





The Micro Premie

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 Children's National Medical Center*

Born Too Soon and Too Small in the United States

In An Average Week in the United States (2)

9,246 babies are born preterm	1,497 babies are born very preterm	6,040 babies are born low birthweight	1,126 babies are born very low birthweight
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Preterm Birth Rates
 2002
 Percent of live births (51 States)

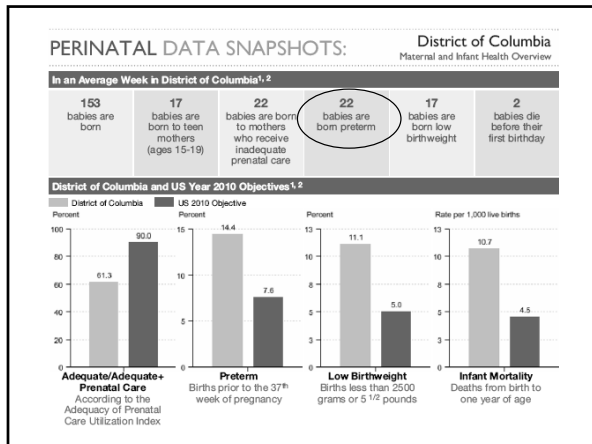
- Over 12.7 (16)
- 11.3-12.7 (21)
- Under 11.3 (14)

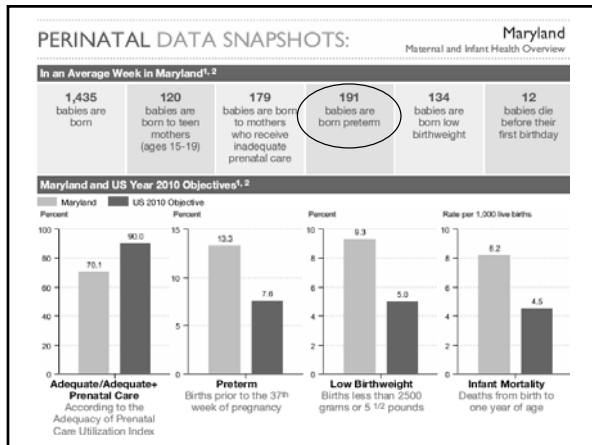
Value ranges are based on an approximately equal number of states in each range.


www.marchofdimes.com

March of Dimes

Preterm and Low Birthweight Births in the United States			
	1992	2002	2010 US Objective
Preterm (3)	10.7%	12.1%	7.6%
Low Birthweight (4)	7.1%	7.8%	5.0%







Gestation

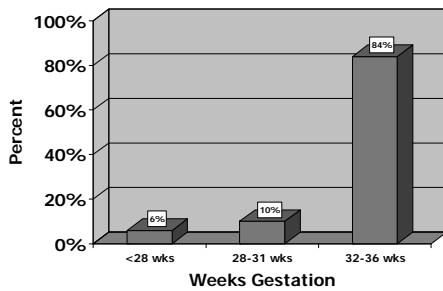
- Term pregnancy ≥ 37 weeks
- Post-term >42 weeks
- Infants <2500 gm, low birthweight
 - Prematurity
 - Small for dates (SGA &/or IUGR)
- Premature Infants
 - <1500 gm, very low birth weight (VLBW)
 - <1000 gm, extremely low birth weight (ELBW)
 - <800 gm, "micropremies"

Prematurity Facts...



- More than 470,000 babies are born prematurely annually in the United States
- 1 out of 8 births results in a preterm infant
- From 1981 – 2002 Premature Rate has increased from 9.4% to 12.1%

Prematurity – Population Distribution



Preterm Birth



- Major cause of infant morbidity & mortality
- Responsible for majority of neonatal deaths & 50% of all causes of neurologic disabilities
- Risk is highest in those born <32 weeks gestation

The Cost of Prematurity

MOD, www.marchofdimes.com - Peristat



- \$18.1 Billion dollars in hospital charges were for infants born prematurely (FY03)
- Average length of stay for premature baby is 24 days, BUT for the very low birthweight (VLBW) it can be 2-3 months
- VLBW infants – 25% long-term problems

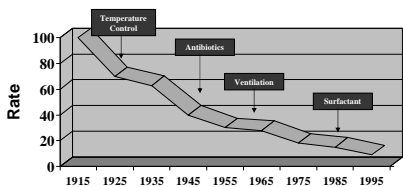
The Cost of Newborn Care in California: A Population-Based Study

Schmitt S, et al: Pediatrics Vol 117, 2006



- LBW infant ALS = 6.2-68.1 days vs 2.3 term infant
- VLBW 0.9% cases by 35.7% of costs
- 5% of infants accounted for 76% of hospital cost

