POST NATAL STEROID FOR BPD PREVENTION

TIMING AND REGIMEN

Dr Pankaj Garg

Vice Chairperson & Senior Consultant,

Department of Neonatology, Institute of Child Health, Sir Ganga Ram Hospital

pankajgarg69@gmail.com; 9810146581

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NOAH LYLES

Rameshbabu Praggnanandhaa

Postnatal Corticosteroids To Prevent Bronchopulmonary Dysplasia

Erik A. Jensen, MD, MSCE,* Kristi L. Watterberg, MD†

*Division of Neonatology, Department of Pediatrics, Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA
†Department of Pediatrics, University of New Mexico Health Sciences Center, Albuquerque, NM

Overview

Will steroids work?

- *Is there a biological rationale?*

Do they work?

- *Evidence for efficacy*

If yes, are they safe?

- *Evidence for harms*

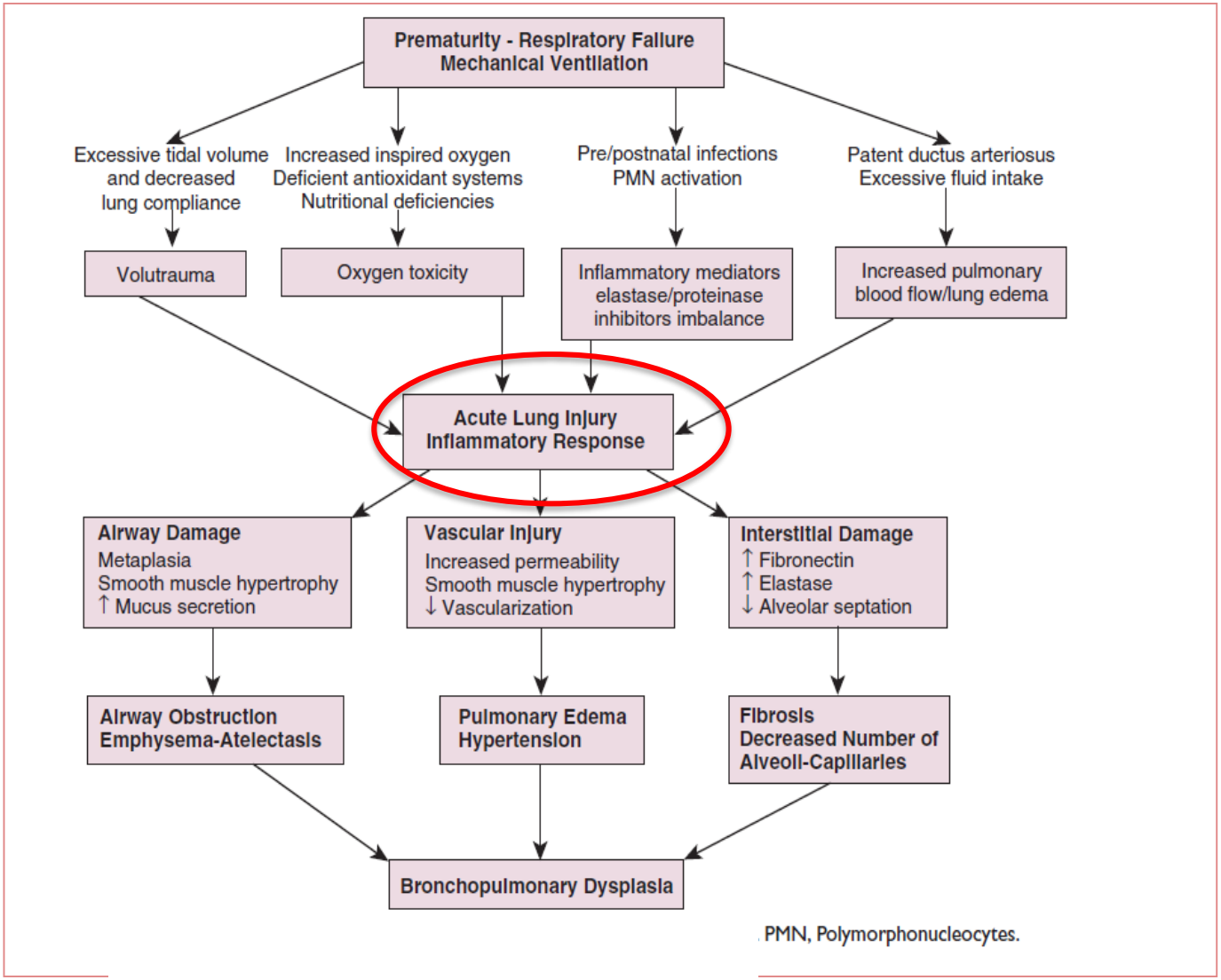
If yes, which one? Route? Dose?

