Bronchopulmonary Dysplasia

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Bronchopulmonary Dysplasia

- Definition
- Incidence
- Pathogenesis
- Pathophysiology
- Respiratory management
- Future therapies

Definition

- Classic BPD as described by Northway in 1967
- "New" BPD

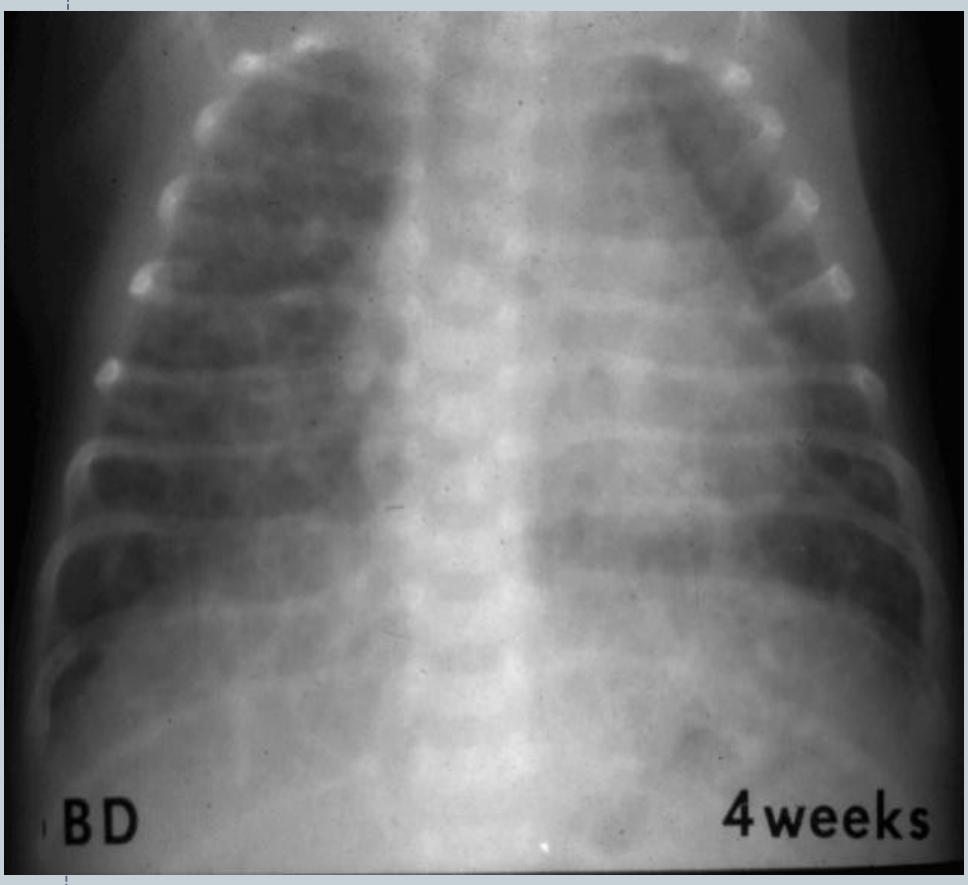
Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline membrane disease. N Engl J Med 1967;276:357.

Classic BPD

- First described by Northway in 1967
- He noticed the chronic lung changes the babies who survived mechanical ventilation for treatment of RDS
- Divided into four stages
  - Stages 1 and 2 occur in 1st ten days of life and are indistinguishable from RDS
  - Stages 3 and 4 transition into chronic stages of lung disease
- Required component:
  - Respiratory support beyond one month of age
  - Ventilation or oxygen therapy

