

Update on Neonatal Postnatal Steroids

Henry L Halliday MD FRCPE FRCP FRCPCH
Regional Neonatal Unit, Royal Maternity
Hospital, Belfast and Department of Child
Health, Queen's University Belfast, Northern
Ireland

William Kidney Founders' Lecture of the Irish and American Paediatric Society and
Paediatric Grand Rounds at Women and Children's Hospital, Buffalo, New York

Irish and American Paediatric Society

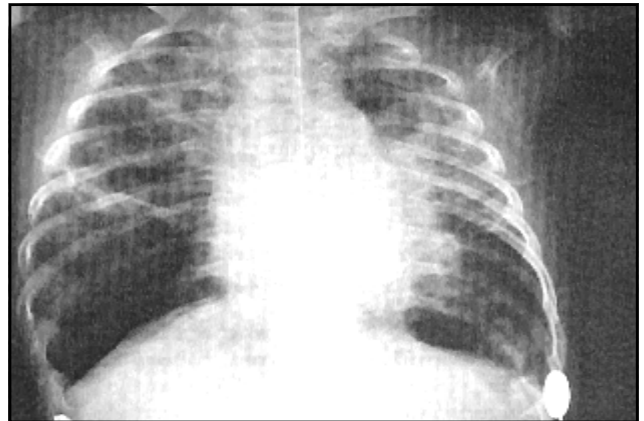
Founded in Portugal in 1962 by 3 eminent
paediatricians:

- **Fred Burke** from Washington
- **Tom Cone** from Boston
- **Bill Kidney** from Dublin

Bill Kidney



Bill Northway



Postnatal Steroids for CLD

History

- Baden et al 1972; Kramer and Hultzen 1978
- Mammel et al 1983; Avery et al 1985
- Many RCTs 1985-1998
- Yeh et al 1998; O'Shea et al 1999; Shinwell et al 2000
- EAPM (2001); AAP/CPS (2002) recommendations
- New consensus or more research?

Postnatal Steroids: first RCT

- Baden et al - Pediatrics 1972
- Hydrocortisone for RDS
- N=44 – “Although no immediate detrimental effects of the therapy were seen, the postnatal use of corticosteroids did not appear to carry any obvious benefit for the infant with RDS”

First RCT: Follow-up Studies

- Taeusch 1973 and Fitzhardinge 1974 – Pediatrics
- Increase in severe IVH at autopsy
- Increase in neurodevelopmental problems and EEG abnormalities
- **“Risks seem to outweigh benefits”**

First Report of Dexamethasone Use

- 11 infants of 27 to 36 weeks' gestation
- Georgetown University Hospital
- Ventilator-dependent with BPD
- Course of dexamethasone (dose unknown)
- Prompt clinical improvement in lung disease
- Dexamethasone “Useful but not Benign”

Kramer and Hultzen, *Pediatr Res* 1978; 12:564A, 1201

Dexamethasone in 1980s

- Mammel et al 1983 and Avery et al 1985
- In total 22 infants with BPD – sequential designs
- Both terminated early for “benefit”
- Large doses – 0.5 better than 0.1 mg/kg/day on basis of responses in 2 infants
- **“Dexamethasone cannot be recommended without further study”** and **“Dexamethasone is a dangerous drug with many side effects”**
- Many RCTs in late 1980s



Postnatal Steroids - Timing

	Trials	Babies
Early (< 96 h)	21	3068
Mod. Early (7-14 d)	7	659
Delayed (> 3 wk)	9	562
Total	37	4289

Halliday et al, Cochrane Library 2001

Postnatal Steroids: Updated Meta-analyses

Early (≤ 7 days): 28 studies and 3740 infants
 Late (> 7 days): 19 studies and 1345 infants

TOTAL: 47 studies and 5085 infants

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

Steroids and CLD (36 wk)

	Babies	RR	95% CI	NNT	95% CI
Early (≤ 7 days)	3286	0.79	0.71-0.88	14	10-25
Late (> 7 days)	471	0.72	0.61-0.85	6	4-11

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

Steroids and Neonatal Mortality

	Babies	RR	95% CI	NNT	95% CI
Early (≤ 7 days)	2950	1.02	0.88-1.19	-	-
Late (> 7 days)	656	0.49	0.28-0.85	17	10-100

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

Steroids and Cerebral Palsy (1st 3 Years)

	Babies	RR	95% CI	NNH	95% CI
Early (≤ 7 days)	1452	1.45	1.06-1.98	33	17-100
Late (> 7 days)	777	1.14	0.79-1.64	-	-

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

Recommendations

EAPM (2001)

- Avoid if at all possible
- No indication to give in first 3-4 days
- Do not give if spontaneously breathing
- May be indicated for very ill ventilator-dependent infants
- Use should be discussed with parents
- Lowest possible dose for shortest possible duration

Recommendations

AAP / CPS (2002)

- Systemic steroids are not recommended
- Limit use to RCTs with long-term outcomes
- Long-term outcomes needed for all trials
- Trials of alternative drugs including inhaled needed
- Outside RCTs limit use to exceptional clinical circumstances (maximal ventilatory support). Parents should be informed.

