Rational Use of Postnatal Steroids

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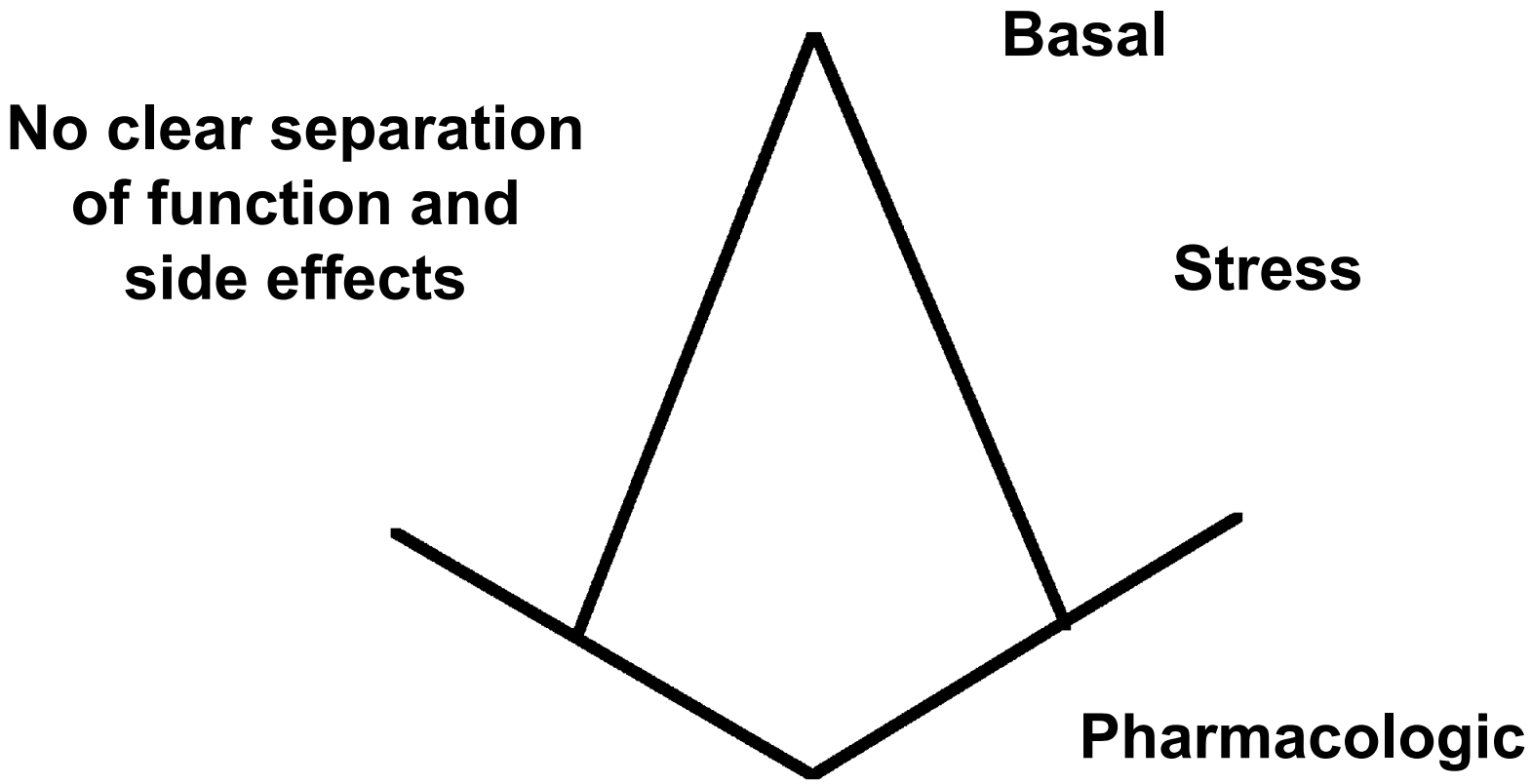
Conflicts of Interest Declaration

	Source:	Purpose:
Grants	B&M Gates Foundation	Antenatal steroid studies
	GSK (Matt Kemp)	Steroid Pharmacokinetics
Gifts for Research	Chiesi	Budesonide for BPD, Surfactant
	Merck	Betamethasone
Consulting	B&M Gates Foundation	Infant mortality in low resource environments
	Chiesi	New treatments for BPD

Content of Presentation:

- Concepts relevant to corticosteroids in the developing human
- The past history of PNS for BPD
- The present usage and new trials
- Some research observations
- The future – speculation

Glucocorticoid Dose



Short-term Use of Oral Corticosteroids and Harm in Adults in US

- 21% of adults received 1 or more oral steroid treatments within 3 years.
- Median days of treatment – 6 days.
- Median dose – 20 mg. prednisone = about 0.05 mg/kg Dex.

Adverse Event Risk		
Sepsis	5.3	CI 3.8 – 7.4
Thrombosis	3.3	CI 2.8 – 4.0
Fracture	1.9	CI 1.7 – 2.1