- *Different steroid prepn. and routes*

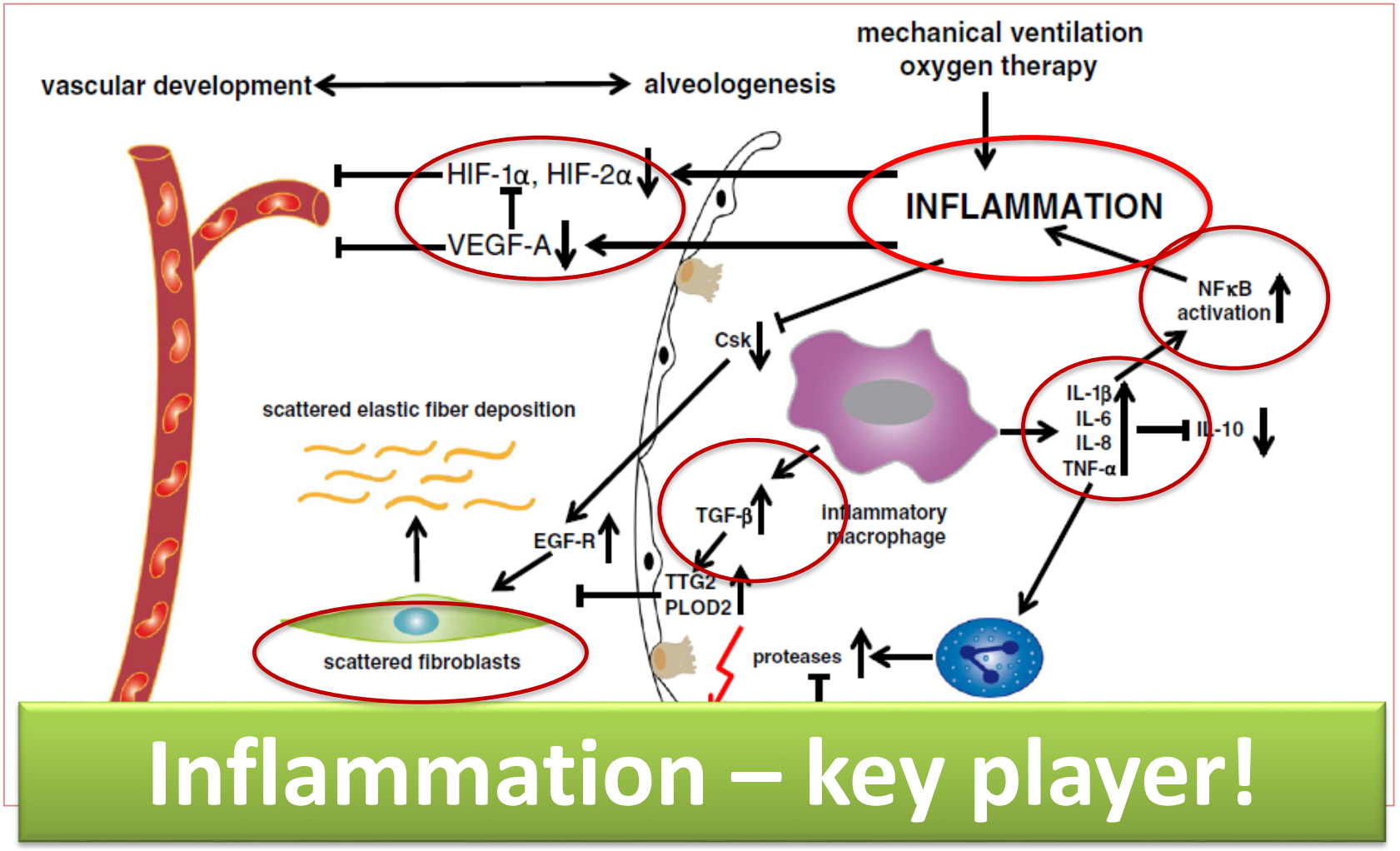
If yes, in whom?

