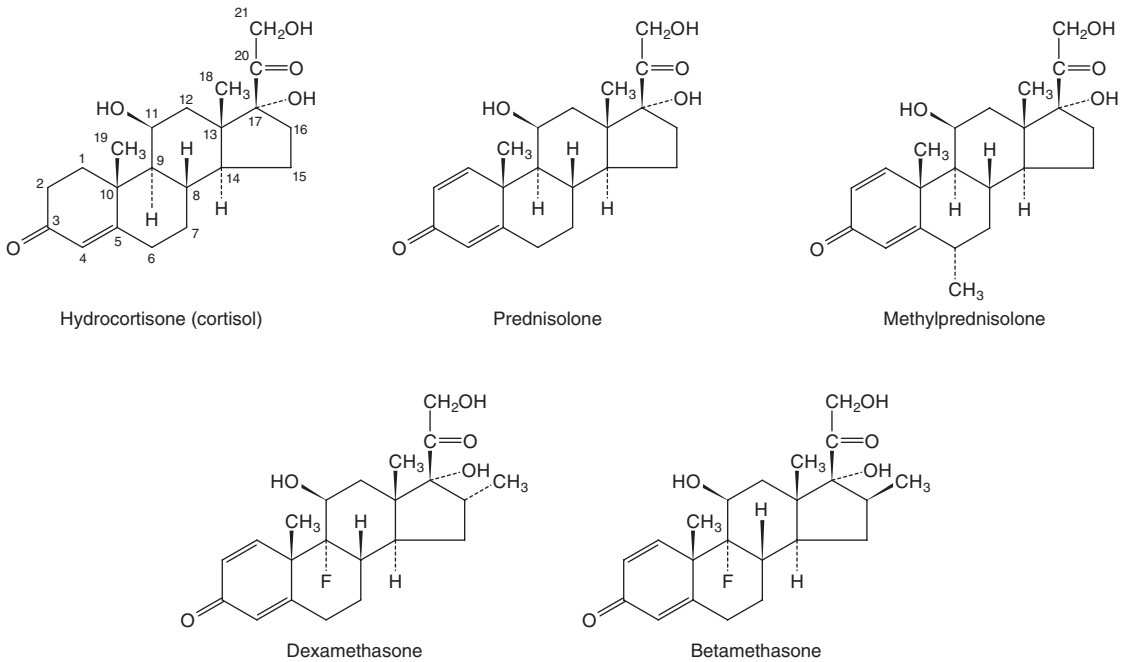

Fig. 1. Structure of corticosteroids. Hydrocortisone (cortisol) is the major physiological corticosteroid and is the parent molecule of anti-inflammatory corticosteroids. Synthetic corticosteroids have higher anti-inflammatory effects because of a double bond between C1 and C2. Fluorination of C9 results in greater potency still. Dexamethasone and betamethasone differ only in the conformation of the methyl group on C16, which is α in dexamethasone and β in betamethasone.

Table II. Benefits of postnatal corticosteroids[45-47]

Outcome	Timing	No. of patients	No. of studies	RR (95% CI)	NNT (95% CI)
CLD at 28 days	E	2621	16	0.85 (0.79, 0.92)	14 (9, 25)
	M	623	6	0.87 (0.81, 0.94)	9 (6, 20)
	D	0	0		
CLD at 36 weeks corrected age	E	2415	15	0.69 (0.60, 0.80)	11 (8, 20)
	M	247	5	0.62 (0.47, 0.82)	4 (3, 8)
	D	118	1	0.76 (0.58, 1.00)	6 (3, 100)
Mortality at 28 days	E	2900	18	1.05 (0.90, 1.22)	
	M	599	6	0.44 (0.24, 0.80)	17 (10, 50)
	D	0	0		
Mortality before discharge	E	3068	21	1.02 (0.90, 1.17)	
	M	288	6	0.66 (0.40, 1.09)	
	D	542	8	1.03 (0.71, 1.51)	
Failure to extubate at 7 days	E	963	6	0.76 (0.66, 0.88)	8 (6, 17)
	M	84	2	0.62 (0.46, 0.84)	3 (2, 7)
	D	288	5	0.69 (0.58, 0.82)	4 (3, 7)
Persistent ductus arteriosus	E	2881	17	0.75 (0.68, 0.83)	10 (7, 14)

