AOA/ACOP PEDIATRIC TRACK

October 24-27, 2010

THE MOSCONE CENTER

SYLLABUS

American College of Osteopathic Pediatricians
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AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

CARING FOR AMERICA'S CHILDREN

Dear Fellow Osteopathic Pediatricians,

Welcome to beautiful San Francisco, California and the American College of Osteopathic Pediatricians Track of the AOA 115th Annual Convention and Scientific Seminar.

The theme of this year's conference is Prevention. The CME committee has lined up an amazing group of speakers, some of whom you know already and others that we hope you will enjoy getting to know. The topics covered are wide ranging and central to ACOP's theme of Prevention. They include vision screening, sexual exploitation, advocacy for children with special needs, a review of influenza and MRSA, pediatric migraines and seizures, and a hands-on workshop on craniosacral interventions in pediatrics. The meeting also includes a Neonatal/Perinatal day with some wonderful and timely topics given by nationally renowned speakers in the fields of bilirubin metabolism, fetal diagnosis, fetal therepy and the use of nitric oxide in the preterm infant. The conference concludes with a 2 hour lecture on the use and implementation of the electronic medical record.

As always, the American College of Osteopathic Pediatricians is committed to teach, inspire and train students and residents. We have specific sessions for students and residents as well as a number of committee meetings. All conference attendees are welcome to attend these sessions.

The location offers a number of exciting opportunities outside of the conference. From exploring historic Fisherman's Wharf and Pier 39, to hiking up to see the gorgeous views by Coit Tower, to taking educational walks to explore the murals in the Mission District, to riding a cable car through the windy city streets, there is no lack for extracurricular activity. San Francisco is also known for its amazing cuisine – you need not go far to have one of the best meals of your life. We are in the process of planning a wine tasting on the evening of Monday, October 25th. Details will be forthcoming on the ACOP website.

We look forward to seeing you in wonderful San Francisco and hope that you have a magnificent time expanding your pediatric repertoire and engaging in meaningful discussions with your colleagues.

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AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

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AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

OSTEOPATHIC PLEDGE OF COMMITMENT

As members of the osteopathic medical profession, in an effort to instill loyalty and strengthen the profession, we recall the tenets on which this profession is founded — the dynamic interaction of mind, body and spirit; the body's ability to heal itself; the primary role of the musculo-skeletal system; and preventive medicine as the key to maintain health. We recognize the work our predecessors have accomplished in building the profession, and we commit ourselves to continuing that work.

I pledge to:

Provide compassionate, quality care to my patients;

Partner with them to promote health;

Display integrity and professionalism throughout my career;

Advance the philosophy, practice and science of osteopathic medicine;

Continue life-long learning;

Support my profession with loyalty in action, word and deed; and

Live by each day as an example of what an osteopathic physician should be.

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2010 AOA/ACOP PEDIATRIC TRACK SCIENTIFIC PROGRAM

SUNDAY, OCTOBER 24, 2010

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP
Co-Moderator (BOT Member) – James Kirk, DO, FACOP

7:00 am – 5:00 pm	**AOA Registration**
8:00 am – 9:00 am	**Unusual and Challenging Fetal Abnormalities: Prenatal Ultrasound Evaluation** Harris J. Finberg, MD
9:00 am – 10:00 am	**Nitric Oxide Use in Neonates** James Kirk, DO, FACOP
10:00 am – 10:30 am	Break
10:30 am – 11:00 am	**Neonatal Dermatology** Melinda F. Greenfield, DO
11:30 am – 12:30 pm	**Fetal Therapy: Here and Now - aka What's Crazy, Sexy and Cool** Garrett Lam, MD
12:30 pm – 2:00 pm	**Lunch On Own**
2:00 pm – 3:00 pm	**Newborn Jaundice:** **Alerts, Evidence and Practice** Vinod K. Bhutani, MD
3:00 pm – 4:00 pm	**Apnea and Bradycardia** Shannon Jenkins, DO
4:00 pm – 5:00 pm	**Assessing Limits of Viability** Carl Backes, DO, FACOP, FAAP
5:00 pm – 8:00 pm	**ACOP Board of Trustees Meeting**