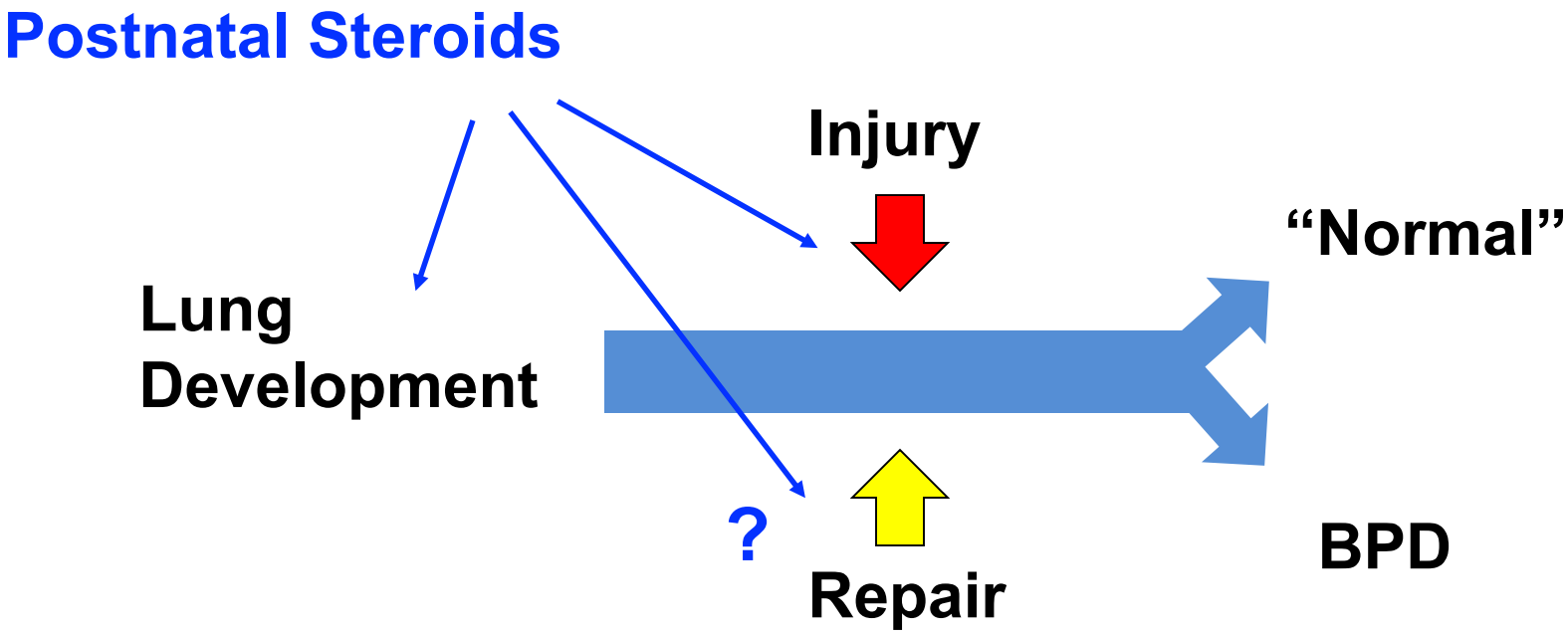
Toxicity of glucocorticoids are dependent on:

- **Dose**
- **Duration of exposure**

Comparison of Human Fetus with Animals used to Study Antenatal Effects of Glucocorticoids

	Saccular to Alveolar Transition	Percent Increase in Weight per day at 80% Gestation
Human	30 wks - 75% gestation	1.6%
Sheep	75% gestation	3.8%
Rabbit	Term	57%
Rat	3 days postnatal	65%
Mouse	4 days postnatal	97%

Major Pathways to BPD



∴ ***Three processes acting simultaneously on the immature lung.***

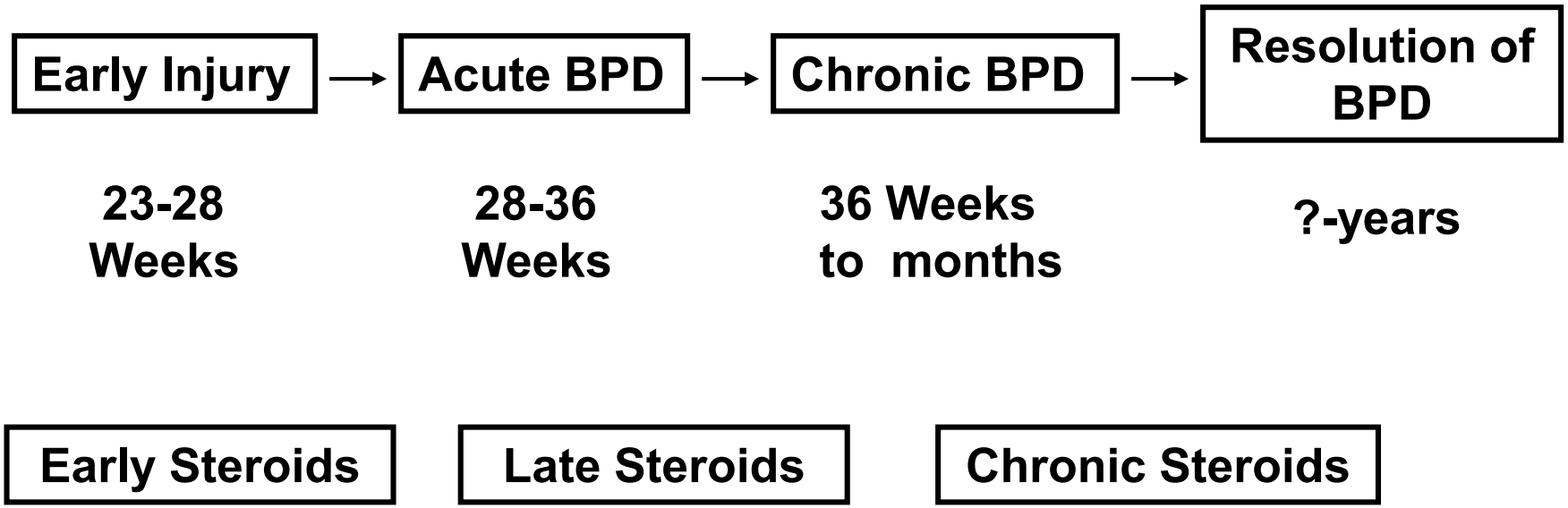
Total Exposure of Preterm Infants to Corticosteroids

$$\sum \text{Steroid Exposure} = \underset{4}{0} \sum \text{Antenatal Steroids} + \sum \text{Early Postnatal Steroids BPD Prevention}$$

$$+ \sum \text{Steroids to decrease severity of BPD} + \sum \text{Chronic Steroids}$$

Total exposure is seldom considered for each steroid treatment.