CLD = chronic lung disease; **D** = delayed (>3 weeks); **E** = early (<96 hours); **M** = moderately early (7–14 days); **NNT** = number needed to treat; **RR** = relative risk.

choice of dexamethasone as the most commonly used corticosteroid in the postnatal period appears to have been arbitrarily based upon it having the greatest anti-inflammatory effects.

6. Systemic Dexamethasone

Studies in the 1980s provided evidence for short-term improvements in respiratory function; however, they were insufficiently powered to determine long-term consequences of postnatal corticosteroids use.[36,37] The objective of three systematic reviews first published in the Cochrane Library in 1999 and subsequently updated, was to pool data from a number of trials to determine if the benefits of postnatal corticosteroid treatment outweighed the risks in preterm infants.[45-47] The trials of postnatal corticosteroids were classified by age at commencement of treatment. In 21 trials this was early (<96 hours), in seven it was moderately early (7–14 days) and in nine it was delayed (>3 weeks). Table II and table III summarise the results of these analyses.

Postnatal corticosteroids, whether started early, moderately early or late, enable earlier extubation and reduce BPD at 36 weeks' corrected gestational age. There is a reduction in mortality at 28 days of age for those treated moderately early but no effect on mortality of infants before discharge from hospital in any of the meta-analyses. Hyperglycaemia, hypertension and hypertrophic cardiomyopathy are all more frequent in corticosteroid-treated neonates and, although generally regarded as transient and reversible, the long-term consequences of these adverse effects in vulnerable, preterm infants is unknown. Growth failure is particularly common in neonates treated early with corticosteroids, with 67 additional babies failing to thrive for every 100 babies treated. Most worryingly among early complications was doubling of the risk of gastrointestinal perforation and haemorrhage among early corticosteroid-treated neonates. The incidence of necrotising enterocolitis was not affected by corticosteroids given at any time in the postnatal period.[45-47]

Long-term neurodevelopmental outcomes have generated the greatest concerns. Those treated early with corticosteroids have a significant increase in risk of neurodevelopmental adverse outcomes, with one additional case of cerebral palsy for every 17 babies treated.[45] The earliest published versions of the systematic reviews suggested higher risks of cerebral palsy, with more than doubling of risk associated with early corticosteroid treatment.[48]

Subsequent publication of follow-up studies that did not show long-term adverse outcomes suggests possible publication bias of the initial outcome studies.

Those babies receiving corticosteroids after 7 days of age do not have an increased risk of cerebral palsy or developmental delay in contrast with those who received corticosteroids in the first 4 days. For every 100 babies treated early with corticosteroids there would be nine less babies with BPD at 36 weeks' corrected gestational age, 12 less ventilated 7 days after commencement and ten less with PDA. However, there would be six more with gastrointestinal haemorrhage and six more children with cerebral palsy compared with those not receiving corticosteroids.[45]

The most common corticosteroid regimen in the studies reviewed in the systematic reviews[45-47] was dexamethasone 0.5 mg/kg/day for 3 days in two divided doses, followed by 0.25 mg/kg/day for 3 days, 0.12 mg/kg/day for 3 days and 0.05 mg/kg/day for 3 days. However, the variation in dose and duration was considerable. Duration ranged from one single dose to 42 days of treatment and the starting dose ranged from 0.15 to 1.0 mg/kg/day. A further complication in interpreting these systematic reviews is that many neonatologists appear to have been reluctant not to prescribe corticosteroids for sick preterm neonates randomised to receive placebo. This use of open-labelled corticosteroid during randomised controlled trials has the effect of reducing the observed difference in outcomes between

Table III. Adverse effects of postnatal corticosteroids[45-47]