Chest X-ray

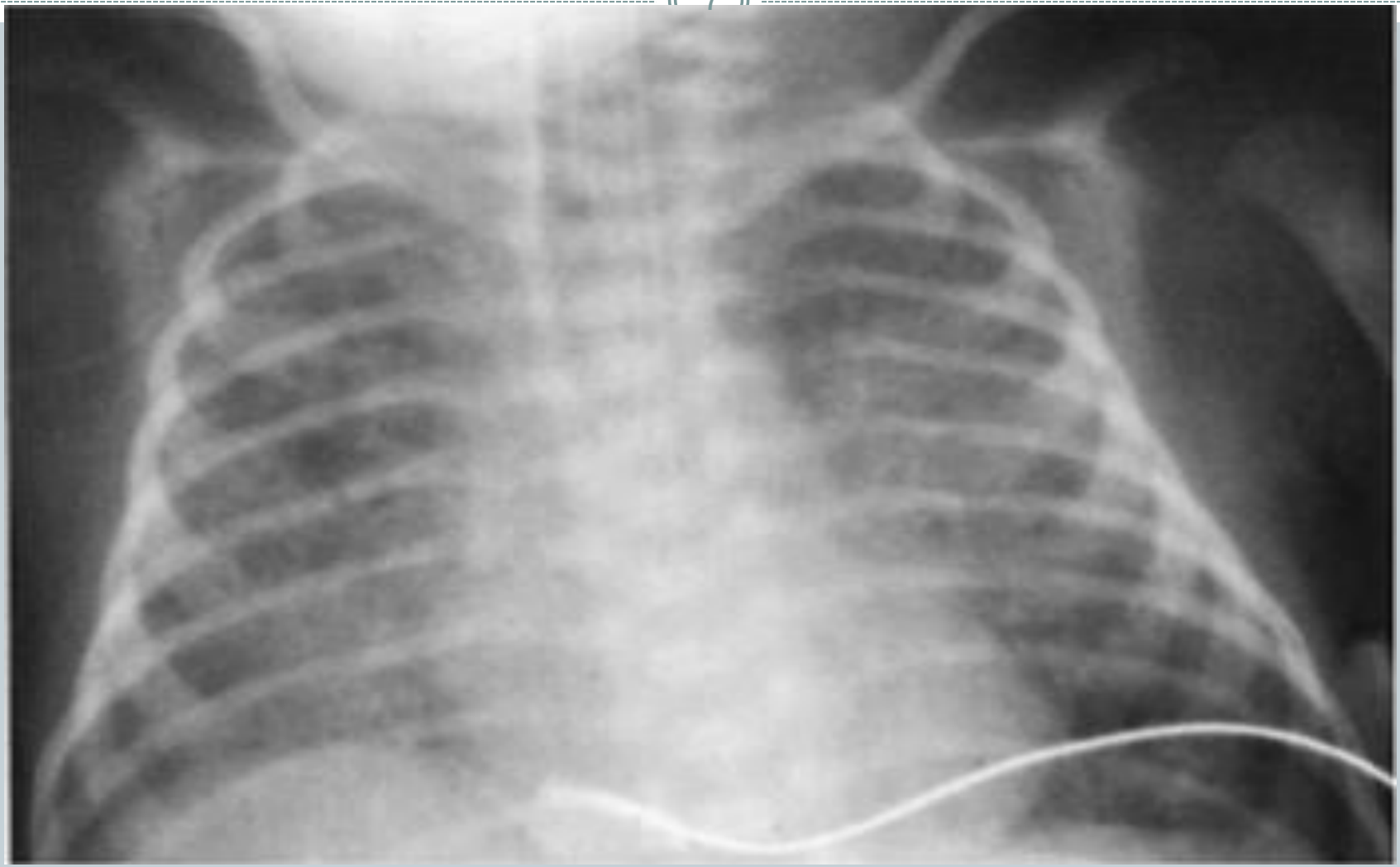
- Cyst formation
- Interstial thickening
- Fibrotic changes
- Hyperexpansion
- Alternating areas of atelectasis



New BPD

- Eduardo Bancalari MD further refined the definition to include
- Ventilation for the first three days of life
- Respiratory symptoms at 28 days of life
  - Tachypnea
  - Auscultatory rales
  - Retractions
- Need for supplemental oxygen to maintain a partial pressure of oxygen at 50 mmHg
- Most important definition is the need for supplemental oxygen at 28 days of life and appropriate radiographic findings