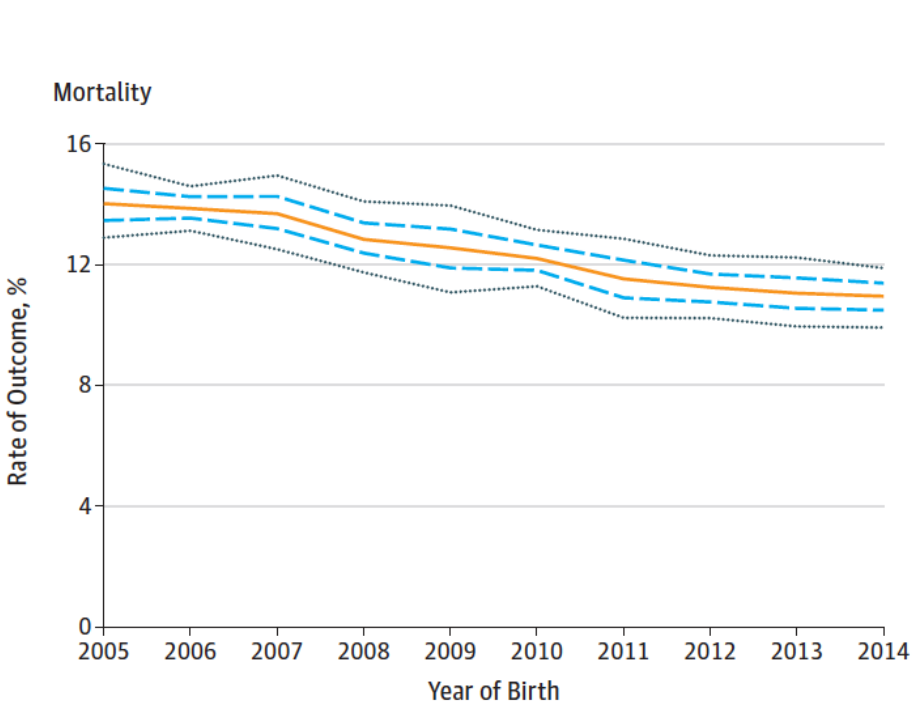
Stages of BPD for Infants with Moderate to Severe BPD

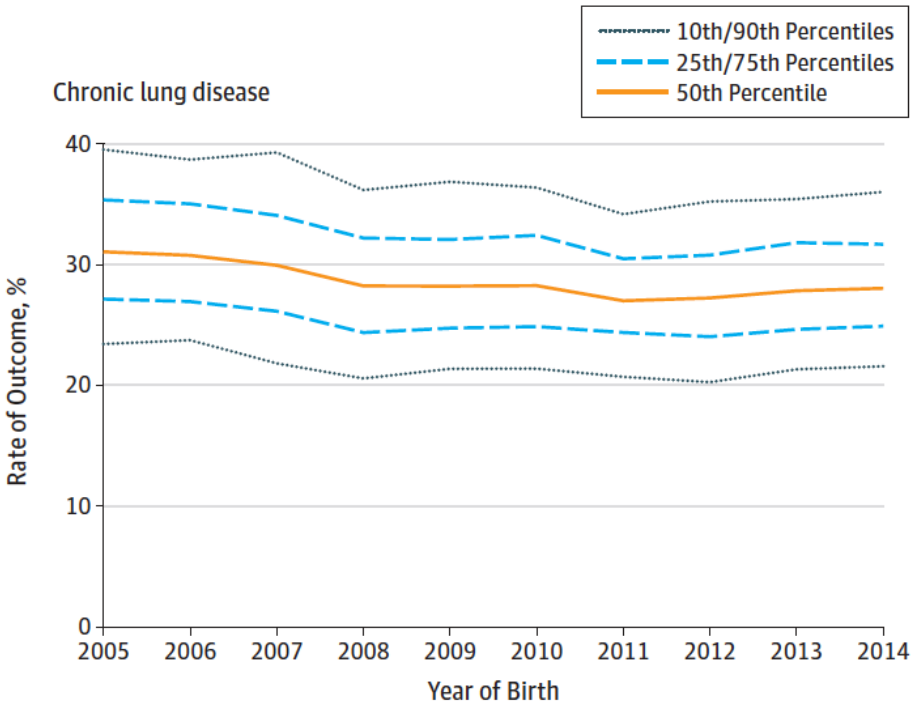


A Brief History of Postnatal Steroids

- **1985 – Avery et al. randomized 8 pairs of infants to a 42d course of Dex (0.5mg/kg) and demonstrated significant improved weaning from mechanical ventilation by 72hrs.**
- **1989 – Cummings et al. evaluated a 42d course as superior to an 18d course.**
- **2000 – Halliday, Ehrenkranz, and Doyle began meta-analysis in Cochrane Library identifying risks and benefits.**
- **2002 – AAP and CPA joint statement that routine use of systemic dexamethasone was not recommended.**
- **2005 – Doyle meta-regression analysis balanced risks with benefits.**
- **2006 – Doyle et al. demonstrated lower dose and a shorter course of steroids was effective – DART Trial.**
- **Present – ongoing controversies about which steroid, how to deliver, how to dose and risks.**

Rates of death and BPD in Vermont – Oxford Network for infants 501 to 1500g





BPD is only neonatal disease that is not decreasing.

Horbar et al, JAMA Peds - 2017

Why Do We Use Postnatal Corticosteroids?

- BPD is a bad disease with associated long term poor neurodevelopment.
- BPD is associated with airway reactivity and increased susceptibility to RSV.
- BPD is associated with inflammation.

Early Postnatal Steroids (<8d) to Prevent BPD
Pulmonary Outcomes

Outcome	Trial N	Patient N	RR	95% CI
Extubation – 7d	7	956	0.75	0.65 - 0.86
BPD – 36wks	21	3286	0.79	0.71 - 0.88
Death	28	3730	1.00	0.89 - 1.12
Death or BPD	22	3317	0.89	0.84 - 0.95

Doyle, Ehrenkranz & Halliday, Cochrane Review-2014

Early Postnatal Steroids (<8d) to Prevent BPD
Adverse Outcomes

Outcome	Trial N	Patient N	RR	95% CI
Hyperglycemia	13	2167	1.33	1.20 - 1.47
Hypertension	11	1993	1.85	1.54 - 2.22
GI Perforation	15	2519	1.81	1.33 - 2.48
NEC	22	3497	0.87	0.70 - 1.08
PDA	23	3492	0.79	0.7 - 0.85

Doyle, Ehrenkranz & Halliday, Cochrane Review-2014

Early Postnatal Steroids (<8d) to Prevent BPD Neurodevelomental Outcomes

Outcome	Trial N	Patient N	RR	95% CI
Cerebral Palsy	12	1452	1.45	1.06 - 1.98
Death or Major Neurosensory Disability	7	1233	0.97	0.81 - 1.17

Doyle, Ehrenkranz & Halliday, Cochrane Review-2014

Conclusions of Doyle, Ehrenkranz and Halliday

“The benefits of early postnatal corticosteroid treatment (≤7d), particularly Dexamethasone, may not outweigh the adverse effects of this treatment.”