Outcome	Timing	No. of patients	No. of studies	RR (95% CI)	NNH (95% CI)
Hyperglycaemia	E	2016	11	1.36 (1.23, 1.51)	9 (7, 13)
	M	659	7	1.51 (1.20, 1.90)	8 (6, 20)
	D	497	6	1.42 (0.97, 2.07)	
Hypertension	E	1946	10	1.84 (1.54, 2.21)	10 (8, 14)
	M	599	6	2.73 (1.25, 5.95)	20 (13, 100)
	D	497	6	2.61 (1.29, 5.26)	17 (10, 50)
Hypertrophic cardiomyopathy	E	50	1	4.33 (1.40, 13.40)	3 (2, 6)
	M	168	3	3.29 (1.50, 7.20)	5 (3, 11)
	D	0	0		
Necrotising enterocolitis	E	1582	12	0.87 (0.62, 1.23)	
	M	563	5	0.76 (0.38, 1.49)	
	D	319	2	2.59 (0.61, 10.90)	
Gastrointestinal haemorrhage	E	1440	9	1.90 (1.35, 2.66)	17 (11, 33)
	M	485	3	1.74 (1.02, 2.98)	17 (9, >200)
	D	437	3	1.13 (0.74, 1.73)	
Infection	E	2752	18	1.01 (0.90, 1.14)	
	M	659	7	1.35 (1.06, 1.71)	11 (7, 50)
	D	497	6	1.03 (0.77, 1.40)	
Growth failure	E	50	1	6.67 (2.27, 19.60)	2 (1, 2)
Abnormal neurological examination	E	829	5	1.81 (1.33, 2.47)	10 (7, 20)
	M	56	2	0.89 (0.38, 2.10)	
	D	164	3	1.13 (0.73, 1.75)	
Cerebral palsy	E	991	9	1.69 (1.20, 2.38)	17 (9, 50)
	M	130	4	0.83 (0.39, 1.74)	
	D	503	6	1.20 (0.77, 1.85)	
Death or cerebral palsy	E	991	6	1.16 (1.00, 1.34)	17 (8, >200)
	M	204	4	0.83 (0.55, 1.23)	
	D	503	6	1.05 (0.82, 1.34)	

D = delayed (>3 weeks); **E** = early (<96 hours); **M** = moderately early (7–14 days); **NNH** = number needed to harm; **RR** = relative risk.

treated and control groups. Another systematic review published in 2001 stratified trials of postnatal corticosteroids into groups depending on degree of this 'contamination'.[49,50] The combined outcome for all eight studies indicated one additional case of neurodevelopmental impairment for every nine babies treated and one additional case of cerebral palsy for every six. When only the four studies with <30% contamination were analysed, the risk of neurodevelopmental impairment was increased to one for every six treated with corticosteroids and the risk of cerebral palsy to one for every four treated.

There is evidence that moderately early administration of corticosteroids is associated with increased adverse effects. A large multicentre trial comprising a 14-day course of dexamethasone commencing at either 2 or 4 weeks of age demonstrated a higher risk of bacteraemia and hyperglycaemia in the group treated earlier without any difference in ventilation requirement or incidence of BPD.[51]

Two possible explanations have been suggested for the increased risk of neurological impairment in early corticosteroid-treated neonates.[52] The first is that preterm neonates are more unstable during the first few days of life and dexamethasone administration during this time may exacerbate the detrimental effects of, for example, acidosis, hypocarbia, hypotension and hypoglycaemia. The other possibility is that earlier treatment of ventilator-dependent preterm neonates inevitably includes more neonates who would subsequently not develop BPD compared with those treated later. Neonates treated earlier would, therefore, be exposed to harmful effects of corticosteroids but with less likelihood for benefit. Therefore, the cost-benefit ratio would be higher in those treated earlier rather than later.[52,53]

