Steroids
Friend or foe?

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Objectives

- Role of postnatal steroids in Rx and prevention of BPD
- Evidence of steroids in BPD treatment
- Steroids and Neurodevelopmental outcome
- Establish a guideline for steroid in Rx of BPD
BPD

- Bronchopulmonary dysplasia (BPD) continues to be a major cause of neonatal morbidity
- **Half** of the infants < 1000 GM will require supplemental oxygen at 36 weeks of postmenstrual age
- The consequences of BPD are not confined to the respiratory system but associated with other neonatal morbidities, such as PDA and increased risk of neonatal sepsis
- Children with BPD have higher rates of neurological morbidity at follow-up and poor postnatal growth
Type of BPD

**Classic BPD**
- Emphysema
- Atelectasis
- Fibrosis
- Smooth muscle hypertrophy.
- Severe Resp. Failure
- PPHN
Type of BPD

New BPD

- ↑ lung fluid
- Diffuse inflammatory response
- ↓ alveolar septation
- Impaired vascular development
• **Preventing** bronchopulmonary dysplasia (BPD) is thus a priority in neonatal medicine and is likely to have benefit beyond respiratory outcomes.
Pathogenesis of BPD
Pathogenesis of BPD

- Prematurity
- Genetic Predisposition
- Ventilatory Trauma
- O2 toxicity
- Inflammatory mediators
- Pulmonary edema
- Pre/postnatal infection
- 1. PDA
- 2. Excessive fluid intake

**INFLAMATION**

- Airway damage
- Vascular Injury
- Interstitial damage
- Atelectasis
- Pul. Edema PPHN
- Fibrosis

**BPD**
Chorioamnionitis and cytokine exposure in utero PLUS postnatal sequential lung injury been shown to induce an inflammatory response in premature airway and pulmonary interstitium.

(Husain AN et al, Hum Pathol. 1998)
Prevention strategies of BPD
Pre/Postnatal infection
Antioxidants
Steroids

Immature lung
Mechanical ventilation
O2 therapy
Pulmonary Edema
Microvasular permeability

Inflammation
Oxidative stress

Rx

Alveolarization ↓
Vascular development ↓

BPD

Rx

iNO
Lower sPO2
Caffeine
Diuretics
PDA Rx

Vitamin A

Prevention strategies for BPD
Anti-inflammatory strategies

Corticosteroids.

Corticosteroids affects pulmonary function and lung disease through several mechanisms

1. Fetal exposure causes increased surfactant synthesis and lung epithelial differentiation
2. In animals, early postnatal exposure causes increased surfactant synthesis.
3. Decrease recruitment of polymorphonuclear leukocytes to the lung, and reduce the production of PGs and other inflammatory mediators. *(Bancalari E. Eur J Pediatr 1998;157(Suppl. 1))*
4. Decrease vascular permeability and pulmonary edema formation.
5. Modulate repair after lung injury by reducing fibronectin production, and subsequent fibrosis.
• Antenatal steroids as an inexpensive, safe, and highly effective way of enhancing neonatal survival and reducing morbidity in preterm infants

• The use of steroids after birth has been more controversial and there remains uncertainty about which steroid to use, indications, safety, and dosage.
Steroid
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What is the evidence?
Steroids & BPD

- Preventive strategy
- Treatment strategy
- Systemic vs Inhaled
- Dexamethasone vs Hydrocortisone
- Steroids Timing and Dose
Steroids' and BPD
• Early 1980s, high dose dexamethasone was used successfully to wean babies with BPD from mech. ventilation. (Mammel MC et al. Lancet 1983 & Avery GB et al. Pediatrics 1985)

• Cummings et al. NEJM 1989

36 infants with high risk of BPD who remained on ventilation at 14 days were treated with either short course (18 days) or prolonged tapering course (42 days):

1. Faster weaning from the ventilator and ↓O2 need.
2. Possible improvement of long term neurodevelopmental outcome.
During 1990s

- High dose dexamethasone became a standard practice.
- It was known that there were some acute adverse effects BUT these they were felt to be manageable and reversible

- The general feeling was
  
  (The benefit of improved lung function, earlier extubation and less BPD outweighed the known short term side effect)
Increase in adverse neurodevelopmental sequelae including Cerebral palsy

Early Dexamethasone Therapy in Preterm Infants: A Follow-up Study
Tsu F. Yeh, Yuh J. Lin, Chao C. Huang, Yung J. Chen, Chyi H. Lin, Hong C. Lin, Wu S. Hsieh and Yu J. Lien
Pediatrics 1998; 101:e7

Early postnatal dexamethasone treatment and increased incidence of cerebral palsy
E S Shinwell, M Karplus, D Reich, et al.
Arch Dis Child Fetal Neonatal Ed 2000 83: F177-F181
doi: 10.1136/fn.83.3.F177
Steroids & BPD

• **Inflammation** seems to be primary mediator of injury in pathogenesis of BPD, role of steroids as anti-inflammatory agent has been extensively studied and proven to be efficacious in management.

• Studies have seriously questioned the routine use especially high-dose dexamethasone due to its **long-term effect on neurodevelopment**.
Postnatal Corticosteroids to Treat or Prevent Chronic Lung Disease in Preterm Infants
Committee on Fetus and Newborn
*Pediatrics* 2002;109;330-338

RECOMMENDATIONS

1. On the basis of limited short-term benefits, the absence of long-term benefits, and the number of serious short- and long-term complications, the routine use of systemic dexamethasone for the prevention or treatment of CLD in infants with VLBW is not recommended.