Doyle, Erenkranz & Halliday, Cochrane Review 2014

Late Postnatal Steroids (>7d) to Prevent BPD
Pulmonary Outcomes

Outcome	Trial N	Patient N	RR	95% CI
Extubation – 7d	10	497	0.64	0.56 - 0.74
BPD – 36wks	9	535	0.76	0.66 - 0.88
Death or BPD	9	535	0.76	0.68 - 0.85
Death - discharge	19	1035	0.86	0.66 - 1.13

Doyle, Ehrenkranz & Halliday, Cochrane Review-2014

Late Postnatal Steroids (>7d) to Prevent BPD
Adverse Outcomes

Outcome	Trial N	Patient N	RR	95% CI
Hyperglycemia	16	1271	1.50	1.25 - 1.80
Hypertension	14	1175	2.12	1.45 - 3.10
GI Perforation	3	159	1.60	0.28 – 9.31
NEC	9	1016	1.03	0.61 - 1.74

Doyle, Ehrenkranz & Halliday, Cochrane Review-2014

Late Postnatal Steroids (>7d) to Prevent BPD
Neurodevelopmental Outcomes

Outcome	Trial N	Patient N	RR	95% CI
Cerebral Palsy at 1-3 yrs	14	876	1.06	0.76 - 1.50
Cerebral Palsy – Latest reported age	15	855	1.12	0.79 - 1.60
Death or Major Neurosensory Disability	8	612	1.04	0.86 – 1.26
Abnormal Neuro Exam	4	200	1.81	1.05 - 3.11

Doyle, Ehrenkranz & Halliday, Cochrane Review-2014

Conclusions of Halliday, Ehrenkranz and Doyle

“Given the evidence of both benefits and harms of treatment, and the limitations of the evidence at present, it appears prudent to reserve the use of late corticosteroids to infants who cannot be weaned from mechanical ventilation and to minimize the dose and duration of any course of treatment.”

Doyle, Erenkranz & Halliday, Cochrane Review 2014

Dosing of Postnatal Corticosteroids

Time of Treatment	Steroid	# Studies	Initial Dose (mg/kg/d)	Duration
<96h -	Hydrocortisone	3	1-50	1-12d
	Dex	3	.15-.2	1-10d
	Dex	15	0.5 or 1mg	2-42d
7-14d	Dex	7	0.5 or 1mg	2-40d
>3wks	Dex	9	0.5 or 1mg	6-42d

Doyle, Erenkranz & Halliday 2014

AAP and CPA Joint Statement

"The routine use of systemic Dexamethasone for the prevention or treatment of chronic lung disease in infants with very low birth weight is not recommended"

Pediatr., 109:330, 2002

Policy Statement – Postnatal Corticosteroids to Prevent or Treat BPD

- **In the absence of randomized trial results showing improved short- and long-term outcomes, therapy with high-dose dexamethasone cannot be recommended.**

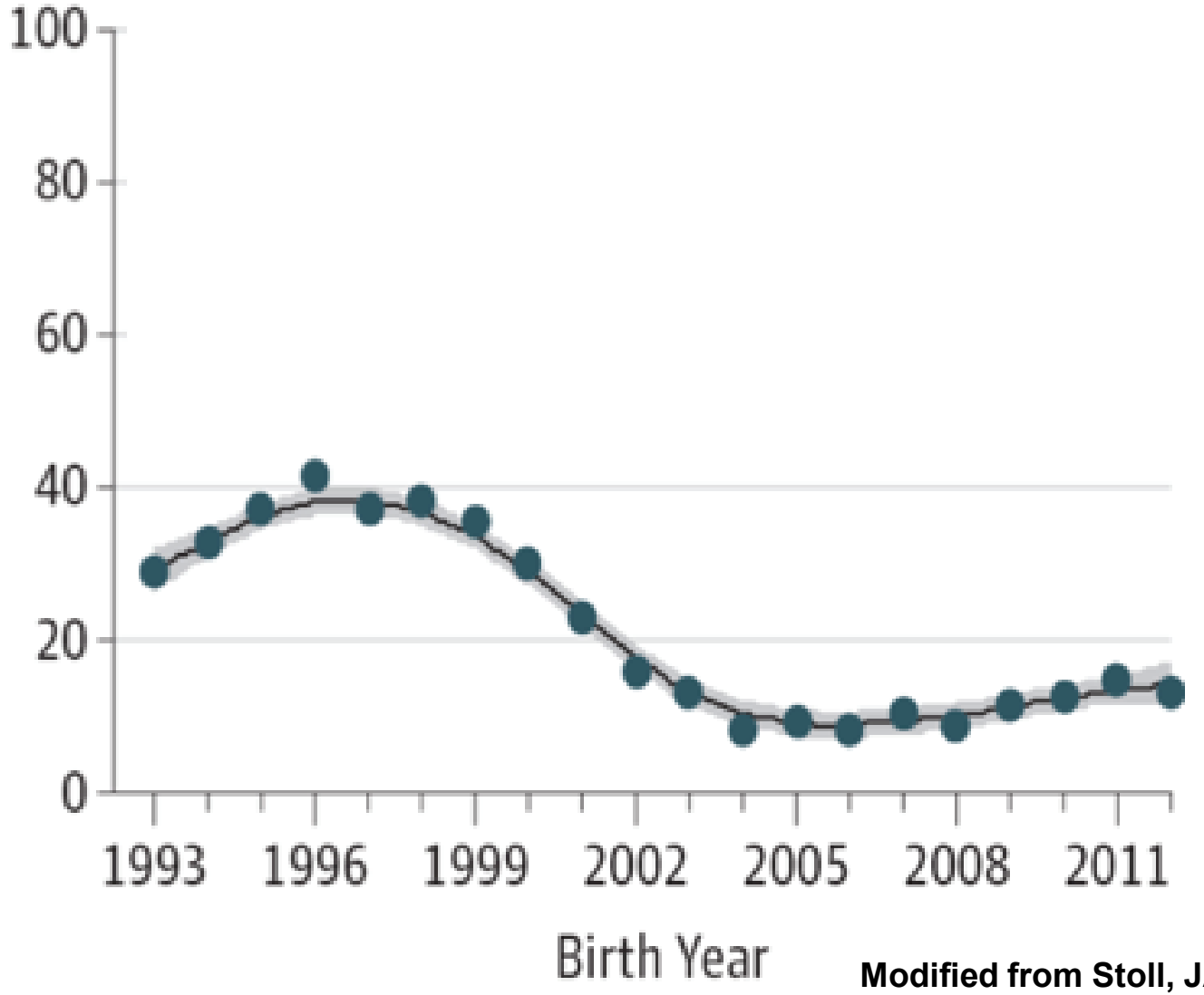
- **There is insufficient evidence to make a recommendation regarding treatment with low-dose dexamethasone.**