Few studies have examined the effect of dose and duration of postnatal corticosteroid treatment. Different doses of dexamethasone have been compared for treatment of ventilator-dependent neonates in the first 2 weeks of life.[54,55] No difference was noted in respiratory function using dexamethasone 0.2 mg/kg/day compared with 0.4 or 0.5 mg/kg/day, suggesting that a lower dose would be as efficacious as a higher one. However, lower doses of dexamethasone can also be associated with adverse effects as demonstrated by a study using a 7-day reducing course of dexamethasone commencing with 0.15 mg/kg/day, which showed an increased risk of intestinal perforation.[56]

Duration of treatment was studied in a trial comparing short (3-day) or long (42-day) courses of dexamethasone in ventilator-dependent 1-week-old preterm neonates. The infants treated with the shorter course had less hypertension and myocardial hypertrophy but needed supplemental oxygen for longer periods.[57] A smaller study comparing 18 and 42 days of dexamethasone demonstrated similar results, with the shorter course resulting in fewer short-term benefits and also a worse long-term neurodevelopmental outcome.[58]

7. Neurotoxicity of Dexamethasone

The mechanisms by which dexamethasone exerts its neurotoxic effects are presently the subject of much speculation.[59] There is some evidence that dexamethasone has direct toxic effects on neurons and that it may impair mechanisms that protect against hypoxia and hypoglycaemia.

It is possible that dexamethasone may be uniquely toxic amongst corticosteroids. A large retrospective observational study of preterm neonates with antenatal exposure to either dexamethasone or betamethasone showed that the latter was associated with a reduced incidence of cystic periventricular leukomalacia compared with non-exposed neonates. However, those exposed to dexamethasone had higher rates of cystic periventricular leukomalacia than controls.[60] Betamethasone differs from dexamethasone only in the conformation of the methyl group on position 16 of the sterol ring (figure 1) and both have similar genomic potencies; however, betamethasone has only a fraction of the nonspecific non-genomic potency of dexamethasone. It has also been speculated that the additives in some preparations of dexamethasone are more toxic than the drug itself.[61] Sulphites, which are used as preservatives in proprietary preparations of dexamethasone in North America and Europe, have been demonstrated

to be toxic *in vitro* to cultures of neurons and *in vivo* to the brains of 3- to 5-day-old mouse pups.[62]

8. Other Systemic Corticosteroids

Alternatives to dexamethasone have been rarely used in neonatal medicine. Methylprednisolone and dexamethasone were compared in a non-randomised trial of preterm neonates treated with a 9-day reducing course of either methylprednisolone (starting with 2.4 mg/kg/day) or dexamethasone (starting with 0.5 mg/kg/day).[63] There was no difference in oxygen requirements or in the rate of weaning from ventilation. However, those treated with methylprednisolone had better weight gain and less hyperglycaemia and cystic periventricular leukomalacia than those treated with dexamethasone. The lack of randomisation means that these findings need to be treated with caution.

A recent randomised controlled study compared tapering courses of hydrocortisone (starting with 5 mg/kg/day; total length of course, 22 days) and dexamethasone (starting with 0.5 mg/kg/day; total length of course, 21 days) with controls.[64] Both of the corticosteroids reduced oxygen requirements compared with controls, but this effect was only significant during the first 3 days of treatment. Early adverse effects of hypertension, hyperglycaemia and poor weight gain were seen in the dexamethasone-treated group but not the hydrocortisone-treated group. Follow-up at 5–7 years found that the dexamethasone-treated children required more special education and had worse neurological outcomes than controls; however, the increased risk of these long-term adverse effects was not seen in the hydrocortisone-treated neonates.[64]

These studies would suggest that hydrocortisone and methylprednisolone may produce similar clinical benefits to dexamethasone with fewer adverse effects. However, another study of hydrocortisone has recently had to be stopped because of increased gastrointestinal perforation in the treatment group.[65] Almost all of those babies with gastrointestinal perforation had received indometacin, suggesting an interaction between corticosteroids and NSAIDs.