2. Postnatal use of systemic dexamethasone for the prevention or treatment of CLD should be limited to carefully designed randomized double-masked controlled trials. The primary outcome of these trials should be survival without long-term developmental impairments, and the potential confounders of contamination and crossover should be avoided.
Steroids & BPD

• Postnatal use of dexamethasone for BPD has decreased since the publication of the AAP statement in 2002

• The incidence of BPD has not decreased. Instead, several reports have suggested that the incidence or severity of BPD may have increased
STEROIDS AND CP ...MYTH OR REAL?

It is your fault

Steroids  Neonatologist
Steroid
Friend or foe?

What is the evidence?
• The benefits of dexamethasone therapy in the first week of life may not outweigh its many adverse effects.

• The treatment after the first postnatal week may reduce mortality rates without increasing adverse long-term neurodevelopmental outcomes although long-term follow-up data remain limited.
systemic meta-analyses

- **Doyle et al (2005) concluded**: The incidence of death or cerebral palsy (CP) was increased among dexamethasone-treated infants compared with placebo-treated infants in studies that enrolled patients *at low risk (<35%) of BPD*

- Dexamethasone treatment decreased the risk of death or CP when infants *at high risk of BPD (≥65%)*

*Infants at the highest risk of BPD, the beneficial effect of dexamethasone in reducing lung disease seemed to outweigh its adverse effect of increasing the risk of CP.*
systemic meta-analyses

- Onland et al (2009) concluded:

  - Higher cumulative dose improved rates of survival without BPD and did not increase adverse long-term effects
Revised policy of AAP 2010

• Current evidence suggests that dexamethasone may
  ◆ decrease mortality rates,
  ◆ facilitate extubation,
  ◆ decrease the incidence of BPD

BUT

• carries a significant risk for impairment of growth and neurodevelopment
Hydrocortisone and BPD
Hydrocortisone

- Significant benefits in early extubation and prevention Rx of CLD (Less No. of studies)

- The short term side effect (Hyperglycemia, HTN) is less than DXM.

- Long term neurodevelopmental outcome following HC treatment is favourable.

- A quantified 3D-MRI showed no effect on brain growth, measured at term equivalent age, after treatment with hydrocortisone for CLD.
  (Manon J, et al. Pediatric research 2009)

- Half life 8-12 hrs
- 25–30 times lower anti-inflammatory potency than DXM

- Animal study showed, HC activate mineralocorticoids receptors which is protective against apoptosis in hippocampus.
### Table 3: RCTs of early hydrocortisone to prevent BPD.

<table>
<thead>
<tr>
<th>Study, no. of centers</th>
<th>n</th>
<th>Population: mechanically ventilated infants</th>
<th>Timing</th>
<th>Hydrocortisone dosing regimen</th>
<th>Rate of survival without BPD HC versus placebo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watterberg et al.</td>
<td>40</td>
<td>BW: 500–999 g</td>
<td>&lt;48 h postnatal age</td>
<td>0.5 mg/kg every 12 h for 9 days 0.25 mg/kg every 12 h for 3 days</td>
<td>60 versus 35 (P = .04)</td>
</tr>
<tr>
<td>Watterberg et al.</td>
<td>360</td>
<td>BW: 500–999 g</td>
<td>&lt;48 h postnatal age</td>
<td>0.5 mg/kg every 12 h for 12 days 0.25 mg/kg every 12 h for 3 days</td>
<td>35 versus 34 (OR: 1.20 (95% CI: 0.72–1.99))</td>
</tr>
<tr>
<td>Peltoniemi et al.</td>
<td>51</td>
<td>BW: 501–1250 g</td>
<td>&lt;36 h postnatal age</td>
<td>2.0 mg/kg/day tapered to 0.75 mg/kg/day over 10 days</td>
<td>64 versus 46 (OR: 1.48 (95% CI: 0.49–4.48))</td>
</tr>
<tr>
<td>Bonsante et al.</td>
<td>50</td>
<td>BW: 500–1249 g</td>
<td>&lt;48 h postnatal age</td>
<td>0.5 mg/kg every 12 h for 9 days; 0.25 mg/kg every 12 h for 3 days</td>
<td>64 versus 32 (P &lt; .05)</td>
</tr>
</tbody>
</table>

• **Recommendation No.1**

• **High daily doses of dexamethasone (0.5 mg/kg/day)**

In the absence of randomized trial results showing improved short- and long term outcomes, therapy with high-dose dexamethasone cannot be recommended.
Revised policy of AAP 2010

• **Recommendation No. 2**
  • **Low-dose dexamethasone (0.2 mg/kg per day)**
    may facilitate extubation and may decrease the incidence of short- and long-term adverse effects observed with higher doses of dexamethasone

• Additional RCTs sufficiently powered to evaluate the effects of low-dose dexamethasone therapy on rates of survival without BPD, as well as on other short- and long-term outcomes, are warranted
Revised policy of AAP 2010

- **Recommendation No.3**

- **Low-dose hydrocortisone (1 mg/kg per day)**
  given for the first 2 weeks of life may increase rates of survival without BPD in specific specific population of patients

- **However**, there is insufficient evidence to recommend its use for all infants at risk of BPD.
Hydrocortisone and neurodevelopmental outcome

- This is an exploratory analysis of secondary outcomes of a randomized clinical trial of extremely preterm infants, early low dose hydrocortisone - *Peltoniemi O, Kari MA, Heinonen K, et al (2005)* - was not associated with a statistically significant difference in neurodevelopment at 2 years of age.

  Baud O et al (2017)
Conclusion

• The use of steroids for BPD should individualized

• Patients selection is the key

• Develop unit based guideline for FIO2 and ventilator setting.

• Preterm with high risk of BPD, steroids should be considered > 2 weeks of life and < 4 weeks of life

• Don’t over do (duration and dose)
Steroid
Friend or foe?

Thanks