- **Early hydrocortisone treatment may be beneficial in a specific population of patients; however, there is insufficient evidence to recommend its use for all infants at risk of BPD.**

- **Existing data are insufficient to make a recommendation regarding treatment with high-dose hydrocortisone.**

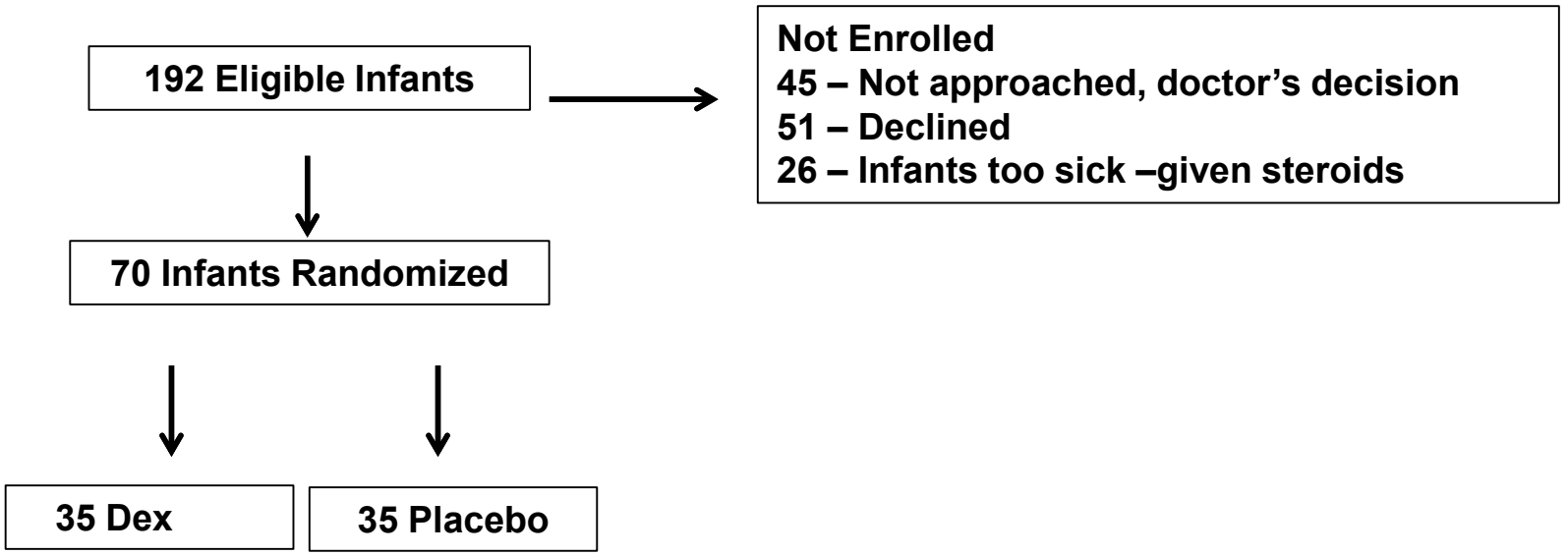
Watterberg, et al. for AAP – Pediatr., 2010

Postnatal Steroid Use in NICHD-NRN for Infants 22-28 wks GA



Modified from Stoll, JAMA, 2015

DART Trial – Low Dose Dex for Extubation
- 0.15 mg/kg x 3d and Taper for 7d
- Median age – 23d



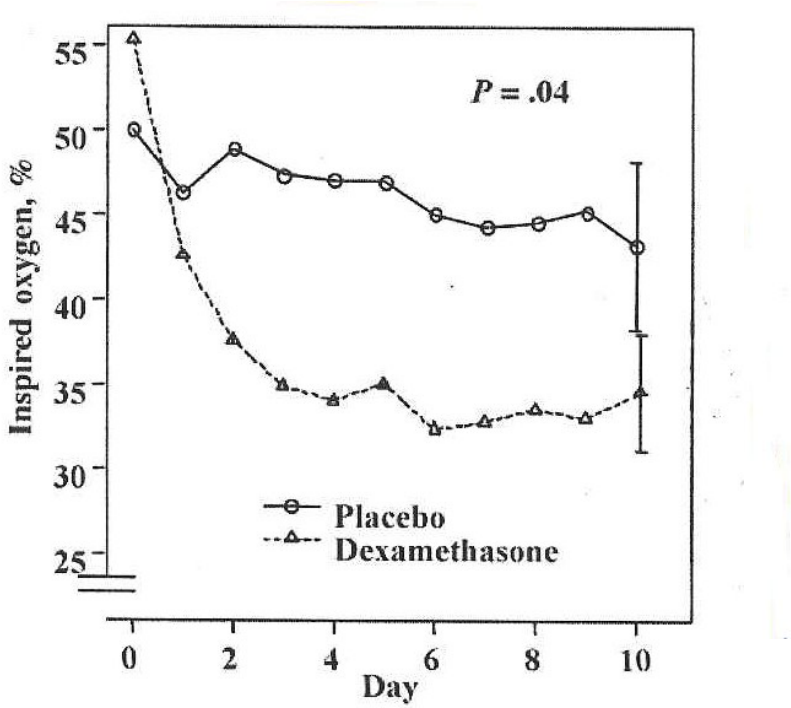
Population: Infants <1kg, <28wks GA on ventilator after 7d