9. Inhaled Corticosteroids

Inhaled corticosteroids should have direct effects on the lungs without the systemic adverse effects. As with systemic administration, inhaled corticosteroids have been used early to prevent BPD and, later, to treat neonates with or developing BPD. Two systematic reviews have examined clinical effects of inhaled corticosteroids compared with placebo.[66,67] One review of early (<2 week of age) treatment analysed five trials: two used beclometasone (one a 3-week reducing course starting with 40 μg/kg/day for 1 week, the other 500 μg/day for 2 weeks), two used fluticasone propionate 500 μg/day for 2 weeks and the other used budesonide 1600 μg/day for 10 days.[66] Early administration of inhaled corticosteroids does not reduce mortality or risk of developing BPD, neither does it have any effect on risk of developing hypertension, hyperglycaemia, sepsis or gastrointestinal adverse effects.

The second systematic review analysed five randomised, placebo-controlled trials of ventilated infants with BPD treated with inhaled dexamethasone, beclometasone, flunisolide or budesonide.[67] This systematic review demonstrated improved rate of extubation; relative risk (RR) for inability to extubate was 0.35 (95% CI 0.20, 0.72), and the number needed to treat (NNT) to prevent one extubation failure was 2 (95% CI 1, 4). There were no adverse effects, but data on outcomes were limited.

Two systematic reviews compared inhaled and systemic corticosteroids.[68,69] In one review corticosteroids were administered within 2 weeks of life to try to prevent BPD and in the other they were administered after 2 weeks. Each analysed two trials and the OSECT (Open Study of Early Corticosteroid Treatment)[70] was included in both reviews. The OSECT was published in 2001 and compared 800 μg/kg/day of inhaled budesonide for 12 days against a 12-day tapering course of dexamethasone that commenced with 0.5 mg/kg/day. Neonates were randomised to receive the corticosteroid either early (postnatal age <72 hours) or later (postnatal age >15 days). The second trial in the early inhaled corticosteroid systematic review compared 1500 μg/day of inhaled beclometasone for 25 days with a 10-

to 28-day tapering course of dexamethasone that started with 0.5 mg/kg/day. The study in the delayed inhaled corticosteroid systematic review compared inhaled beclometasone 400–800 μg/kg/day with a reducing course of dexamethasone starting with 0.5 mg/kg/day. Neither of these systematic reviews demonstrated any significant difference in mortality or incidence of BPD. The use of early inhaled corticosteroids rather than systemic dexamethasone is associated with increased time on a ventilator (mean of 3.89 additional days, 95% CI 0.24, 7.57), increased time in oxygen (mean of 11.10 additional days, 95% CI 1.97, 20.22) and reduced risk of hyperglycaemia (RR 0.52, 95% CI 0.32, 0.71), which is equivalent to one less case for every four treated early with inhaled corticosteroids rather than dexamethasone (95% CI 3, 7). There were no differences in the risk of adverse effects in those treated after 2 weeks of age.[68,69]

In summary, there is no evidence that inhaled corticosteroids are effective for prevention or treatment of BPD. There is evidence that they are less effective in reducing ventilation and oxygen requirements compared with systemic dexamethasone and they may have fewer adverse effects. To date, no follow-up studies have been published of infants treated with inhaled corticosteroids to determine if they carry the same risk of neurodevelopmental delay as systemic dexamethasone.

10. Alternatives to Corticosteroids

Avoidance of risk factors for development of BPD (table I) should take priority over the introduction of new and potentially harmful interventions not tested in randomised controlled trials. Given the central role of prematurity in the development of BPD, any strategy to reduce the incidence of preterm birth should reduce the frequency of BPD. Alternative methods of respiratory support have also been suggested to reduce pulmonary barotrauma and volutrauma. A systematic review analysed two randomised controlled trials comparing ventilated preterm neonates whose arterial carbon dioxide tension ($PaCO_2$) was allowed to rise (permissive hypercarbia) with those whose $PaCO_2$ was kept lower.[71] There was no difference in the risk of BPD, mortality or adverse effects.