Infant Mortality by Year: *United States*

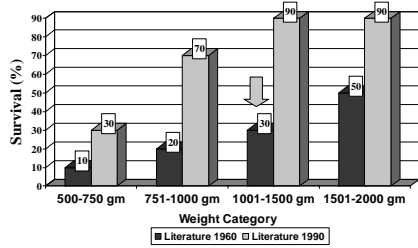


*Rate, per 1000 live births



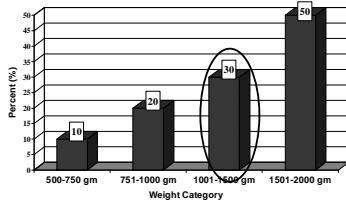
Neonatal Survival:

Historical Perspective



Neonatology – 1960's

*1963, Patrick Bouvier Kennedy,
Born at 32 weeks gestation...Died*





"About all that can be done for a victim of hyaline membrane disease is to monitor the infant's blood chemistry and to try to keep it near normal levels. Thus, the battle for the Kennedy baby was lost only because medical science has not yet advanced far enough to accomplish as quickly as necessary what the body can do by itself in its own time".

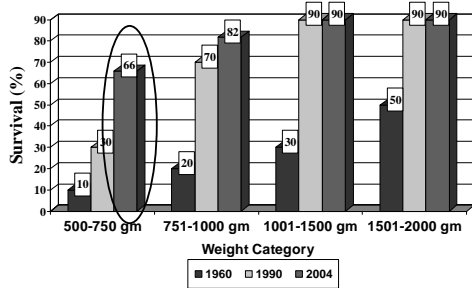
Neonatology – 1960's

Development of Neonatal Intensive Care

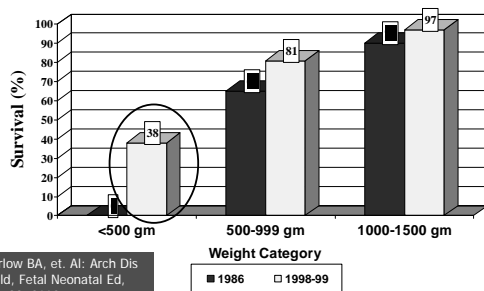
- 1960's – NIH funded a laboratory concerned with the study of the transitional circulation and its relation to neonatal cardiorespiratory disease

Neonatology

Improving Outcome of the Premature Infant

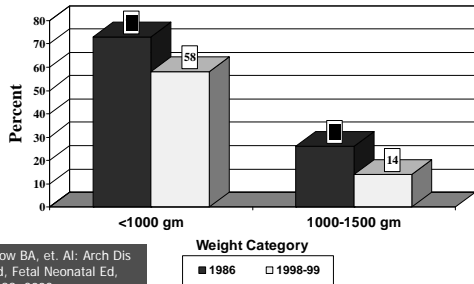


Low Birth Weight Infants Improved Outcome: New Zealand



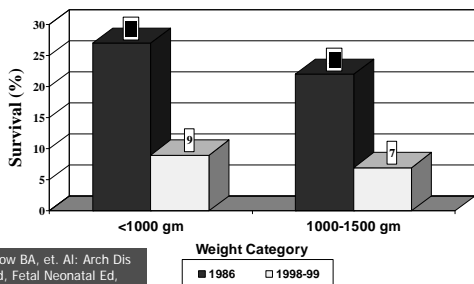
Darlow BA, et. Al: Arch Dis Child, Fetal Neonatal Ed, Vol. 88, 2003

Low Birth Weight Infants
CLD: Oxygen at 28 days



Darlow BA, et. Al: Arch Dis Child, Fetal Neonatal Ed, Vol. 88, 2003

Low Birth Weight Infants
IVH: Grade II or III



Darlow BA, et. Al: Arch Dis Child, Fetal Neonatal Ed, Vol. 88, 2003

Improved Neonatal Outcome
New Zealand Experience

- Antenatal glucocorticoid use: 58% vs 80%
- Level III NICU delivery hospital, 72% vs 87% - better regionalization
- Surfactant use

VLBW Infant: Trends in Outcome

Vermont Oxford Network

(Hobar JD, et al:Pediatrics, Vol 110, 2002)

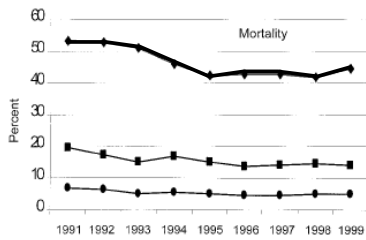


Fig 2. Mortality for infants 501 to 1500 g, 1991 to 1999, by birth weight category at all 362 network hospitals. (501-750 g: diamond markers, 751-1000 g: square markers, 1000-1500 g: circle markers).