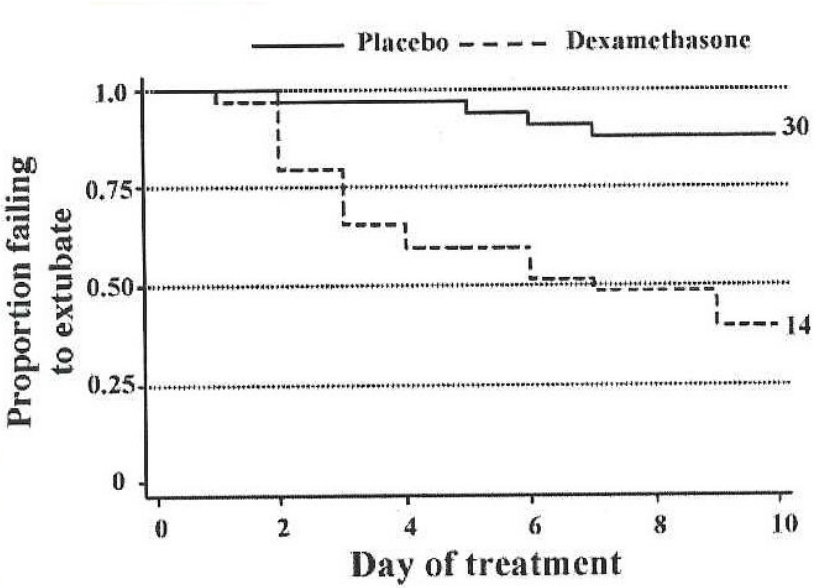
Power calculation/goal – 814 patients

Doyle, et al., Pediatr, 117:77, 2006

DART Trial – Low Dose Dex for Extubation

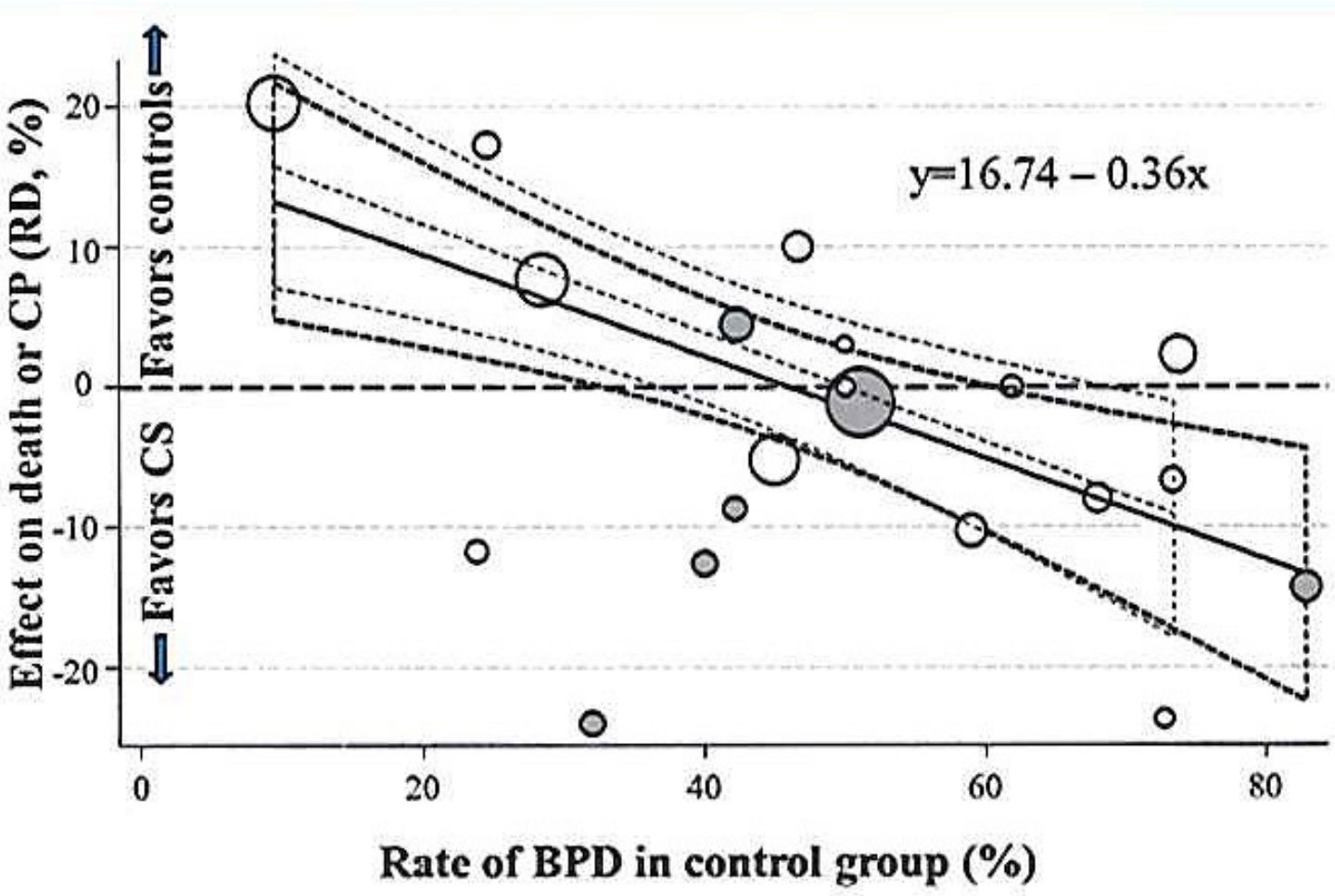
- 0.15 mg/kg x 3d and Taper for 7d
- Median age – 23d





Doyle, et al., Pediatr, 117:77, 2006

Meta-regression Analysis of Trials of 20 Trials of Postnatal Steroids for BPD



Doyle, et al., J.Pediatr 2014

Recent Early Steroid Trials that Challenge Present Treatment Strategies

- **Aerosolized Steroids**
- **Early low dose hydrocortisone**
- **Early surfactant + Steroid**

Fluticasone by Metered Dose Inhaler to Prevent BPD

Treatment 2xday beginning on day 1 for intubated infants continued to extubation.