MONDAY, OCTOBER 25, 2010

Moderator – Edwin Spitzmiller, DO, FACOP
Co-Moderator (BOT Member) – James E. Foy, DO, FACOP

7:00 am – 4:30 pm	**AOA Registration**
8:00 am – 9:30 am	**AOA Opening Session/Keynote Address**
9:30 am – 10:30 am	**Vision Screening Update** **and to Refer or Treat?** Kenneth P. Adams, DO, JD
10:30 am – 11:30 am	**Sexual Exploitation – What It Is and What It Isn't** Marty Klein, PhD
11:30 am – 1:00 pm	**Alumni Lunches**
1:00 pm – 2:00 pm	**What is a Meaningful Use of Electronic** **Information as Directed by the American Recovery and Investment Act?** Michael G. Hunt, DO, FACOP, FAAP
2:00 pm – 2:45 pm	**State of the College** Margaret Orcutt Tuddenham, DO, FACEP, FACOP
2:45 pm – 3:00 pm	Break
3:00 pm – 4:00 pm	**Discharge Planning for NICU Patients** Ronald S. Cohen, MD

MONDAY, OCTOBER 25, 2010 (CONTINUED)

4:00 pm – 5:00 pm	**Medical Information: Is it Really Portable?** Michael G. Hunt, DO, FACOP, FAAP
5:00 pm – 7:00 pm	**CME Committee, Pediatric Program Director and Vaccine Committee Meetings**

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

8:00 am – 9:00 am	**Pediatric Office Dermatology** Melinda F. Greenfield, DO
8:00 am - 10:00 am	**AOA Town Hall Meeting**
9:00 am – 9:45 am	**Prep for Court/Depositions** Mary Angel Meyer, JD
9:45 am – 10:15 am	**Break**
10:15 am – 11:00 am	**Special Needs Advocation** Barbara L. Baldwin, DO, FACOP
11:00 am – 12:00 n	**Gastric Banding as Treatment for Adolescent Obesity** Alison A. Clarey, DO
12:00 n – 1:00 pm	**Lunch On Own/Posters and Exhibits**
1:00 pm – 2.00 pm	**A Case-Based Review of Influenza** James H. Brien, DO, FAAP
2:00 pm – 3:00 pm	**A Case-Based Review of MRSA** James H. Brien, DO, FAAP
3:00 pm – 4:00 pm	**Optimizing Revenue in Your Pediatric Practice** Mary Jean Sage, CMA-AC
4:00 pm – 5:30 pm	**CME Committee, Pediatric Education Leadership Committee, e*Journal***
7:00 pm – 10:00 pm	**AOA/AAOA President's Reception**

WEDNESDAY, OCTOBER 27, 2010

Moderator – Margaret Orcutt Tuddenham, DO, FACEP, FACOP

8:00 am – 9:00 am	**Craniosacral Interventions in Pediatrics** Susan Cislo, DO
9:00 am – 10:00 am	**Craniosacral Interventions in Pediatrics - Workshop** Susan Cislo, DO
10:00 am – 10:30 am	Break
10:30 am – 11:30 am	**The Comprehensive Diagnosis and Treatment of Pediatric Migraine** Marc DiSabella, DO
11:30 am – 12:30 pm	**Pediatric Spells: Not All That Moves Is a Seizure** Marc DiSabella, DO
12:30 pm – 2:00 pm	**Lunch**
2:00 pm – 3:00 pm	**Clinical Management of Toxic Substance Exposure in Children** Michael D. Reed, PharmD, FCCP, FCP
3:00 pm – 4:00 pm	**Pediatric Arrhythmia - the Good, the Bad and the Ugly** Alok Bose, MD
4:00 pm - 5:00 pm	**Chest Pain and Syncope - When to Worry** Alok Bose, MD
6:00 pm – 8:00 pm	**AOA Dinner Seminar** *(Must sign in for extra CME)*