VLBW Infant: Trends in Outcome

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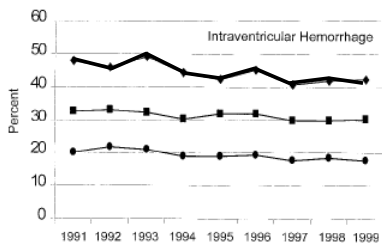


Fig 4. IVH for infants 501 to 1500 g, 1991 to 1999, by birth weight category at all 362 network hospitals. (501-75 g: diamond markers, 751-1000 g: square markers, 1000-1500 g: circle markers).

VLBW Infant: Trends in Outcome

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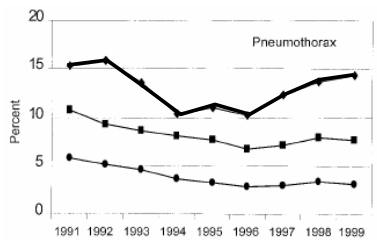


Fig 3. Pneumothorax for infants 501 to 1500 g, 1991 to 1999, by birth weight category at all 362 network hospitals. (501-75 g: diamond markers, 751-1000 g: square markers, 1000-1500 g: circle markers).

VLBW Infant: Trends in Outcome *Vermont Oxford*

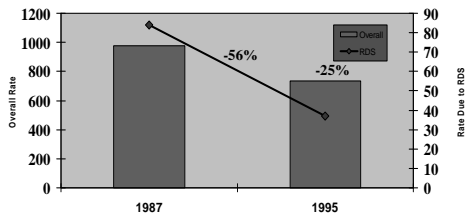
(Hobar JD, et al: *Pediatrics*, Vol 110, 2002)

- Antenatal steroids, increased 3x (24% to 72%)
- Postnatal surfactant, increased from 49% to 62%

Infant Mortality: 1985 – 1997

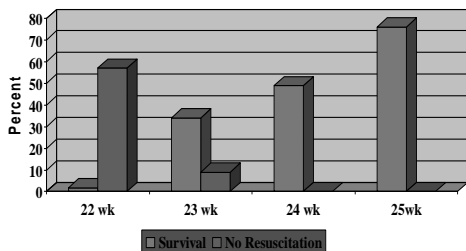
Malloy MH, Freeman DH, *J of Perinatology*,
20:414-420, 2000

*Deaths per 100,000 live births



The Limits of Viability in the Mid-1990's

El-Metwally D, *J Pediatr*, 137:616-622, 2000



Data from 1993-1997

Survival = discharge home

What Really is a "micropremie"

Case Reports: Infants <400 gms BW

Author	GA	BW	IUGR	Vent Days	F/U
Ginsberg	25	380	SGA	56	NI 20mo
Muraska	26	280	SGA	61	NI 24 mo
Sherer	26	345	SGA	32	NI 18.8mo
Amato	25	390	SGA	28	NI 27.2 mo
Report	25	300	SGA	23	NI 15mo

**BW 280 grams,
14 Years of age**

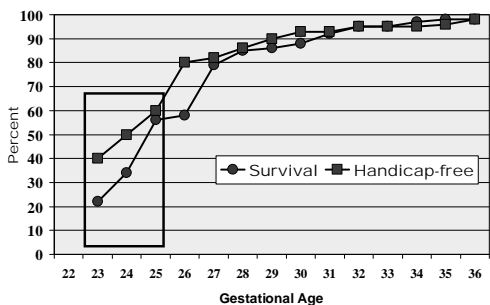
- Average grade point, 3.70
- High-school entrance exams = 83%
- 50% for weight & height