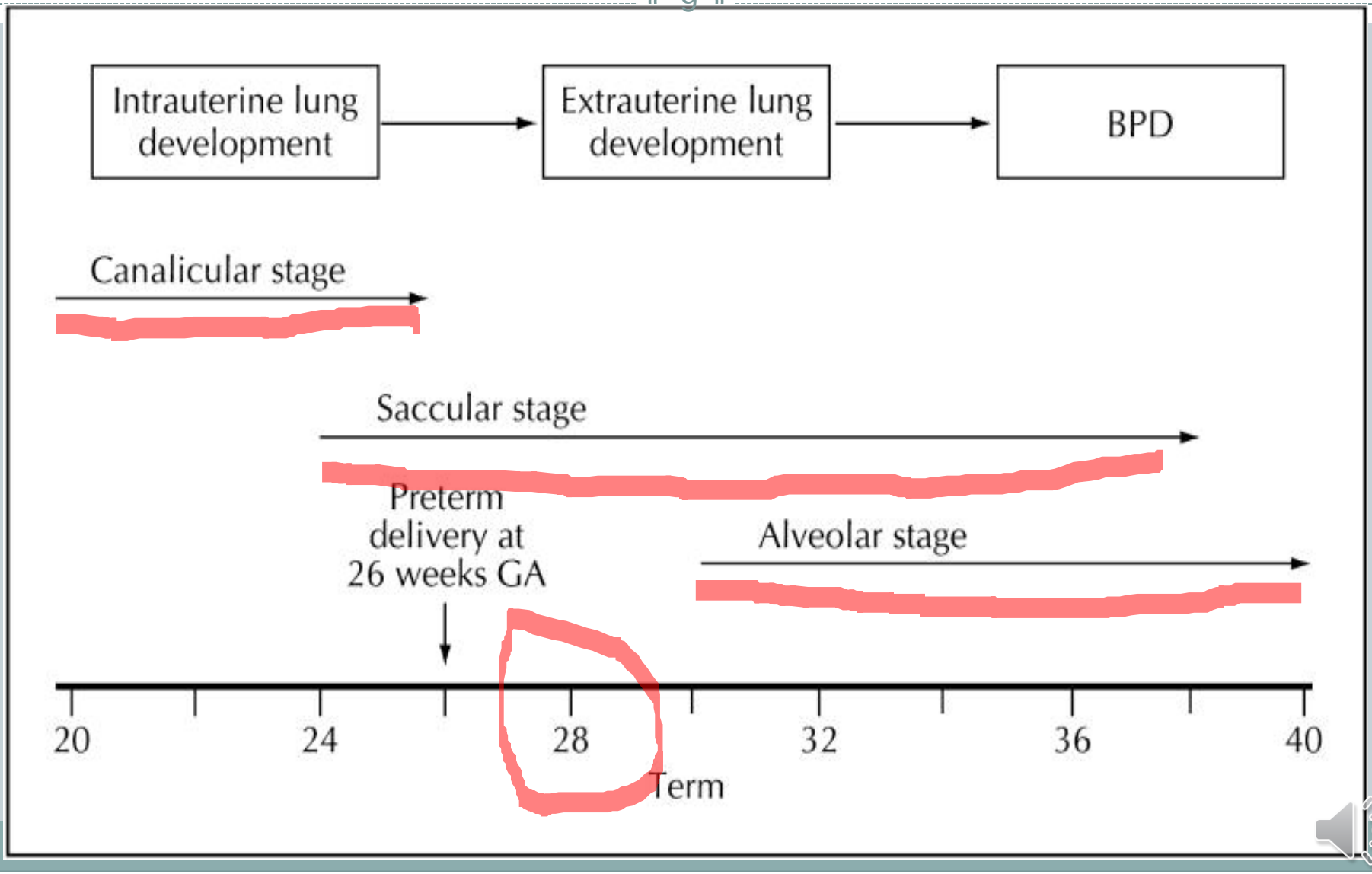
BPD X-ray



Incidence

- Depends on birth weight and is inversely related
- <1000 g: 40-85%
- 1000-1500 g: 10-30%
- >1500 g: 3-5%