- *Ideal candidate for therapy*

BPD: Pathophysiology

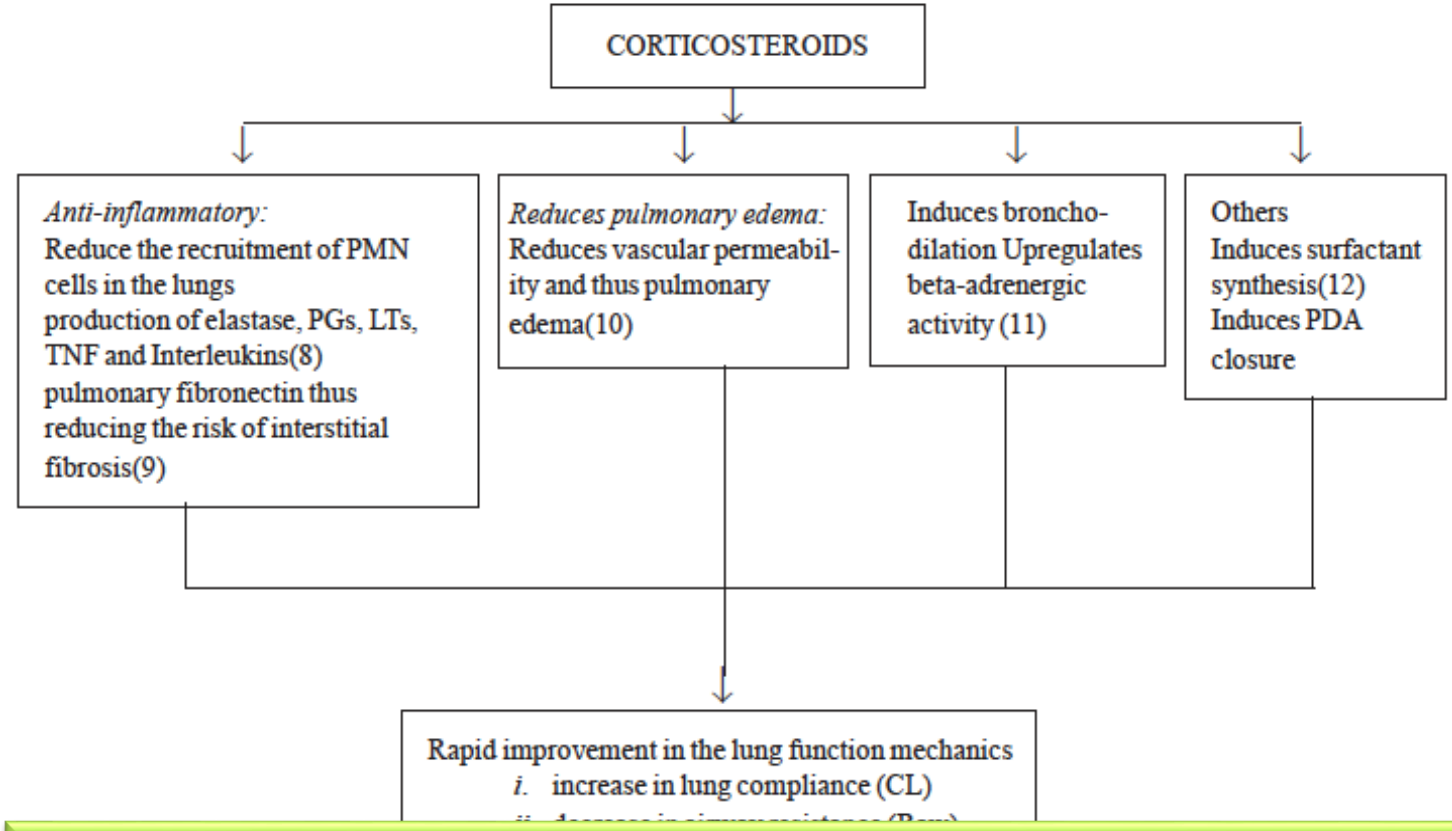


BPD: Pathophysiology



Inflammation – key player!