Postnatal Steroids – Which Dose?

- Courses differ in timing, dose and duration
- Most frequent regimen:
 - Dexamethasone
 - 0.5 mg/kg/day for 3 days
 - Halving every three days
 - Total course – 12 days

Postnatal Steroids – Which Dose?

3 randomized trials compared doses of dexamethasone:

- 1994 Ramanathan et al - 0.2 vs 0.4 mg/kg/day: no difference
- 1996 McEvoy et al - 0.2 vs 0.5 mg/kg/day: higher dose better at reducing ventilation requirements but survival was not different
- 2001 Durand et al - 0.2 vs 0.5 mg/kg/day: no difference in lung function improvement

DART Study

- RCT < 28 wk or < 1000 g and > 1 wk PNA
- Dexamethasone: starting at 0.15 mg/kg and reducing over 10 days (0.89 mg/kg)
- Primary outcome at 18 months
- Poor recruitment and stopped early

Doyle et al. Pediatrics 2006

DART Study Results

n = 70 from 11 centres in Australia

GA 24.9 wk, BW 701 g and PNA 23 days

Extubated by 10 days (60% vs 12%)

OR 11.2; 95% CI 3.2-39.0

Mortality - OR 0.52; 95% CI 0.14-1.95

Oxygen at 36 wk – OR 0.58; 0.13-2.66

Doyle et al. Pediatrics 2006

Higher vs Lower Dexamethasone Doses

- 6 studies and 209 infants – meta-analysis
- 2 studies higher cumulative doses (> 2.7 mg/kg) and 4 studies lower (\leq 2.7 mg/kg)
- Similar rates of death and neurodevelopmental sequelae in higher and lower groups
- Higher dose more effective at reducing CLD
- Several drawbacks: small, heterogeneity, late rescue, missing neurodevelopmental data

Onland et al. Pediatrics 2008; 122: 92-101

Finding a Dosage Regimen

- 16 RCTs of dexamethasone > 7 days
- Meta-analysis and meta-regression
- Higher doses better at reducing death/BPD
- Largest effect with cumulative dose > 4 mg/kg
- Dose not related to neurodevelopmental outcome in > 3 week subgroup
- In 7-14 day subgroup death/CP decreased by 6% for each mg/kg increase in cumulative dose

Onland et al. Pediatrics 2009; 123: 367-377

Which Steroid?

- Retrospective observational study of 833 preterm infants born to mothers in Paris
- Assessed rates of cystic periventricular leukomalacia (PVL) in 3 non-randomized groups:
- Prenatal betamethasone rate was 4.4%
- Prenatal dexamethasone rate was 11.0%
- Untreated control group rate was 8.4%

Baud et al NEJM 1999; 341: 1190

Antenatal Dexamethasone vs Betamethasone (NICHD)

Outcome	Dexa (n=1227)	Beta (n=1738)	None (n=635)
PVL (%)	2.9	3.5	4.4
Severe IVH (%)	9.4	10.3	12.8
Neonatal* Death (%)	7.9	7.4	11.0

* Adjusted OR (95%CI) = 1.66 (1.07-2.57)

Lee et al, Pediatrics 2006

Postnatal Steroids: Other Systemic Steroids

- **Methylprednisolone**: shorter half life, fewer adverse effects and apparently as effective as dexamethasone in weaning from ventilation BUT no randomized trials (RCTs) yet
- **Betamethasone**: fewer adverse effects (poor weight gain and hyperglycaemia) and similar short term outcomes as dexamethasone but not a RCT
- Low dose **hydrocortisone** (1 mg/kg/day) reduced risk of CLD in one small study BUT two larger RCTs showed increases in gastrointestinal perforations and were stopped early

Low dose hydrocortisone (RCTs)

Watterberg et al, 1999 – 12 days; n=40
Watterberg et al, 2004 – 15 days; n=360
Peltoniemi et al, 2005 – 10 days; n=51

Latter 2 studies stopped early

Vandermeer, 2006 – unpublished data

Low dose hydrocortisone vs placebo

Outcome	Number	RR	95%CI
GI perforation*	451	2.08	1.08-4.00
Survival without BPD at 36 wk (all)	448	1.14	0.90-1.43
Survival without BPD at 36 wk (chorioamnionitis)	171	1.82	0.95-3.50

* Many also had indomethacin

Vandermeer, 2006 – unpublished data

Dexamethasone vs Hydrocortisone

OUTCOME	Babies	RR	95%CI
CLD (36 wk)			
Dexamethasone	2840	0.70	0.61 to 0.81
Hydrocortisone	802	0.96	0.82 to 1.12
Death/CLD (36 wk)			
Dexamethasone	2484	0.87	0.80 to 0.94
Hydrocortisone	836	0.95	0.86 to 1.06
Death in Hospital			
Dexamethasone	2840	1.03	0.90 to 1.18
Hydrocortisone	880	0.88	0.67 to 1.17

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009

Early Steroids (≤ 7 days) : Cerebral Palsy

Steroid	Babies	RR	95%CI	NNH	95%CI
Dexamethasone	921	1.75	1.20 to 2.55	20	11 to 100
Hydrocortisone	531	0.97	0.55 to 1.69	--	-----