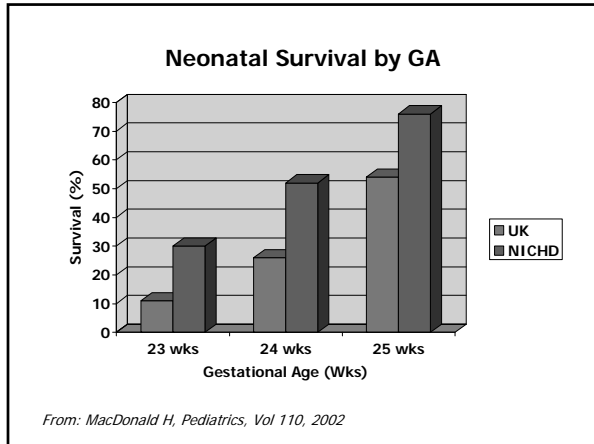


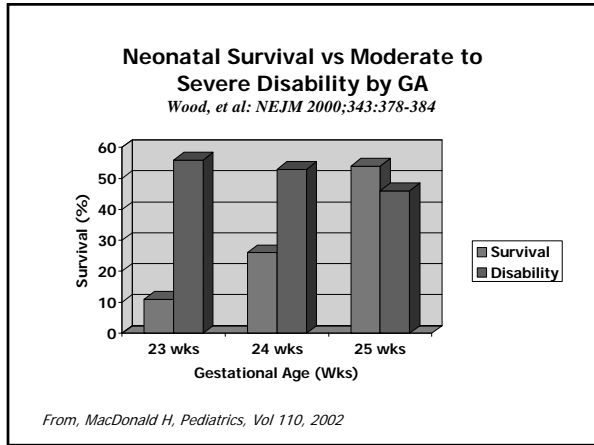
Muraskas J, et al: NEJM, Vol 351(8), 2004

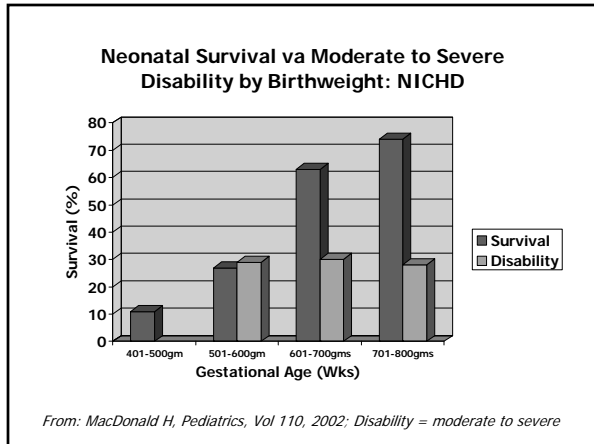
Neonatal Survival/Outcome

Morse, et al: Pediatrics, 105:1046-1050, 2000









Preterm Birth

- Incidence has risen over the last 15 years to about 12% of all births
- Estimated to be 480,000 preterm births each year in the US
- Continues to be 2x as high in black women compared to white

Racial & Gender Differences in the Viability of ELBW Infants: A Population Based Study

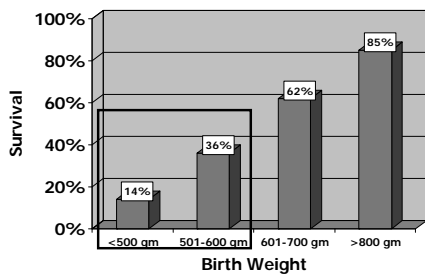
Morse SB, et al, Pediatrics, Vol 117, 2006

- N=5076, years 1996-2000
- BW 300-1000 gms
- Survival rate 60-62%, no change over 5 year period
- Survival advantage at all BW categories:
 - Females > males
 - Black > white
- Black females infants had 2.1 > odds of survival then while male infants

State of Florida

Racial & Gender Differences in the Viability of ELBW Infants: A Population Based Study

Morse SB, et al, Pediatrics, Vol 117, 2006



State of Florida

Neonatal Mortality

Alexander GR, et al: Pediatrics; 2003, 111:e61-e66

- Newborns with BW < 1500gms
 - Account for >50% of neonatal deaths among white & Hispanic populations
 - Account for >75% of the neonatal deaths among the black population
- Blacks have higher proportions of preterm & LBW births
- Blacks experience lower risks of neonatal mortality for preterm & LBW infants, but higher for term, postterm, normal birth weight births

What Has Changed in Our Care to Improve Outcome ?



Preterm Labor - Prevention

- Tocolysis – treatment has not shown to reduce the incidence of preterm delivery
- WHY USE THEM??
 - Have shown in some studies to delay delivery by 24-48 hrs
 - Steroid therapy can be given to mature the lungs of the fetus

Preterm Labor - Prevention

DaFonseca EB, et al: Am J Obstet Gynecol 2003,188:419-429

- Hormone therapy -Progesterone – trial
 - 157 women, high risk for premature birth were randomized, progesterone Tx
 - Reduced rate of preterm birth, 14% vs 29%
 - Additional studies have not shown progesterone to reduce preterm delivery in multiple birth pregnancies

Preterm Labor - Prevention

Meis PJ: Obstet Gynecol Vol. 105, 2006

- Hormone therapy -Progesterone – trial
 - Reduced rate of preterm birth 33% prior to 35 weeks gestation; 42% reduction prior to 32 weeks gestation
 - First to show improved outcome:
 - Reduced NEC
 - Reduced IVH
 - Reduced need for supplemental oxygen