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SUNDAY, OCTOBER 24, 2010

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP
Co-Moderator (BOT Member) – James Kirk, DO, FACOP

7:00 am – 5:00 pm	**AOA Registration**
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5:00 pm – 8:00 pm	**ACOP Board of Trustees Meeting**

SUNDAY, OCTOBER 24, 2010

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP

Co-Moderator (BOT Member) – James Kirk, DO, FACOP

8:00 am – 9:00 am

Unusual and Challenging Fetal Abnormalities: Prenatal Ultrasound Evaluation

Harris J. Finberg, MD

Objective: Upon completion of this lecture, the participant will be able to demonstrate how a careful analysis of an abnormal fetal sonogram may identify a “tell-tale detail” that will indicate a unique diagnosis or a sharply limited differential diagnosis, and explain how sonographic diagnosis of fetal malformations helps direct and improve prenatal and neonatal management and prognosis.

SUNDAY, OCTOBER 26, 2008

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP
Co-Moderator (BOT Member) – James Kirk, DO, FACOP

9:00 am – 10:00 am

Nitric Oxide Use in Neonates

James Kirk, DO, FACOP

Objective: Upon completion of this lecture, the participant will be able to review the physiology of nitric oxide and its role in regulating pulmonary blood flow, discuss the established uses of inhaled nitric oxide in term infants with hypoxic respiratory failure, and discuss the potential uses of inhaled nitric oxide in preterm infants for the prevention of chronic lung disease.

Clinical Uses of Inhaled
Nitric Oxide In The Neonate

CLINICAL USES OF INHALED
NITRIC OXIDE
IN THE NEONATE

Clinical Uses of Inhaled
Nitric Oxide In The
Neonate

I HAVE NO RELEVANT RELATIONSHIPS
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Clinical Uses of Inhaled Nitric Oxide In The Neonate

Nitric Oxide

- Soluable gas produced by Endothelial cells Macrophages and some neurons
- Acts in a paracine manner on target cells through induction of cAMP

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Nitric Oxide
One half life is seconds so it only acts on cells in close proximity to where its produced.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Nitric Oxide
- Plays an important role in regulating vascular tone
- Is a potent vasodilator
- Reduces platelet adhesion
- Inhabit mast cell induced inflammation

Clinical Uses of Inhaled Nitric Oxide In The Neonate

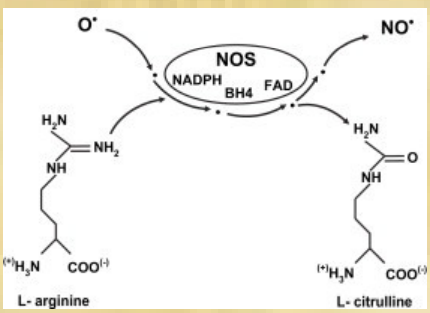
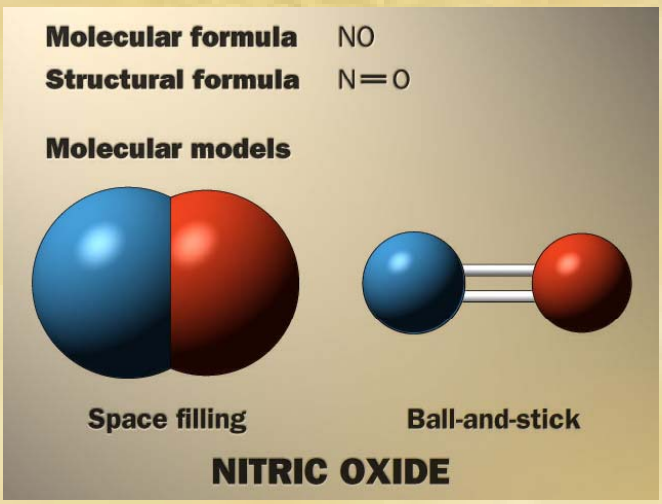