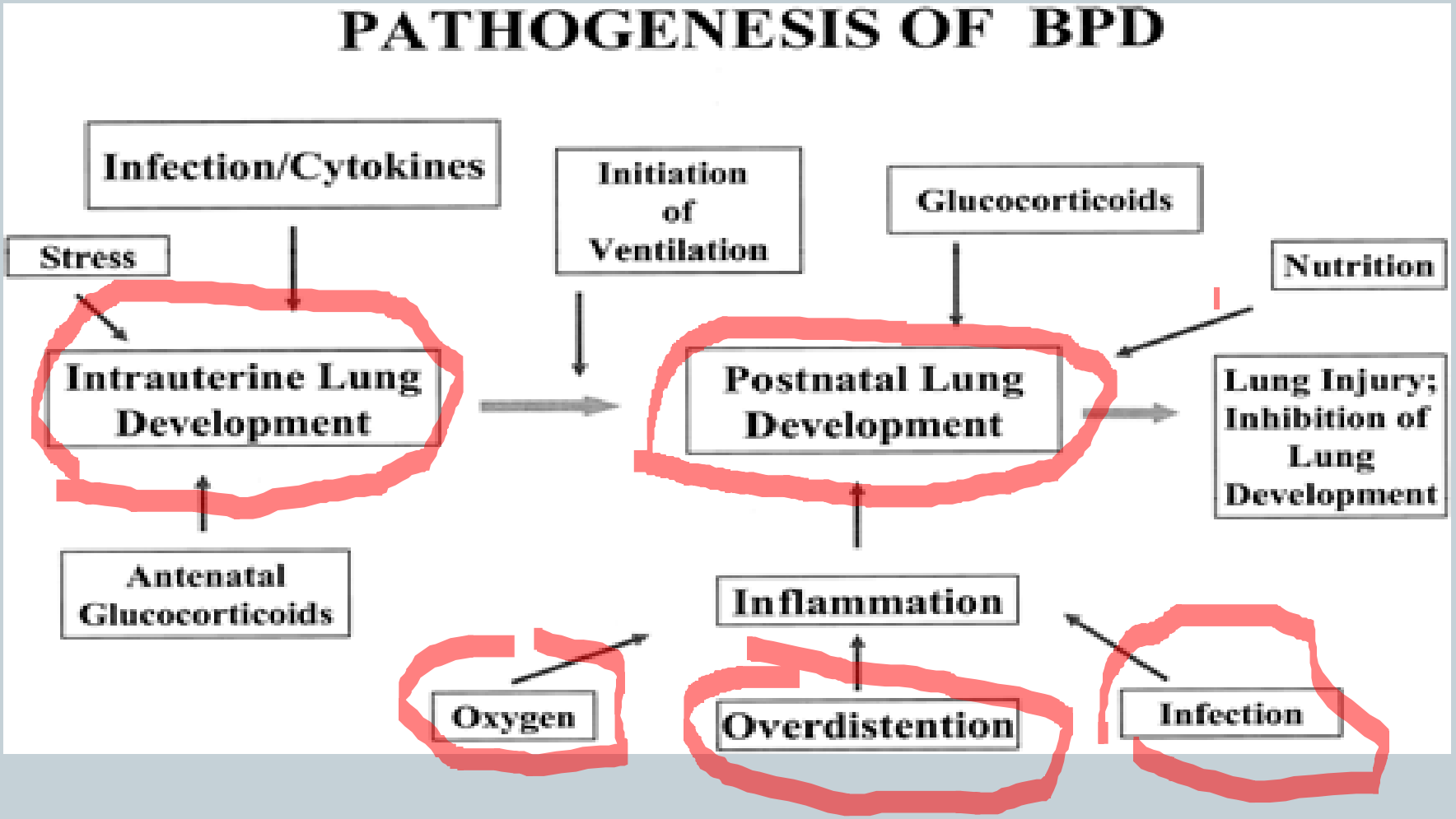
Pathogenesis



Pathogenesis

- At 26 weeks saccules function as “alveoli”
- Vascular proliferation finishes at 26 weeks
- Alveolar hypoplasia
- Alveoli appear around 30 weeks
- Fetal lung must continue to develop

Pathogenesis



No single factor has been identified as the cause of BPD

- Barotrauma/Volutrauma
- Oxygen/antioxidants
- Inflammation
- Infection
- Nutrition
- Genetics

Barotrauma/Volutrauma

- Positive pressure ventilation provokes complex inflammatory cascade
- Cytokine release
- Surfactant deficiency
  - Increased surface tension
- Pulmonary interstitial emphysema (PIE)/Pneumothorax
- Strongly associated with the development of BPD