First drug to actually show a reduction in premature birth

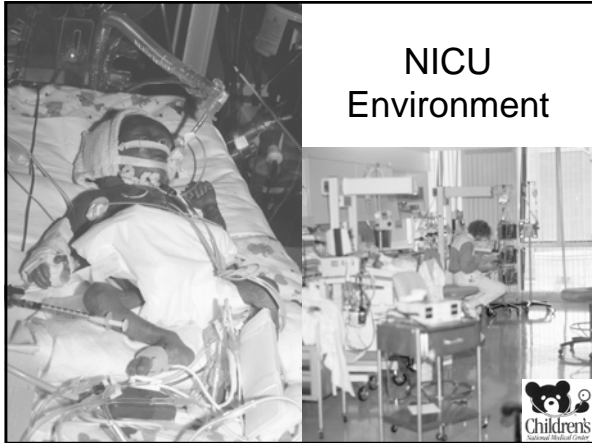
Limitations of Use:

- Singleton pregnancies only
- Previous history of preterm delivery after premature rupture of membranes

Neonatal Intensive Care Unit



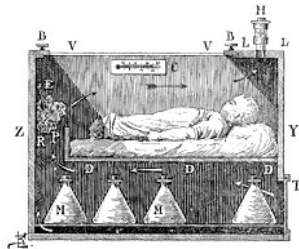
NICU Environment

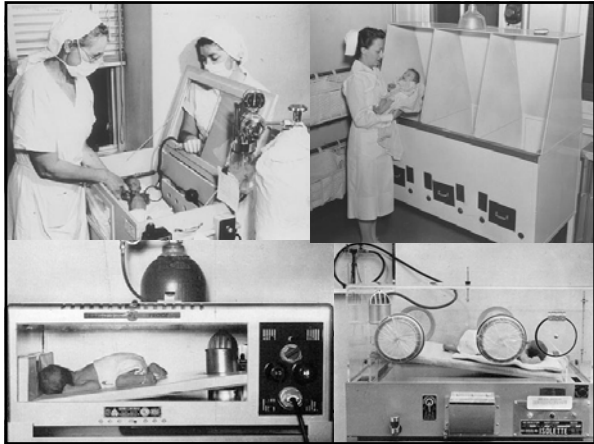


The Incubator

Stephane Tarnier (1828-1897)

Visited the Paris Zoo 1878, poultry section ..
Designed Incubator like the "brooding hen house"






Focus - Global:

- Temperature control
- Humidification – fluid balance
- Noise – reduction of harmful levels
- Clinical treatment – reduces need for moving infant
- Family Centered – designed to enhance parent interactions with their infant



Problems of Prematurity

- Respiratory
- Cardiovascular
- Neurologic
- Gastrointestinal
- Ophthalmologic
- Immunologic

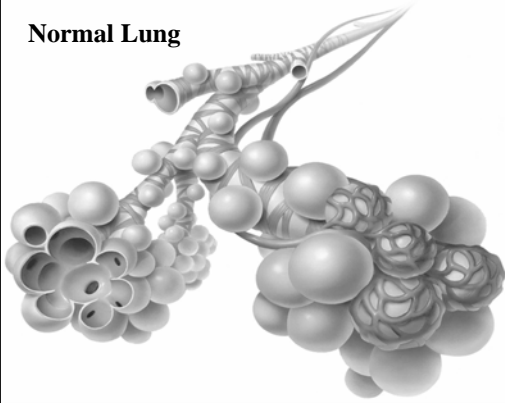


Problems of Prematurity

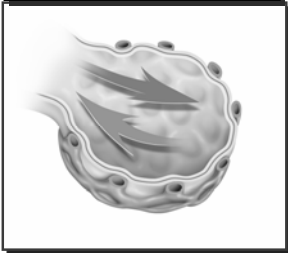
- Respiratory
 - Hyaline membrane disease
 - Chronic lung disease
 - Pneumonia – congenital
 - Decreased respiratory effort
 - Apnea