BPD: Postnatal steroids

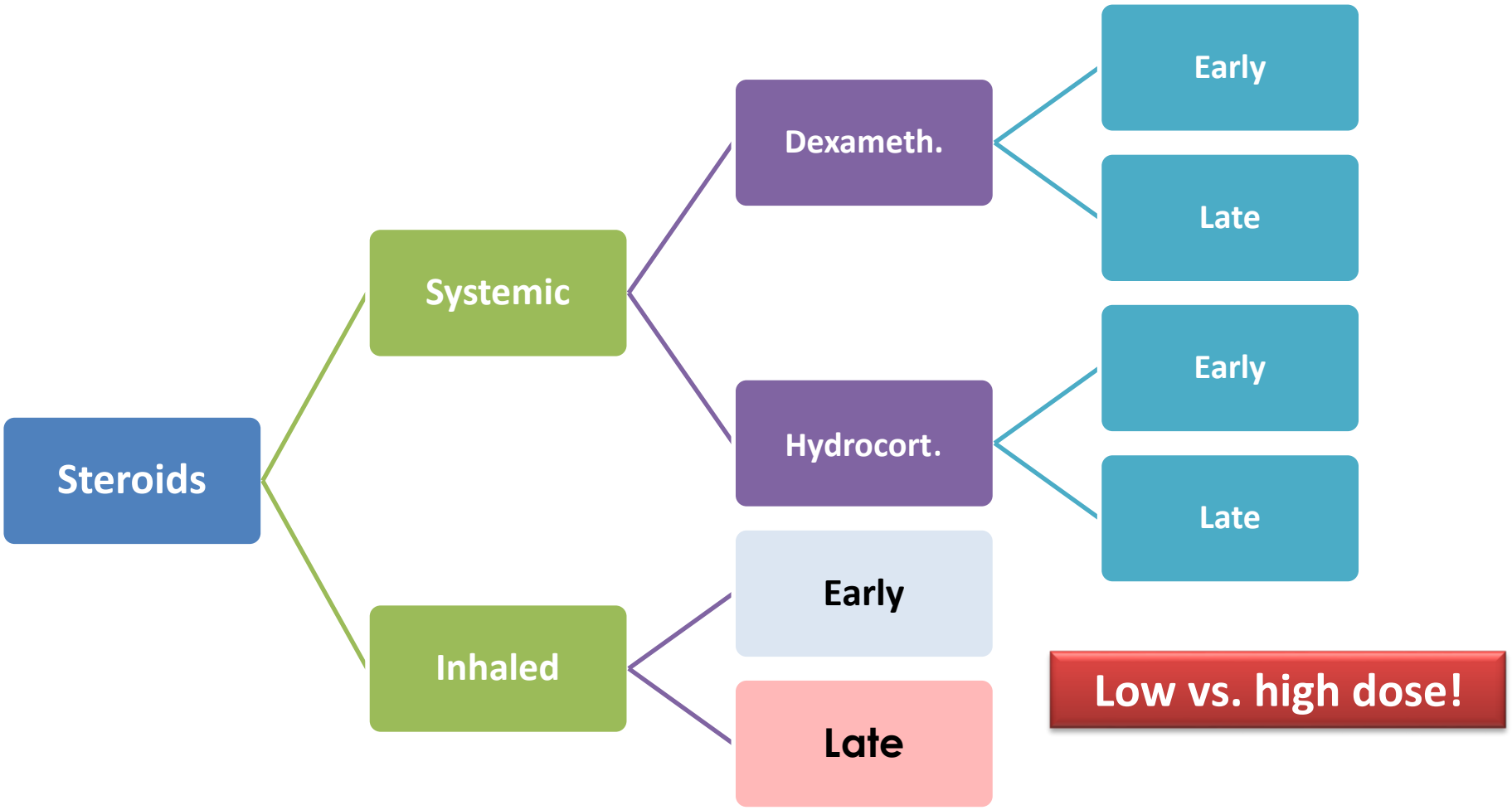


Potent anti-inflammatory agent!

BPD PREVENTION IS IMPORTANT

BRAIN IS MORE IMPORTANT

Postnatal steroids



KEY MESSAGE NO 1

Current evidence does not support the administration of dexamethasone during the first week after birth in very preterm infants
due to the increased risk of neurodevelopmental impairment in early childhood.

Drug, Route, and Timing of Initiation	Death or BPD at 36 Weeks' PMA	BPD at 36 Weeks' PMA	Death at the Last Reported Age	Death or Cerebral Palsy	Cerebral Palsy
Systemic					
<7 days of age					
Dexamethasone	0.88 (0.81-0.95) 17 trials, n=2791	0.72 (0.63-0.82)[a] 15 trials, n=1948	1.02 (0.90-1.16) 20 trials, n=2940	1.18 (1.01-1.37) 7 trials, n=921	1.85 (1.31-2.61)[a] 7 trials, n=587
Hydrocortisone	0.90 (0.82-0.99) 9 trials, n=1376	0.89 (0.78-1.02)[a] 9 trials, n=1145	0.80 (0.65-0.99) 11 trials, n=1433	0.86 (0.71-1.05) 6 trials, n=1052	1.01 (0.65-1.58)[a] 6 trials, n=742
≥7 days of age					
Dexamethasone	0.75 (0.67-0.84) 12 trials, n=553	0.80 (0.69-0.93[a] 7 trials, n=278	0.85 (0.66-1.11) 19 trials, n=993	0.95 (0.77-1.16) 15 trials, n=855	1.14 (0.75-1.74)[a] 15 trials, n=591
Hydrocortisone[b]	0.97 (0.92-1.02) 3 trials, n=1235	0.98 (0.92-1.04)[a] 3 trials, n=1099	0.83 (0.64-1.06) 3 trials, n=1235	0.95 (0.75-1.19) 3 trials, n=1184	1.25 (0.85-1.83)[a] 3 trials, n=951

Glucocorticoid drugs that have little or no mineralocorticoid activity, such as dexamethasone

Suppress natural cortisol secretion

leave mineralocorticoid receptors unoccupied for prolonged periods of time.

neuronal apoptosis.

These cellular effects may explain the neurodevelopmental deficits that have been observed with dexamethasone but not with hydrocortisone

Early steroids: **GI perforation**

3% (absolute) increase!