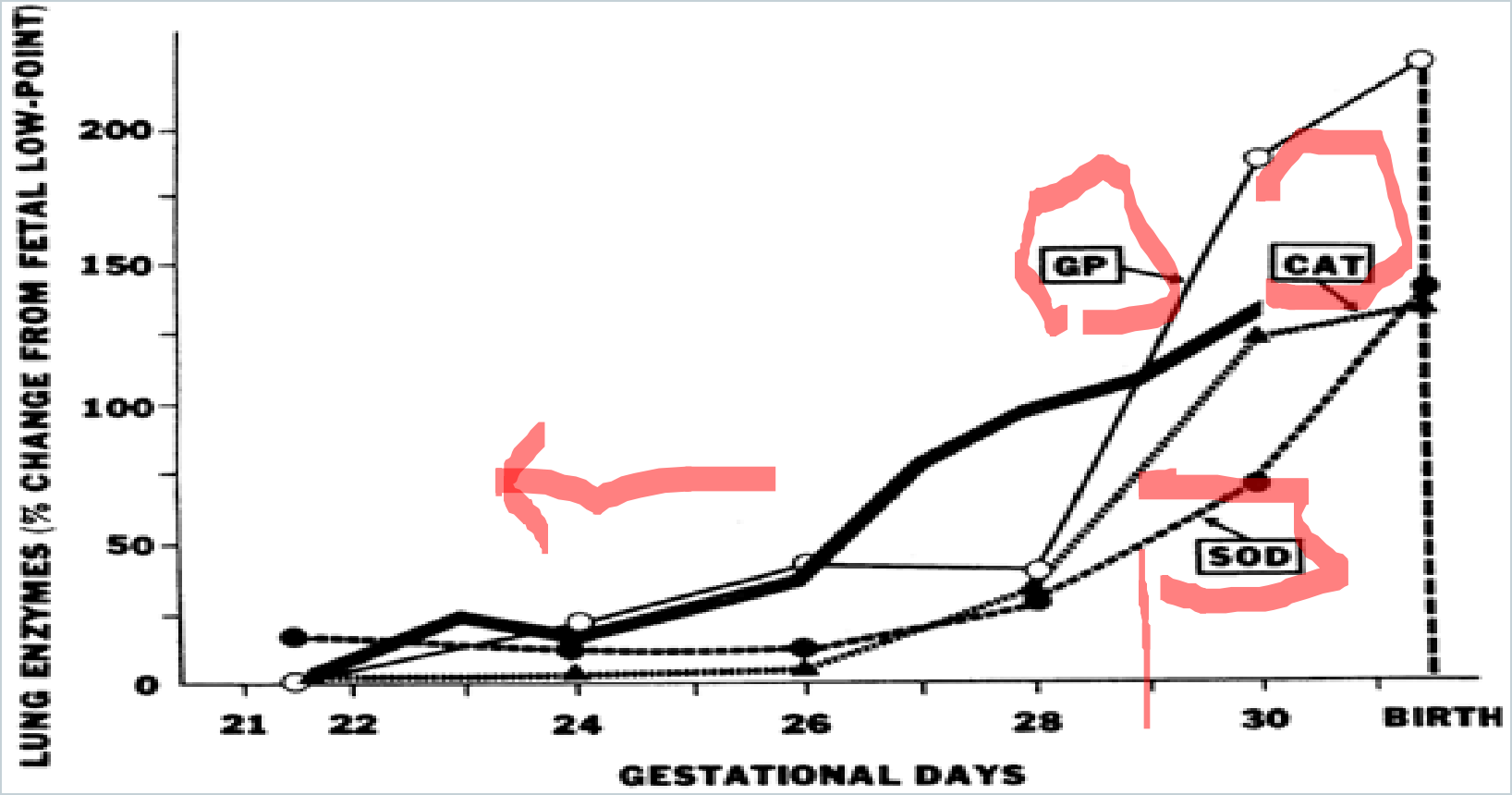
Oxygen/antioxidants

- Balance between oxygen free radicals and antioxidant defense
- Free radicals are toxic to living cells
- During oxidative metabolism free radicals are formed
- Hypoxia and inflammation increases free radical formation

Oxygen/antioxidants

- Inadequate concentrations of antioxidants at birth
- Damage caused by free radicals include
  - lipid peroxidation
  - mitochondria injury
  - protein nitration
  - unraveling of nucleic acids
- Chronic hyperoxia induces inflammation and lung injury
- Epithelial and endothelial cells extremely susceptible to oxidant injury leading to edema and cell dysfunction

Antioxidants versus GA



Free radicals

Radical	Symbol	Antioxidant
Superoxide anion	O_2^-	Superoxide dismutase, uric acid, vitamin E
Singlet oxygen	$^1O_2$	β-carotene, uric acid, vitamin E
Hydrogen peroxide	H_2O_2	Catalase, glutathione peroxidase, glutathione
Hydroxyl radical	$OH^\bullet$	Vitamins C and E
Peroxide radical	$LOO^\bullet$	Vitamins C and E
Hydroperoxyl radical	LOOH	Glutathione transferase, glutathione peroxidase