Normal Lung

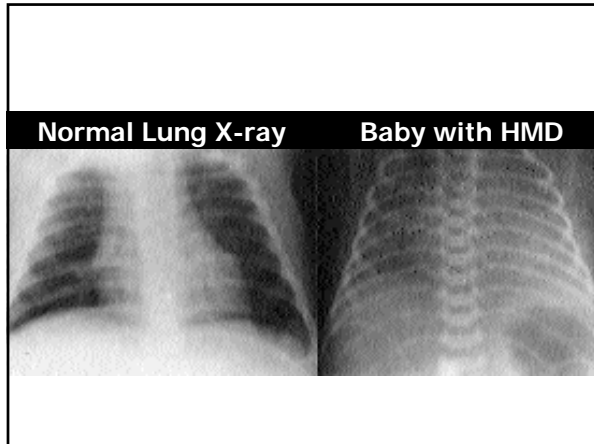


Normal Alveoli with Surfactant



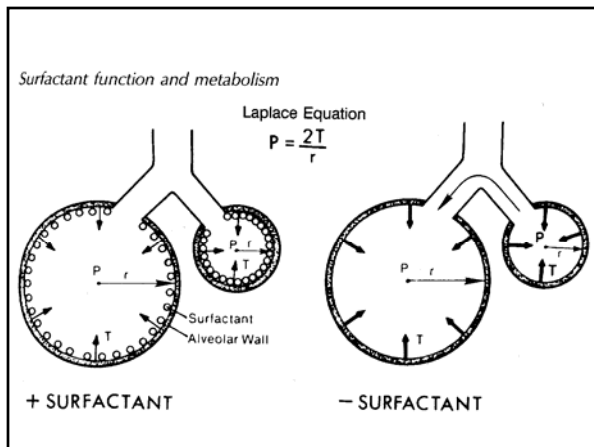
Surfactant Deficient Alveoli

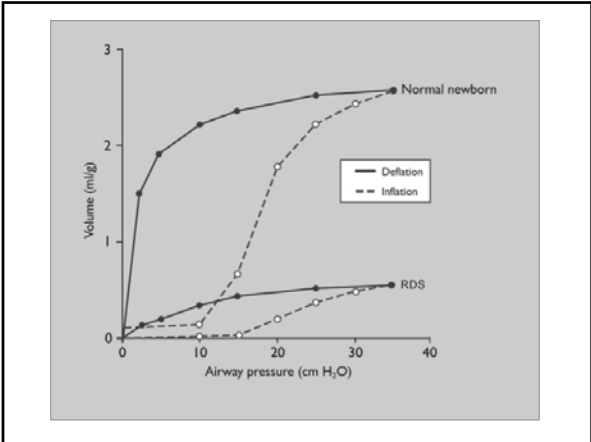


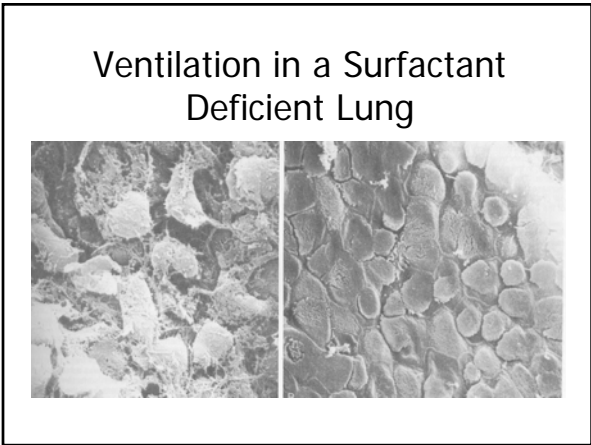


Chemical Composition of Pulmonary Surfactant

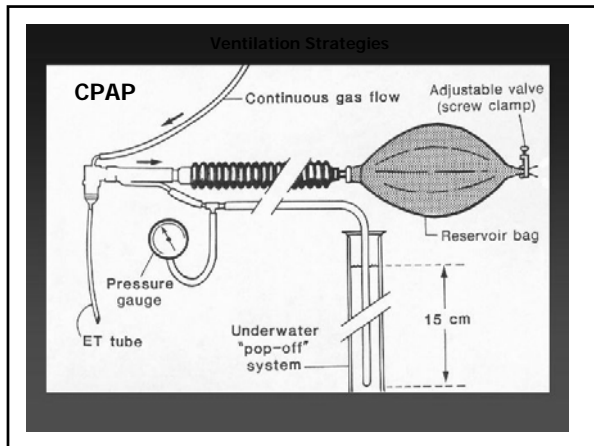
- Surfactants contain protein-phospholipid complexes
 - 90% phospholipids
 - Dipalmitoylphosphatidylcholine (DPPC)
 - Phosphatidylcholine (PC)
 - 10% protein – SP-A, SP-B, SP-C, SP-D
 - SP-A, SP-D: host defense
 - SP-B: spreading & lateral stability
 - SP-C: spreading