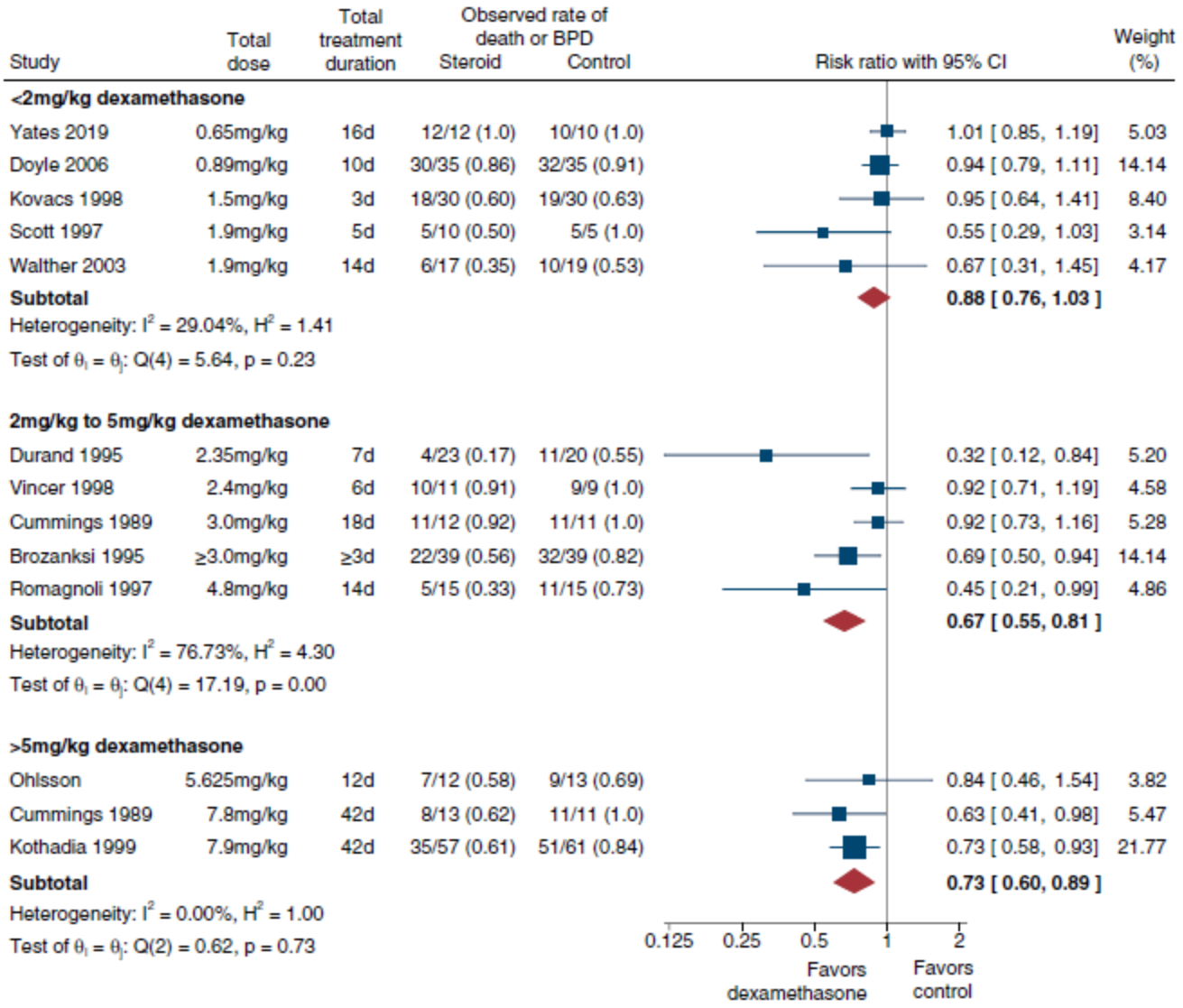
Doyle 2017

KEY MESSAGE 2

Low-dose <2MG/KG dexamethasone increase the likelihood of successful extubation in extremely preterm infants receiving mechanical ventilation WITHOUT HARM.

NO REDUCTION IN BPD

only trials of moderate or higher cumulative doses of late dexamethasone (>2 mg/kg) have been shown to decrease BPD rates.



KEY MESSAGE 3

As these latter trials were not powered to measure important differences in neurodevelopment, the safety of higher dose dexamethasone has not been established and its use is not recommended.

Low vs. high dose steroids

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with higher cumulative dose dexamethasone regimen	Risk difference with Lower
Death or bronchopulmonary dysplasia at 36 weeks' PMA - Moderate versus high cumulative dose regimen	55 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1 2 3]	RR 1.35 (1.00 to 1.82)	Study population	
				19/29 (65.5%)	229 more per 1000 (0 fewer to 537 more)
				Moderate	
				65.1%	228 more per 1000 (0 fewer to 534 more)
Death or bronchopulmonary dysplasia at 36 weeks' PMA - Low versus moderate cumulative dose regimen	154 (4 RCTs)	⊕⊖⊖⊖ VERY LOW [2 4]	RR 0.83 (0.50 to 1.40)	Study population	
				19/76 (25.0%)	43 fewer per 1000 (125 fewer to 100 more)
				Moderate	
				18.7%	32 fewer per 1000

Moderate dose:
Increased BPD and CP!

Effect modification by risk of BPD in control group

- **Risk < 35%**: Treatment increased the chance of death or CP
- **Risk >65%**: Significant benefit with corticosteroids