	Fluticasone	Placebo	P
Patient Number	107	104	---
Gestational Age (weeks)	26.1	26.2	0.6
Birth Weight (g)	784	784	0.99
Antenatal Steroids (%)	42.1	40.4	0.89

Nakamura et al Arch Dis Child, 2016

Fluticasone by Metered Dose Inhaler to Prevent BPD

Treatment 2xday beginning on day 1 for intubated infants continued to extubation.

	Fluticasone	Placebo	P
Death (%)	9.4	6.9	0.62
Death or 0_2 at Discharge			
- All Patients (%)	14	22	0.15
- 24-26 weeks GA (%)	12.5	29	0.03
- With Chorioamnionitis (%)	14.3	40.6	0.03
Death or NDI at 3 years (%)	34.1	32.3	1.00
Death or CP at 3 years (%)	21.7	19.4	0.93

Nakamura et al Arch Dis Child, 2016

Some benefits in subgroups without adverse effects on development

Budesonide by Metered Dose Inhaler to Prevent BPD

Treated 2xday for 14 days from day 1 and 1 dose /day until 32 weeks or off oxygen and positive pressure.

	Budesonide	Placebo	P
Patient Number	437	419	---
Gestational Age (weeks)	26.1	26.1	---
Birth Weight (g)	78.9	803	---
Antenatal Steroids (%)	88.8	91.4	---

Bassler et al NEJM, 2015

Budesonide by Metered Dose Inhaler to Prevent BPD

Treated 2xday for 14 days from day 1 and 1 dose /day until 32 weeks or off oxygen and positive pressure.

	Budesonide	Placebo	P
Death %	16.9	13.6	0.17
Survival with BPD (%)	27.8	38.0	0.004
Death + BPD (%)	40.0	46.3	0.05
- With Chorioamnionitis (%)	37.7	42.1	0.42
GA at last use of positive pressure (weeks)	33.1	33.4	0.07
GA at last use of oxygen	31.6	33.1	0.05

Bassler et al NEJM, 2015

A BPD benefit with possible risk of death.

Budesonide by MDI to Prevent BPD – 21 month Outcomes

	Budesonide	Placebo	P
Mental Dev. Index	88	86	0.14
Cerebral Palsy	3.3%	2.9%	0.77
Medical Hospital Admissions	40%	48%	0.60
Death	20%	15%	0.04

Bassler et al NEJM, 2018

Increased death overall.

Early Low-Dose Hydrocortisone to Prevent BPD.

1 mg/kg hydrocortisone from day 1 for 7 days and 0.05 mg/kg to day 10.

	Hydrocortisone	Placebo	P
Patient Number	255	266	---
Gestational Age (weeks)	26.4	26.5	---
Birth Weight (g)	860	840	---
Antenatal Steroids (%)	93	92	---

Baud et al Lancet, 2016

Early Low-Dose Hydrocortisone to Prevent BPD

1 mg/kg hydrocortisone from day 1 for 7 days and 0.05 mg/kg to day 10.

	Hydrocortisone	Placebo	P
Death (%)	22	26	0.33
BPD (%)	22	26	0.25
Survival without BPD (%)	60	51	0.04
Chorio without death or BPD (%)	65	53	0.05
Extubated by day 10 (%)	60	40	< 0.01

Baud et al Lancet, 2016

A benefit as a combined Death + BPD outcome with low-dose exposure.

Surfactant plus Steroid to Prevent BPD

Initial surfactant doses mixed with 0.25 mg/kg budesonide compared to surfactant.

	Surf + Budesonide	Surf	P
Patient Number	131	134	---
Gestational Age (weeks)	26.5	26.8	---
Birth Weight (g)	882	935	---
Antenatal Steroids (%)	85	79	
Age of Surf Treatment (hr)	2.0	1.8	
FiO_2 at Surf Treatment	0.61	0.63	---

Yeh et al AJRCCM, 2016

Surfactant plus Steroid to Prevent BPD

Initial surfactant doses mixed with 0.25 mg/kg budesonide compared to surfactant.

	Surf + Budesonide	Surf	P
Death (%)	13	16	0.54
BPD (%)	29	50	<0.001
Death or BPD (%)	42	66	<0.001
Severe BPD	9	19	0.03
2-3 year follow up (N)	85	87	---
Mod to severe Neuromotor injury (%)	9.4	9.2	---
MDI	83.4	81.5	---
PDI	77.9	77.6	---

Yeh et al AJRCCM, 2016

Innovative trial with a large treatment effect.

Summary of Recent Early Steroid Trials:

	Inhaled Steroid	10 day Hydrocortisone	Steroid + Surf
Steroid Exposure	Relatively targeted to lung, but higher dose	Very low dose, but systemic	Targeted to lung
Duration of Treatment	Off support or 32 weeks	10 days	Surfactant Treatments
Death	Increased 3.3%	Decreased 5 %	Decreased 3 %
BPD	Decreased 10.2 %	Decreased 4 %	Decreased 21 %