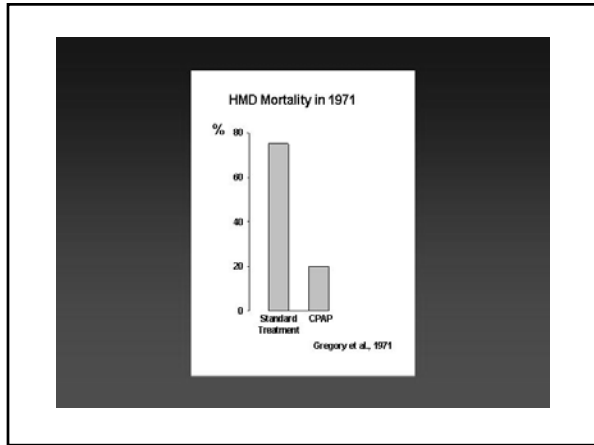






- ## Surfactants
- 1990 - Synthetic non-protein containing – *Exosurf*[®]
 - 1991 – Calf lung extract, protein containing - *Survanta*[®]
 - 1998 – Calf lung lavage, protein containing - *Infasurf*[®]
 - 1999 – Pig lung extract, protein containing - *Curosurf*[®]
 - 2006 – Synthetic, protein containing – *Surfaxin*[®]

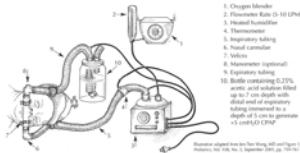








Bubble CPAP



Used at GW NICU

High-flow nasal cannula

- Vapotherm – high-humidity

Other Products:

Fisher-Paykel - heated wire circuit with a cannula

Maquet (Siemens) - non-invasive nasal CPAP

Dräger – non-invasive nasal CPAP



At CNMC, Vapotherm has almost replaced CPAP; routine to extubate to Vapotherm now instead of CPAP.

Neonatal Ventilators - Typical Modes of Ventilation

- IMV
- SIMV
- SIMV & PS
- Assist Control



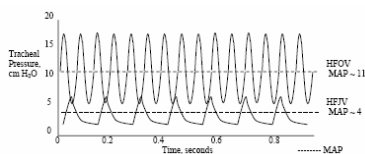
Newer Modes of "Conventional" Ventililation

- **Pressure Modes**
 - TCPL
 - Pressure Control
 - Pressure Support
- **Volume Modes**
 - Volume Targeted (Limited)
 - Volume Guarantee
 - Pressure Regulated Volume Control (PRVC)
- **Combined**
 - VAPS



High-Frequency Ventilation

- High frequency jet ventilation
- High frequency oscillatory ventilation





iNO in Premature infants

Author	N	GA	Entry Criteria	Initial iNO Dose	Findings
Schreiber	207	<34 wks	Vent. & surfactant	10ppm	↓ Death or CLD
NICHD*	420	<34 wks	OI ≥ 10, 5, 7.5	5 or 10ppm	No effect on death or CLD

Schreiber, et al: *NEJM*, Vol. 349, 2003

*Van Meurs KP, et al: *Pediatric Research*, Vol 24, 1997

Long-term Outcome Studies Pending

Respiratory Outcomes of Prematurity

Overall incidence of BPD in Ventilated Newborns 20%



Bronchopulmonary Dysplasia

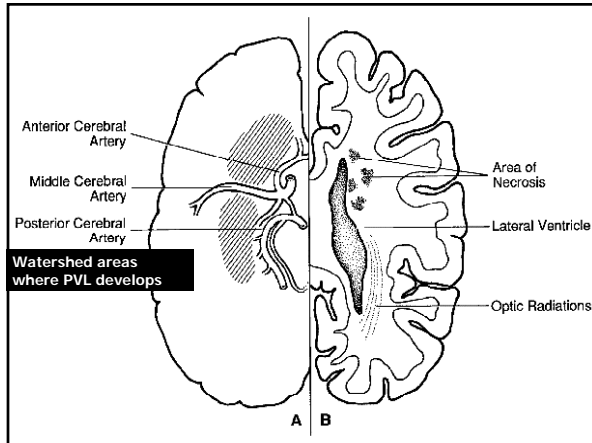
- Most Common in infants <1000 grams
- Seen in infants <1000 grams *without* significant underlying lung disease
- Oxygen & barotrauma still play a role, but aberration of lung development may be more important in this population

See BPD presentation for more details.

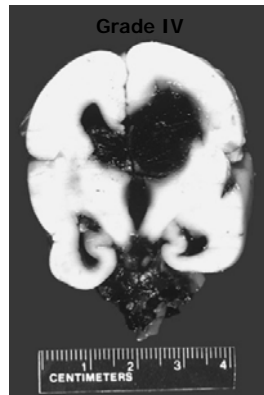
Problems of Prematurity

- Neurologic
 - Intraventricular Hemorrhage
 - Periventricular Leukomalacia





Intraventricular Hemorrhage:
Grade III, IV – highly correlated to poor developmental outcome



Adverse Neurodevelopmental Outcome Among Extremely LBW Infants with Normal HUS

Abbot R., et al: *Pediatrics* Vol 115, 2005

- 30% of ELBW infants had CP (9.4%) or a low MDI (25.3%)
- Associated Risk Factors:
 - Pneumothorax
 - Prolonged mechanical ventilation
 - Educational & economic disadvantage