Halliday, Ehrenkranz and Doyle, Cochrane Library 2009



Postnatal Steroids – Inhaled or Systemic

- Cochrane review (Shah et al, 2004) : 7 trials
No outcome differences between inhaled steroids and placebo except less use of late dexamethasone
- OSECT trial (Halliday et al, Pediatrics 2001): n=570
Inhaled budesonide (800 $\mu\text{g}/\text{kg}/\text{day}$) vs systemic dexamethasone (starting at 0.5 $\text{mg}/\text{kg}/\text{day}$): both early and late:
Inhaled as effective though fewer adverse effects

Postnatal Steroids – Inhaled vs Systemic

Dexamethasone Treatment Showed

- Earlier extubation
- Reduced oxygen needs
- Improved lung mechanics
- Hypertension
- Hyperglycaemia

Shah et al, Cochrane Library 2004

Inhaled vs Systemic Steroids

- 5 trials but 2 excluded
- No difference in CLD at 36 weeks
- No difference in death by 36 weeks
- No differences in adverse events
- No evidence that inhaled steroids better than systemic for ventilator-dependent preterm infants

Shah et al, Cochrane Library, 2007

OSECT Follow-up : UK and Ireland Dexamethasone vs Budesonide

	Odds Ratio*	95% Confidence Intervals
SBP > 95th percentile	3.23	1.00 – 10.4
Diagnosis of Asthma	2.60	1.11 – 6.07

*adjusted for gestation, birth weight, gender, antenatal steroids, method of delivery, Apgar score at 5 minutes and CRIB score

Wilson et al, Pediatrics 2006; 117: 2196-205

Instilled Budesonide with Surfactant

- Pilot RCT of 116 infants < 1500 g with severe RDS
- 60 treated with 0.25 mg/kg Budesonide and 100 mg/kg Beractant every 8 hours
- 56 treated with 100 mg/kg Beractant every 8 hours
- Primary endpoint was death/CLD at 36 wk PMA

Yeh et al, Pediatrics 2008; 121: e1310-e1318

Instilled Budesonide and Beractant

	Budesonide (n=60)	Control (n=56)
Birth weight (g) mean (SD)	881 (245)	919 (272)
Gestation (wk) mean (SD)	26.4 (2.2)	26.7 (2.3)
Male n (%)	31 (52)	27 (48)

Yeh et al, Pediatrics 2008; 121: e1310-e1318

Instilled Budesonide and Beractant

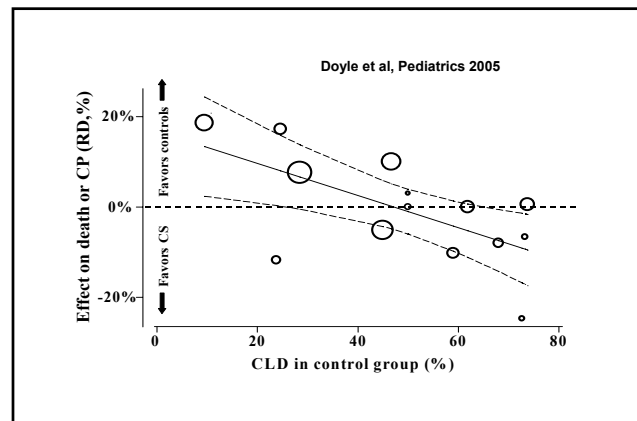
	Budesonide (n=60)	Control (n=56)
Prenatal steroids n (%)	46 (77)	42 (75)
Postnatal age (h) mean (SD)	2.1 (2.2)	2.1 (1.4)
FiO₂ mean (SD)	0.74 (0.18)	0.73 (0.15)

Yeh et al, Pediatrics 2008; 121: e1310-e1318

Instilled Budesonide and Beractant

Outcome	Budesonide (n=60)	Control (n=56)	p value
Death - n (%)	10 (17)	18 (32)	0.08
CLD - n (%)	9 (15)	16 (29)	0.12
Death/CLD - n (%)	19 (32)	34 (61)	0.003
SBP on d 3 (mmHg) mean (SD)	50 (7)	46 (9)	<0.001

Yeh et al, Pediatrics 2008; 121: e1310-e1318



Suggested "New" Recommendations

- Don't give in the first week of life
- Consider if ventilator-dependent after the first 7-10 days of life
- Discuss risks and benefits with parents
- Use lowest dose for shortest duration
- No role yet for inhaled steroids
- Further studies needed

BAPM Working Group, 2005

NEONATAL EUROPEAN STUDY OF INHALED STEROIDS



Steering Committee

Dirk Bassler
Virgilio Carnielli
Henry Halliday
Mikko Hallman
Pierre-Henri Jarreau
Richard Plavka
Christian Poets
Matthias Schwab
Eric Shinwell
John van den Anker

Trial Management Team

Priscilla Herrmann
Jana Johannsen
Christoph Meisner
Susanne Stoppel
Gabriele von Oldershausen



THANK YOU