Reference : Avery's Neonatology

The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity, a randomized, controlled trial. Pediatrics 2000;105:295

- Multicenter trial in 2000 published in Pediatrics
- Study question- 'Determine if high FIO2 would prevent the development of severe ROP"
- Results-
  - Minimal effect on eyes
  - 55% increase of BPD and pulmonary infections

Inflammation

- Inflammation is central to the pathogenesis of BPD
- Causes-
  - Oxygen free radicals
  - Pulmonary barotrauma
  - Infectious agents
- Mechanism
  - Activation of leukocytes and neutrophils to site of injury
- Inflammatory mediators
  - Cytokines
  - Tumor necrosis factor-alpha
  - Interleukin1-beta
  - Interleukin 8
  - Transforming growth factor- beta

Infection

- Studies show that infection leads to inflammation
- Types of common infection
  - Intrauterine infection
  - Chorioamnionitis
  - Funisitis
- Strong correlation between the presence of BPD and the development of late-onset sepsis
- Severity of BPD increased LOS and mortality

Nutrition

- Adequate calories and essential nutrients for growth may be lacking
- Immunologic and antioxidant defenses may be inadequate due to poor nutrition
- Increased metabolic needs and rapid growth requirements
- Antioxidant enzymes (e.g., copper, zinc, selenium)
- Vitamin deficiency- vitamin E and C

Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. New Engl J Med 1999;340:1962.

- Multicenter trial of vitamin A supplementation in premature infants at risk for developing BPD
- Demonstrated that large doses of intramuscular vitamin A three times per week
  - 7% reduction in the incidence of BPD
- Findings- Vitamin A deficiency is an important contributor to lung injury.

Genetics

- Strong family history for asthma
- Family history of airway hyperactivity
- Genetic research for BPD will potentially pave the way to improved preventive and therapeutic approaches

Respiratory Management

- Mechanical Ventilation
- Oxygen
- High frequency ventilation
- Continuous positive airway pressure
- Permissive hypercapnea
- Inhaled nitric oxide
- Bronchodilators
- Corticosteroids

Mechanical Ventilation

- Prolonged ventilatory support
- Early Phase
  - Short inspiratory times .24-.4 seconds
  - Rapid rates 40-60
  - Low PIP 14-20 cmH20
  - PEEP 4-6
  - VT- 3-6 mL/kg
  - FIO2@ < 50%
  - Blood gases
    - Pa02 40-60 mmHg
    - PaC02 45-55 mmHg

Mechanical Ventilation

- Mean airway pressure maximized to reduce atelectasis
- Adequate humidity and temperature of 36.5 – 37.0
- Methylxanthines before extubation or NCPAP just after extubation may facilitate successful extubation
- HFOV as rescue if conventional ventilation fails
- Permissive hypercapnea (pH 7.28-7.35)

Oxygen

- Chronic hypoxia
- Vasoconstriction
- Pulmonary hypertension
- Oxygen is a pulmonary vasodilator- stimulating the production of endogenous NO
- PaO2 should be maintained between 50 and 70 mm Hg in infants with BPD
- Maintain oxygen saturations at 88% to 92%
- If oxygen-dependent infants can maintain an SaO2 of more than or equal to 90% for at least 40 minutes in room air they can be successfully weaned from supplemental oxygen

HFOV

- Henderson-Smart DJ, Bhuta T, Cools F, et al. “Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants” Cochrane Database System Rev; 2003: CD000104

- Meta-analysis

- Randomized 1771 preterm or low birth weight infants with respiratory failure to HFOV versus conventional ventilation

- Reduction in BPD at 36 weeks postmenstrual age (PMA) of borderline significance (random effects model RR = 0.70; 95% CI = 0.46-1.06)

HFOV

- Courtney SE, Durand DJ, Asselin JM, et al. “High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants” N Engl J Med 2002; 347:643-652

- Randomized clinical trial
- 500 infants born at 601-1200g
- HFOV versus conventional ventilation before 4 hours of age
- Reduced the need for supplemental oxygen need at 36 weeks PMA from 56% to 47%

CPAP

- Avery ME, Tooley WH, Keller JB, et al.” Is chronic lung disease in low birth weight infants preventable? A survey of eight centers” Pediatrics 1987; 79:26-30

- First to consider the possibility that the use of CPAP, a gentler less invasive form of respiratory support, might reduce pulmonary injury and subsequent BPD