The use of nasal continuous positive airway pressure (CPAP) in the neonatal period has been examined in several systematic reviews. None of these demonstrated that CPAP, whether commenced early to prevent lung disease or later after extubation, significantly altered risk of developing BPD.[72-74] High-frequency oscillatory ventilation has been compared with conventional ventilation in a systematic review of 11 studies.[75] In studies which used a lung volume recruitment strategy there was a reduction in the risk of BPD (RR 0.53, 95% CI 0.36, 0.76; NNT 6, 95% CI 4, 12).

The use of erythromycin to prevent or eradicate *Ureaplasma urealyticum* colonisation of the respiratory system has also been analysed in a systematic review.[76] In the two studies included there was no effect of erythromycin on BPD or mortality in either those neonates at risk of colonisation or those with positive cultures of *U. urealyticum*.

Use of diuretics for pulmonary oedema in babies with BPD has been examined in three systematic reviews. The loop diuretic furosemide (frusemide) improves lung compliance and oxygenation but does not affect the rate of extubation.[77] An 8-week course of a thiazide diuretic and spironolactone in preterm infants with BPD reduced mortality before discharge (RR 0.30, 95% CI 0.09, 0.93) and the NNT was three to prevent one death (95% CI 2, 14).[78] There was no effect on extubation or oxygen requirements, but there was an increased need for electrolyte supplementation. This was based on meta-analysis of two studies with a total of only 77 neonates and, therefore, further studies are clearly warranted. Aerosolised diuretics were found to have no significant clinical effects.[79] A systematic review of inhaled bronchodilators to manage BPD found only one study, using salbutamol, and this demonstrated no significant clinical benefits or adverse effects.[80]

Retinol (vitamin A) derivatives promote alveolarisation in animal models and, therefore, theoretically should reverse the structural changes in 'new BPD'.[81] A systematic review of retinol supplemen-

tation analysed seven trials.[82] The studies varied in dose and method of administration. In one study oral retinol 5000 IU/kg was given daily during the first 28 days of life. In others parenteral retinol 4000–5000IU was given on alternate days during the first month of life. Retinol significantly reduced the combined outcome of death or oxygen requirement at 1 month (RR 0.93, 95% CI 0.88, 0.99; NNT 20, 95% CI 10, 100) and BPD at 36 weeks' corrected age (RR 0.87, 95% CI 0.77, 0.99; NNT 14, 95% CI 7, 100).

The finding that free radicals have a role in the pathogenesis of BPD has led to the advocation of antioxidant administration to prevent oxidative lung damage. In a meta-analysis of 26 randomised controlled trials tocopherol (vitamin E) supplementation had no effects on BPD.[83] A systematic review of the use of the enzyme superoxide dismutase, which can be administered either intratracheally or subcutaneously, found no differences in the rates of death or BPD compared with placebo.[84] However, there was a small but significant reduction in respiratory problems after discharge in the superoxide dismutase-treated neonates (RR 0.33, 95% CI 0.11, 0.96; NNT 2, 95% CI 1, 8).

11. Published Guidelines

Guidelines for use of postnatal corticosteroids in preterm neonates have been endorsed by paediatric associations in North America and Europe. These recommendations were largely based upon early versions of the systematic reviews published in the Cochrane Library, which suggested a higher risk of adverse neurological outcome for both early and delayed systemic corticosteroids.

The American Academy of Pediatrics and the Canadian Paediatric Society recommendations[85] can be summarised as follows.

1. The routine use of systemic corticosteroids for the prevention or treatment of BPD in very low birthweight infants is not recommended.
2. Postnatal use of systemic dexamethasone should be limited to carefully designed randomised, double-blind, controlled trials.
3. Long-term neurodevelopmental assessment of infants who are, or have been, subjects in trials of dexamethasone is strongly encouraged.
4. Clinical trials investigating the use of alternative anti-inflammatory corticosteroids, both systemic and inhaled, are required before additional recommendations can be made.
5. Outside the context of a randomised controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances (e.g. an infant on maximal ventilatory and oxygen support).

The European Association of Perinatal Medicine has also produced the following guidelines[86] on the use of neonatal corticosteroids.