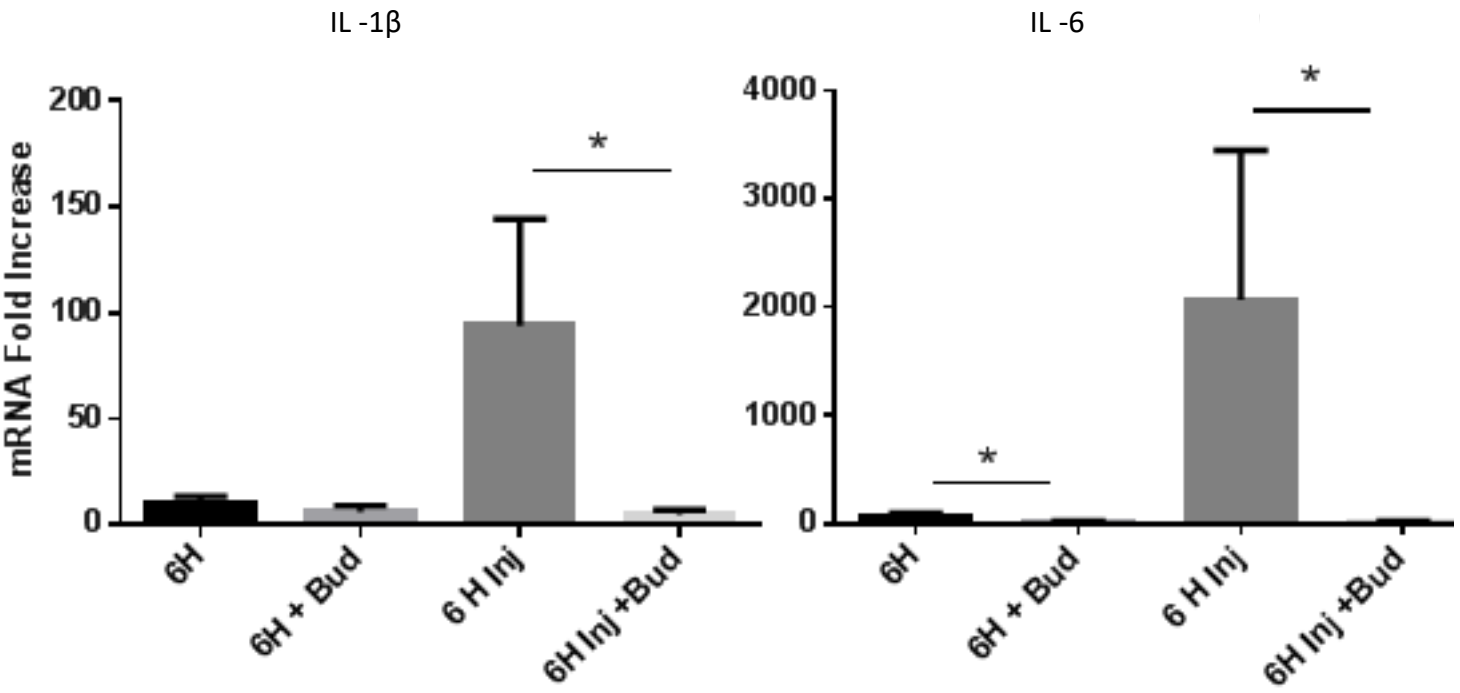
These results are a convincing proof of principle that early steroid treatments are effective.

Which treatment strategy do you prefer?

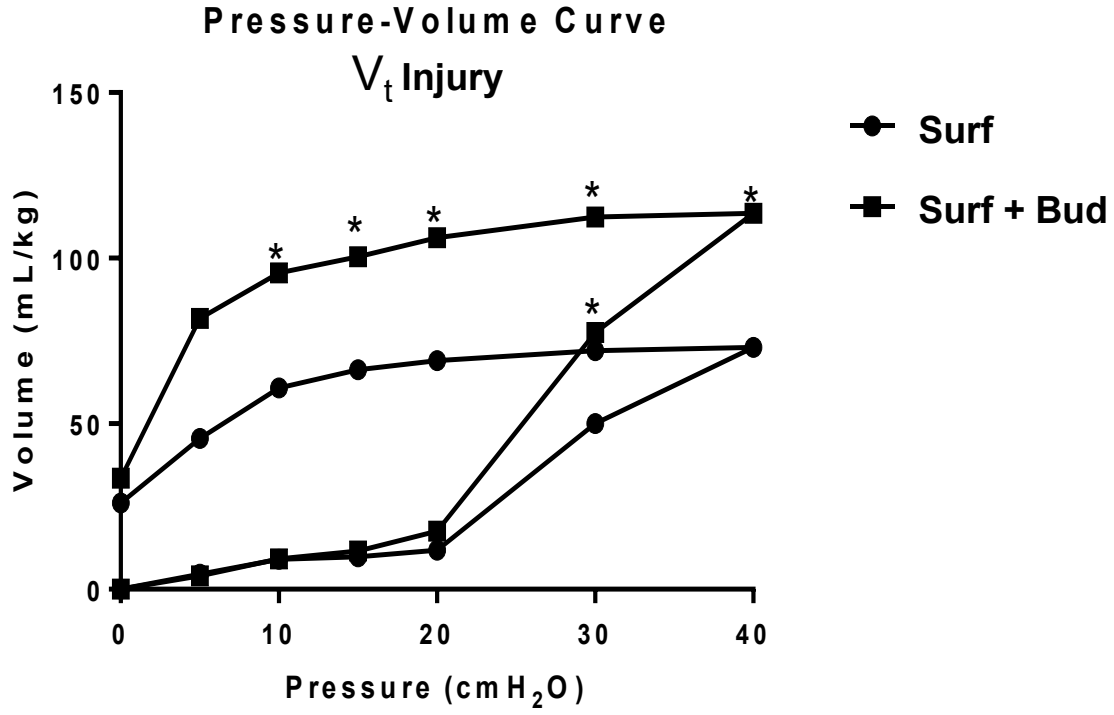
Experimental Results with Surfactant and Budesonide

- Preterm lambs randomized to 15 min. of normal or high tidal volume ventilation (injury).
- Treatment with Curosurf +/- 0.25 mg/kg Budesonide.
- Assessed at 6 hr. for inflammation.

Anti-inflammatory Effects of 0.25 mg/kg Budesonide in Surfactant



Physiological Effects of 0.25 mg/kg Budesonide in Surfactant 6 hr. After Injury in Preterm Sheep



A Concern – Repeated Exposures of ELBW Infants to Steroids.

- **> 80% of ELBW infants exposed to 1 or more ANS treatments.**
- **Early use of steroids for hypotension.**
- **Steroid use to treat BPD (Dart or Hydrocortisone).**
- **More steroids for extubation.**
- **Post discharge steroid for wheezing.**

How do I use Postnatal Glucocorticoids?

- **Suspect that very early therapy has more risk (<7d)**
- **Anticipate that therapy at >4 weeks will be less effective**
- **Have a defined goal - generally extubation in 3-5 days**
- **Give 0.15 mg/kg Dexamethasone for 3 days, and if there is no clinical response, stop therapy (DART protocol)**
- **If there is a clinical response, wean rapidly**
  - **0.07 mg/kg x 3d**
  - **0.04 mg/kg x 3d**

My view of future – we need to:

- Resolve debate about Dex vs. hydrocortisone for late treatment of BPD.
- Decide on an early treatment option.
- Test if late Surf + Budesonide is effective to treat BPD.
- Learn if more targeted anti-inflammatories are of benefit.
- Remain concerned about adverse effects.

- **All who drink of this treatment recover in a short time, except those whom it does not help, who all die.**
- **It is obvious, therefore, that it fails only in incurable cases.**

Galen