- After controlling for known confounding factors, the NICU with the highest use of CPAP had the lowest rate of BPD

- Evidence-based approach is lacking

Continuous Positive Airway pressure

- Narendran V, et al." Early bubble CPAP and outcomes in ELBW preterm infants' Perinatol 2003; 23:195-199

- Observational study of 171 infants born at 401-1000g
- Bubble CPAP used as the initial mode
- 10% trend toward improvement in the composite outcome of death or oxygen requirement at 36 weeks PMA

CPAP

- Thomson MA, Yoder BA, Winter VT, et al.”Treatment of immature baboons for 28 days with early nasal continuous positive airway pressure” Am J Respir Crit Care Med 2004; 169:1054-1062
- CPAP was used in an extremely preterm baboon model of BPD
- 125 days gestation (term baboon gestation is 185 days)

Thomson et al.

- Preterm baboon infants were given two doses of surfactant, daily caffeine, and were extubated to CPAP at 24 hours of age versus conventional ventilation
- Evaluations at 28 days of the CPAP-treated animals showed
  - minimal evidence of pulmonary injury
  - minimal fibrosis or inflammation
  - pulmonary compliance similar to 156-day full term baboon infants

Permissive hypercapnea

- Provide adequate oxygenation and ventilation without associated lung injury
- “Gentle ventilation”
- Minimize barotrauma and volutrauma
- New data from the lamb model of BPD suggest that the benefits of permissive hypercapnea might extend beyond the reduction in pressure-induced pulmonary injury

Permissive hypercapnea

- Strand M, Ikegami M, Jobe AH.
- Effects of high PCO2 on ventilated preterm lamb lungs.
- Pediatr Res 2003; 53:468-472

Strand et al.

- Preterm lambs subjected to identical peak inspiratory pressures, tidal volumes, and inspired oxygen
- Supplemental exogenous carbon dioxide to reach targeted $PaCO_2$ levels ~100 mm Hg (control $PaCO_2$s ~40-50 mm Hg)
- Results……
- Decreased pulmonary inflammation
  - Decreased WBC
  - Decreased hydrogen peroxide (free radical)
  - Decreased IL-1 and ,IL-8 (inflammatory cytokines)
- Suggesting a beneficial effect of higher $PaCO_2$ independent of minimal ventilation-related reduction in barotrauma

Permissive hypercapnea

- Carlo WA, Stark AR, Wright LL, et al. “Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants” J Pediatr 2002; 141:370-374
- Randomized factorial design trial
- Primary outcome of death or BPD at 36 weeks PMA
- 220 infants

Carlo et al.

- 501-1000g requiring MV < 12 hours of age for a total of 10 days
- Used conventional ventilation
- FIO2 >= .30 and dexamethasone
- (PaCO2 <48 mm Hg) OR (PaCO2 >52 mm Hg)
- Relative risk for death or BPD at 36 weeks PMA was 0.93 (95% CI = 0.77-1.12)
- Ventilator support was significantly reduced at 36 weeks in the hypercapnea group (1% vs 16%; P < 0.01)

Inhaled nitric oxide

- Schreiber MD, Gin-Mestan K, Marks JD, et al. “Inhaled nitric oxide in premature infants with the respiratory distress syndrome “ . N Engl J Med 2003; 349:2099-2107
- Randomized clinical trial of 207 infants
- Significant reduction in the composite outcome of death or BPD at 36 weeks PMA
- iNO treated (49% vs 64%).

Schreiber et al.

- Magnitude of this effect was greater among infants whose respiratory illness was less severe (oxygenation index <6.94)
- Mortality rates among control subjects in the study population were higher than have been observed at some centers, raising questions regarding whether the study results are generalizable to broader populations
- Take a prudent approach to iNO therapy among preterm infants

Bronchodilators

- β2-agonist is the agent of choice in the treatment of reversible bronchospasm in infants with BPD
- Ipratropium bromide is a related muscarinic antagonist
- Methylxanthines (e.g., caffeine, theophylline)

Corticosteroids

- Potent anti-inflammatory properties
- Dexamethasone
- Down-regulation of the inflammatory cascade
- Improvements in pulmonary function in infants with severe BPD
- Excessive doses and prolonged use of corticosteroids result in…
  - Impair head growth
  - Neurodevelopmental outcome
  - Poor lung structure
  - Decreased long-term survival

Summary

- BPD is here to stay
- Gentle ventilation
- CPAP
- Prenatal care

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