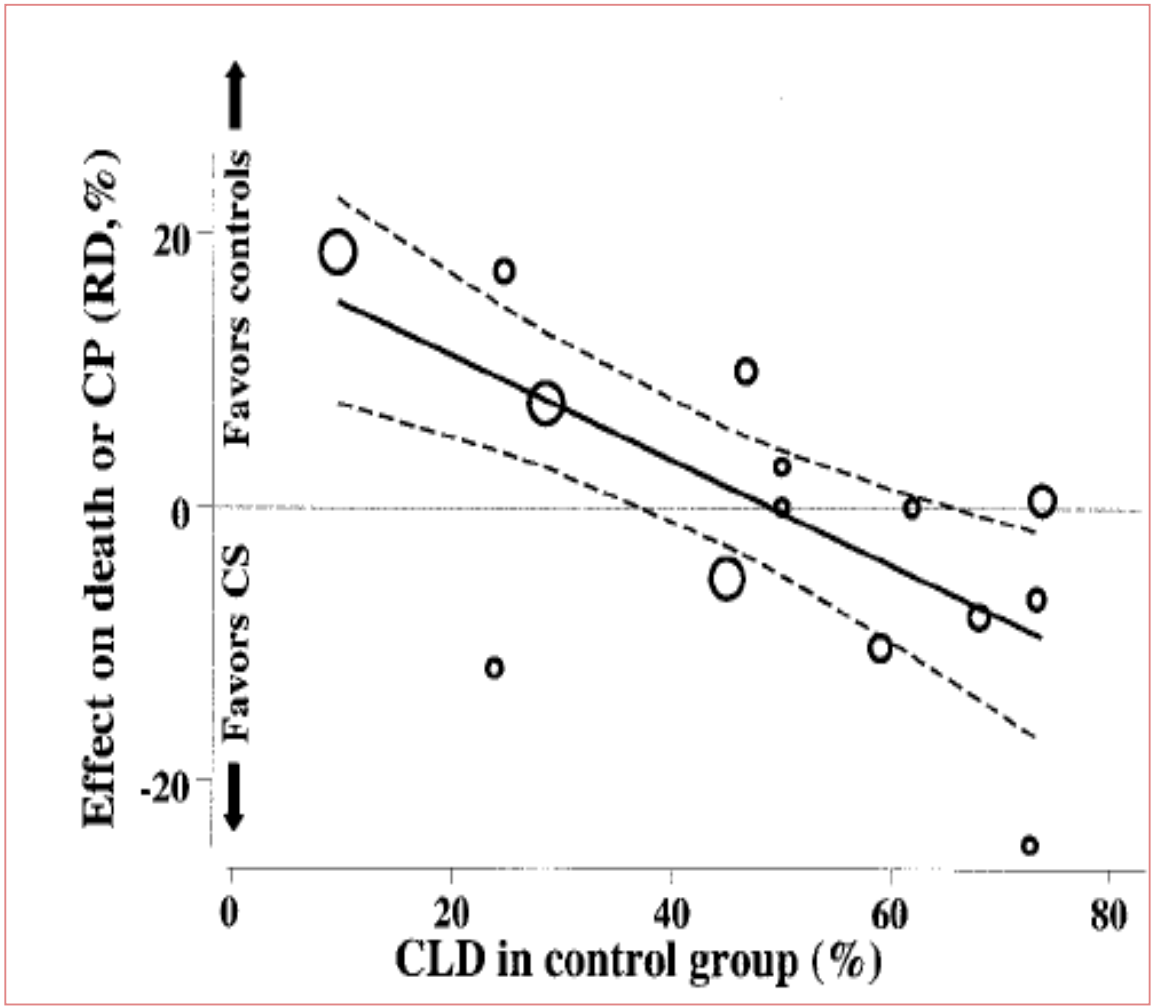
For every 10% increase in the rate of CLD in the control group

- Risk for **death fell by 1.7%** (0.4% to 3.9%)
- Risk for **CP fell by 2.3%** (0.3% to 4.3%)

Doyle 2005

Who will benefit then?

Effect modification by risk of BPD in control group



Doyle 2005

NICHD web-based estimator

Neonatal BPD Outcome Estimator
Infants with GA 23-30 weeks & Birth Weight 501-1249g

Please review your input for the following...
Birth Weight is a required field and must be between 501 and 1249 grams.

Information at Time of Birth	
Gestational Age (Weeks)	30
Birth Weight (Grams)	981
Sex	Male
Race / Ethnicity	Black
Postnatal Day	7
Ventilator Type	IMV/SIMV
FiO2[1]	40

Calculate Clear Cancel

Laughon et al Am J Respir Crit Care Med 2011

NICHD web-based estimator

NICHD
NEONATAL RESEARCH NETWORK

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Neonatal BPD Outcome Estimator
Infants with GA 23-30 weeks & Birth Weight 501-1249g

Gestational Age (Weeks)	27
Birth Weight (Grams)	981
Sex	Male
Race / Ethnicity	Black

Probability of Outcome
(expressed as a percent)

Time Period	Ventilator Type	FiO2	Death	Severe BPD	Moderate BPD	Mild BPD	No BPD
Day 7	IMV/SIMV	40	7.5	18.3	32.9	34.6	6.8

New Calculation

Laughon et al Am J Respir Crit Care Med 2011

Summary

S.No.		Recommendations	Comments
1.	Target population	ELBW babies on ventilator support even after 10-14 days of age	For babies on CPAP or Oxygen: Risks may outweigh benefits; treatment may be individualized.
2.	Timing	Moderately early steroid therapy (*i.e.*, after 10-14 days of age)	Early:definite adverse neurodevelop-mental outcome Late: may not be beneficial
3.	Drug	Dexamethasone	Others: not studied in detail
4.	Route	Parenteral	Inhaled steroids: may be reserved for 'wheezy infants' and for BPD spells
5.	Dosage	Low dose: Starting dose of 0.1 to 0.2 mg/kg/d	DART study (21) used 0.15 mg/kg/d and showed that it facilitated extubation
6.	Duration	Short duration 3 to 10 days	DART study (21) used 10 day tapering course

KEY MESSAGE NO 4

Prophylactic hydrocortisone (8.5mg/kg) over 10 days initiated within the first day after birth in 24-27 weeks may increase survival, although most published guidelines suggest against routine use of this therapy until further trial data are available.

Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial

Prof Olivier Baud, PhD [a] · Laure Maury, MD [a] · Florence Lebail, MD [b] · Duksha Ramful, MD [c] · Fatima El Moussawi, MD [d] · Claire Nicaise, MD [e] · et al. Show more

- **SURVIVAL WITHOUT BPD: 60% VS 51%; OR 1.48 (1.02-2.16)**
- **Decreased PDA ligation**
- **Increased extubation by D10**
- **Increased LOS; 31.13%vs24.8%; OR 1.3 (0.94-1.81)**
  - **24-25 weeks; 39.8% vs 23.3% (p0.02)**

KEY MESSAGE 5

- Early initiation of inhaled budesonide (23-27 weeks' gestation ON supplemental respiratory support at less than 12 hours of age to receive inhaled budesonide (400 ug every 12 hours for 14 days and then 200 ug every 12 hours thereafter)

may reduce BPD (deathor BPD (40.0% vs 46.3%; RR, 0.86; 95% CI, 0.75–1.00).

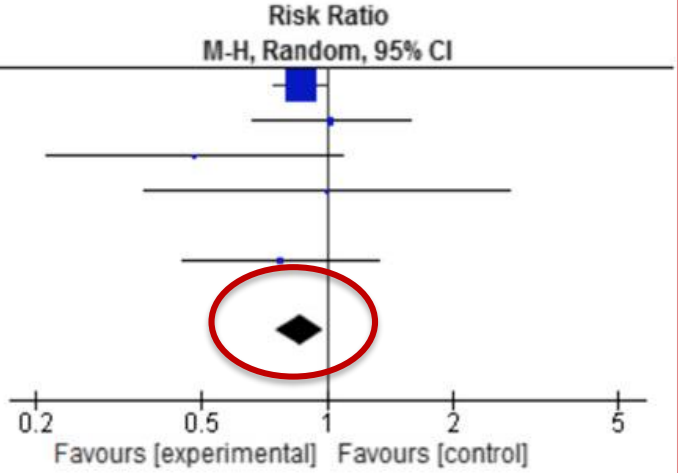
but the observed increase in mortality (2 years of age showed increased mortality in the budesonide group (19.9% vs 14.5%; RR, 1.27; 95% CI, 1.01–1.86) With this therapy prevents routine use.

Inhaled steroids: **Death or BPD**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassler 2015	175	437	194	419	79.1%	0.86 [0.74, 1.01]
Cole 1999	30	123	31	130	9.8%	1.02 [0.66, 1.58]
Fok 1999	6	27	12	26	2.8%	0.48 [0.21, 1.09]
Jangaard 2002	6	30	6	30	1.8%	1.00 [0.36, 2.75]
Merz 1999	0	12	0	11		Not estimable
Yong 1999	10	20	13	20	6.4%	0.77 [0.45, 1.32]
Total (95% CI)		**649**		**636**	**100.0%**	**0.86 [0.75, 0.99]**
Total events	227		256			

Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 4 (P = 0.59); I² = 0%

Test for overall effect: Z = 2.14 (P = 0.03)



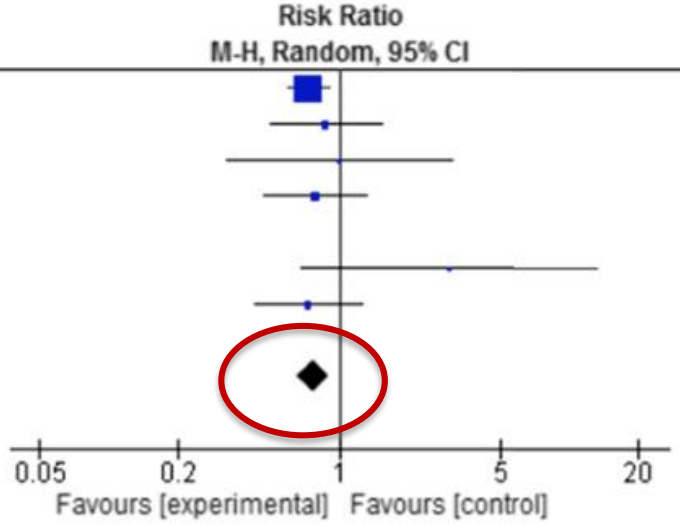
016

14% reduction!

Inhaled steroids: **BPD**

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassler 2015	101	363	138	363	65.4%	0.73 [0.59, 0.90]
Cole 1999	19	123	23	130	9.5%	0.87 [0.50, 1.52]
Jangaard 2002	5	30	5	30	2.3%	1.00 [0.32, 3.10]
Jonsson 2000	8	13	11	14	11.3%	0.78 [0.47, 1.30]
Merz 1999	0	12	0	11		Not estimable
Yong 1999	6	20	2	20	1.3%	3.00 [0.69, 13.12]
Zimmermann 2000	10	20	13	19	10.2%	0.73 [0.43, 1.25]
Total (95% CI)		**581**		**587**	**100.0%**	**0.77 [0.65, 0.91]**
Total events	149		192			

Heterogeneity: Tau² = 0.00; Chi² = 3.96, df = 5 (P = 0.56); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)



23% reduction!

016

KEY MESSAGE 6

1. Intratracheal instillation of budesonide with surfactant during the immediate newborn period may safely reduce BPD, but this potential benefit requires confirmation in ongoing trials.