NICHD Network

Outcome of ELBW Infants at Highest Risk:
GA \leq 24 weeks, BW \leq 750gms, & 1-Minute Apgar $<$ 3
Shankaran, S., et al: *Am J OB/GYN*, Vol. 191, 2004

- N=246
- 30% CP
- 5% hearing impairment
- 2% blind
- MDI $<$ 70 46%
- PDI $<$ 70 in 36%

NICHD Network

Outcome of ELBW Infants at Highest Risk:
GA \leq 24 weeks, BW \leq 750gms, & 1-Minute Apgar $<$ 3
Shankaran, S., et al: *Am J OB/GYN*, Vol. 191, 2004

- | | |
|--|--|
| <ul style="list-style-type: none">■ Predictors MDI $<$70<ul style="list-style-type: none">■ Grade III-IV ICH■ Cystic PVL■ Male gender■ Black race■ Medical insurance | <ul style="list-style-type: none">■ Predictors PDI $<$70<ul style="list-style-type: none">■ Grade III-IV ICH■ Cystic PVL■ Steroids for BPD■ Medical insurance |
|--|--|

NICHD Database

ELBW Neonates with Protracted Ventilation: Mortality & 18-Month Neurodevelopmental Outcome
Walsh MC, et al: J Pediatrics, Vol. 146, 2005

- ELBW infants, 500-1000gms
 - Overall survival = 71%
- Ventilation for survivors = mean 23days
- 7% ventilated >60 days
 - 24% survived without impairment
- Ventilated >90 days
 - 7% survived without impairment
- Ventilated >120 days
 - None survived without impairment

NICHD Database

Transition of Extremely Low-Birth-Weight Infants from Adolescence to Young Adulthood
Saigal S., et al: JAMA, Vol 295(6): 2006

- N=166 ELBW (1977-1982) & 145 NBW
- Prospective longitudinal, population –based study, central-west Ontario, CA
- Markers of successful transition to adulthood:
 - educational attainment
 - student &/or worker role
 - independent living
 - getting married
 - parenthood

Transition of Extremely Low-Birth-Weight Infants from Adolescence to Young Adulthood
Saigal S., et al: JAMA, Vol 295(6): 2006

Parameter	VLBW	NBW
Graduated from High School	82%	87%
Pursuing postsecondary education	32%	33%
Employment status	48%	57%
Living Independently	42%	53%
Married/cohabitating	23%	25%
Children	11%	14%

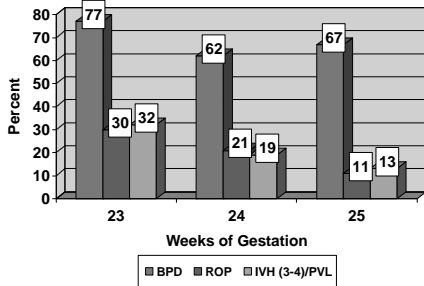
Problems of Prematurity

- Gastrointestinal
 - NEC
- Ophthalmologic
 - ROP
- Immunologic
 - Immature response to infections



Outcome of the Premature Infant: BPD, ROP, & IVH

*Ringer, SA, Neonatal outcome & brain development,
Perspectives in Neonatology, 2001; 2(1): 4-15*



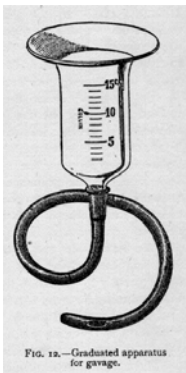


FIG. 12.—Graduated apparatus for gavage.

Challenges for Future

- Nutrition –
 - TPN
 - Type of fat (Omega-3 vs Omega-6; protein)
 - Timing - continuous, pulse
- Enteral
 - Continuous vs bolus
 - Composition of formula

Fetal & Neonatal Origins of Adult Disorders

- Adult "metabolic syndrome"
- SGA & VLBW Infants
- Characterized by:
 - Hypertension
 - Insulin resistance
 - Obesity

Neonatology – the Future

- Quality issues – BSI, antimicrobial resistance, safety issues
- Environment – sound, light, humidity
- Nutrition
- <22 weeks gestation, different forms of ventilation- "artificial placenta - ECLS"
- The Brain – IVH
- The Eye - ROP

Behind Every Premature Baby, Is a Family in Distress



- Family involvement in decision making
 - Prenatally
 - Postnatally
- Family Support
- Education – decision making based on evidence

The Neonatal Team

Neonatologist

The NICU Nurse



RT
Nutritionists
Pharmacist
Social Work



...thanks for listening!

www.neonatology.com