1. Corticosteroids should be avoided if at all possible.
2. There is no indication to give dexamethasone in the first 3–4 days of life.
3. Spontaneously breathing infants should not be given corticosteroids.
4. Corticosteroids might be indicated for very ill, ventilator-dependent infants.
5. Corticosteroid use under these circumstances should be discussed with the parents, taking into account the benefits and the risks.
6. The lowest possible dose for the shortest possible duration should be used.

The Vermont Oxford Neonatal Network has surveyed the changes in management and outcomes of very low birthweight neonates born between 1991 and 1999.[4] This survey demonstrated a rise in the use of postnatal corticosteroids from 19% in 1991 to a peak of 29% in 1997. Despite the mounting evidence concerning their long-term effects, 27% of neonates in this study received corticosteroids in 1999. A survey of postnatal corticosteroid administration in 14 European countries performed between 1999 and 2000 demonstrated variation both between and within countries.[87] In total, 67% of neonatal units prescribed postnatal corticosteroids, dexamethasone being the most prescribed. Forty-eight percent of neonatal units prescribed corticosteroids to non-ventilated infants, indicating, in the opinion of the authors of this study, the continued misuse of postnatal corticosteroids through inappropriate,

non-evidence-based prescribing. However, the most recent evidence suggests that dexamethasone treatment is being used more sparingly by neonatologists without detrimental effects.[88]

12. Conclusion and Recommendations

The evidence from systematic reviews is that postnatal corticosteroids should not be used in the first 4 days of life and after the first week their role is limited. The emphasis should be on the prevention of BPD by reducing premature birth and avoiding risk factors contributing to BPD. There is a need for further randomised controlled trials of different strategies of respiratory support in the first days of life to determine which strategies are associated with reduced incidence of BPD. Consideration could be given to use of retinol supplementation, as this reduces BPD; however, the long-term consequences of its use have not been examined and follow-up studies are required.

There may be a role for postnatal corticosteroids to treat BPD in circumstances where the short-term benefits are considered to outweigh the long-term risks. An example of this would be a ventilator-dependent infant after the second week of life who cannot be weaned from ventilation and whose condition is worsening. There is no evidence than non-ventilated infants benefit from postnatal corticosteroids and, at present, there is insufficient evidence to recommend the use of inhaled corticosteroids in preterm neonates either to prevent or treat BPD.

When used, corticosteroids should be administered at the lowest effective dose and for the shortest possible time. Evidence suggests that a starting dose of dexamethasone 0.2 mg/kg/day is as effective as higher doses. A tapering course of dexamethasone starting with 0.2 mg/kg/day in two divided doses for 3 days followed by 0.1 mg/kg/day for 3 days and then 0.05 mg/kg/day for 3 days might balance the short-term benefits and adverse effects. There is also anecdotal evidence that even lower doses of dexamethasone (0.05 mg/kg/day) are effective in promoting extubation within 3 days,[89] but this needs to be tested in a prospective randomised trial. Those neonates receiving corticosteroids should have blood pressure and blood glucose monitored with reduction of dose if clinically significant hypertension or hyperglycaemia occurs. Interaction between corticosteroids and NSAIDs may increase gastrointestinal adverse events and this combination should be avoided. All infants receiving corticosteroids in the neonatal period should have appropriate long-term neurodevelopmental follow-up.

There should be continued efforts to follow-up the subjects of randomised controlled trials of postnatal corticosteroids to determine the true consequences of their use, since the results of early follow-up studies may have biased the systematic reviews. Despite the need for new large randomised controlled trials, particularly to determine the dose and duration of dexamethasone treatment, it is unlikely that any new large trials will be started until these follow-up studies are published. Larger trials are also required before corticosteroids other than dexamethasone can be recommended.

The use of corticosteroids in ventilated babies in the second week of life could provide the greatest respiratory benefits; however, they could only be recommended for routine use in this group of infants if future follow-up studies indicate no neurodevelopmental adverse effects.

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