	Intervention Group (*n* = 131)	Control Group (*n* = 134)	Difference (95% CI)	RR (95% CI)	*P* Value
BPD or death	55/131 (42%)	89/134 (66%)	−0.24 (−0.36 to −0.13)	0.58 (0.44 to 0.77)	<0.001
Death	17/131 (13%)	22/134 (16%)	−0.03 (−0.12 to 0.05)	0.96 (0.87 to 1.06)	0.54
BPD	38/131 (29%)	67/134 (50%)	−0.21 (−0.32 to −0.10)	0.70 (0.58 to 0.86)	<0.001

Yeh 2016

Summary

Recommendations

1. **NOT** to use routine postnatal **systemic** corticosteroids to prevent BPD (**Grade 1B**)
2. **NOT** to routinely use **inhaled corticosteroids** to reduce the risk of BPD (**Grade 1B**)

3. Use only in intubated neonates

4. Between 7-14 days preferably

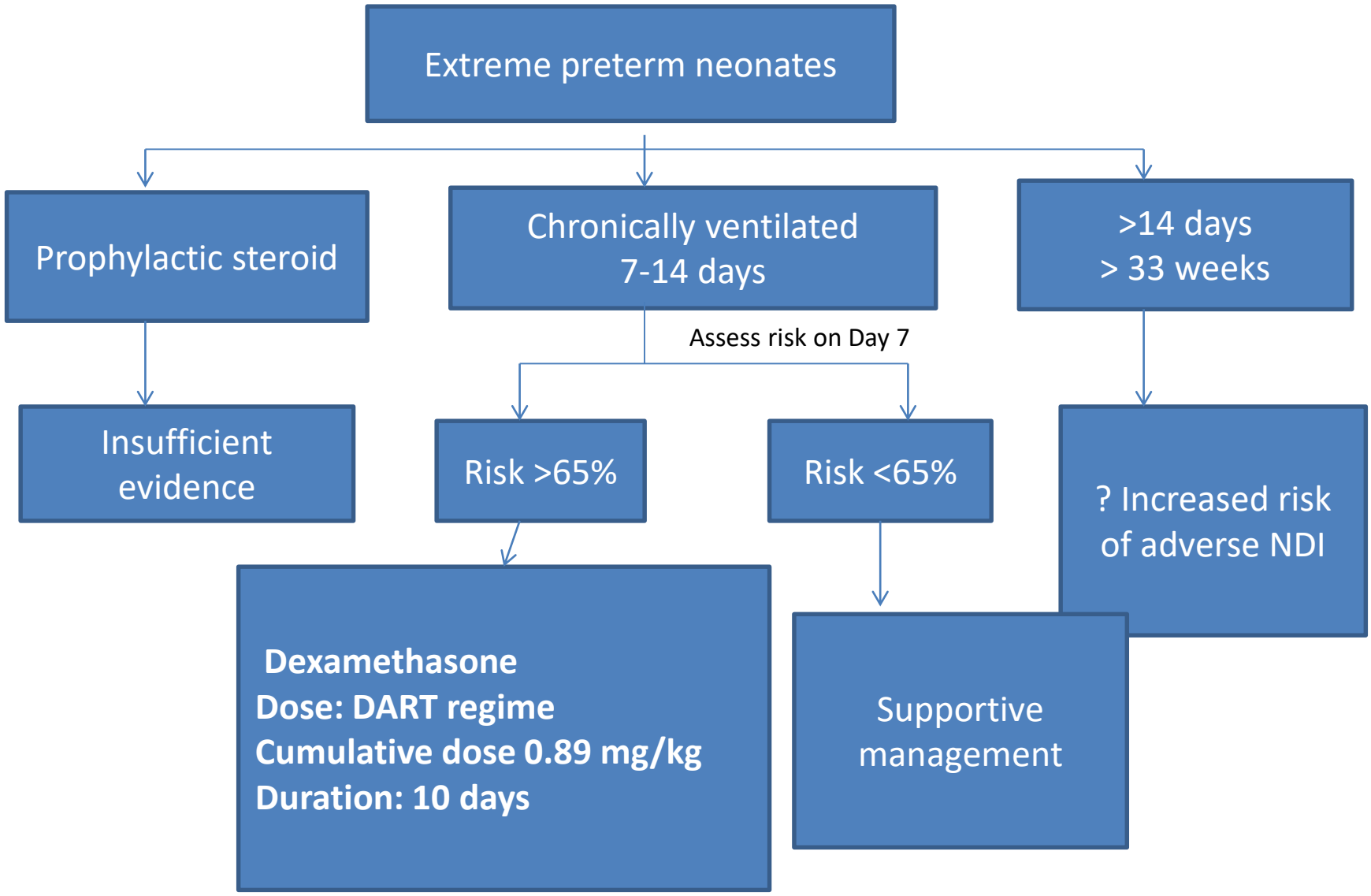
5. Dexamethasone is preferred in this age group

6. Low dose helps in weaning from Ventilator but doesn't reduce BPD but doesn't harm brain as well

7. Neonates at risk of severe BPD are likely to be helped more

UpToDate 2019

Proposed algorithm: Risk based approach



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