Fig. 1 Synthesisof NO by NO synthase. NO is produced when an electron from oxygen is transferredto an amino terminal nitrogen of l-arginine. Electrontransfer is facilitated by the enzyme nitric oxide synthase (NOS) and uses variouscofactors, including NADPH, 6(R)-5,6,7,8-tetrahydrobiopterin (BH4) and flavin adeninedinucleotide and flavin mononucleo-tide (FAD). Completion of the reaction producesNO and H_2O while converting l-arginineto l-citrulline.

Clinical Uses of Inhaled Nitric Oxide
In The Neonate



Clinical Uses of Inhaled Nitric Oxide
In The Neonate

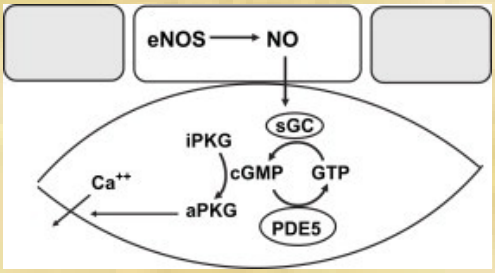
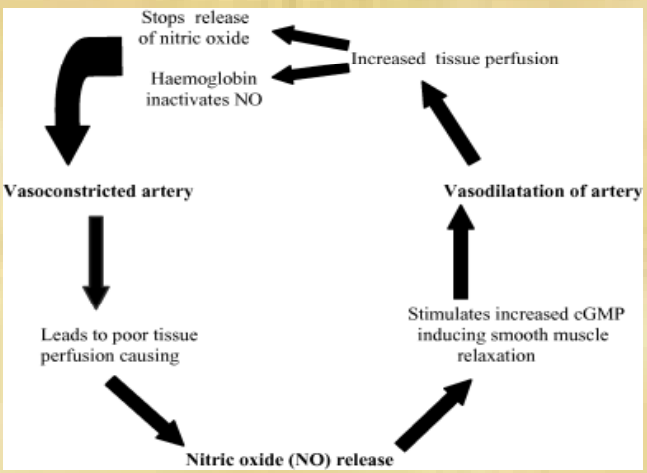


Fig. 2 NO/cGMP/PKGpathway. Highly lipid soluble NO produced in the vascular endothelium diffuses rapidlyacross cell membranes and activates soluble guanylyl cyclase (sGC) in the cytoplasmof the smooth muscle cell. Binding to sGC results in increased intracellular cGMPlevels that activate cGMP-dependent protein kinase (PKG), which acts on various downstreamtargets to decrease intracellular calcium concentrations $[Ca^{++}]_i$and thereby cause vasorelaxation.

Clinical Uses of Inhaled Nitric Oxide In The Neonate



Clinical Uses of Inhaled Nitric Oxide In The Neonate

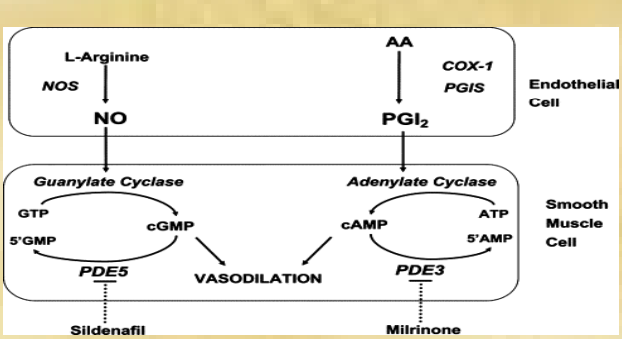
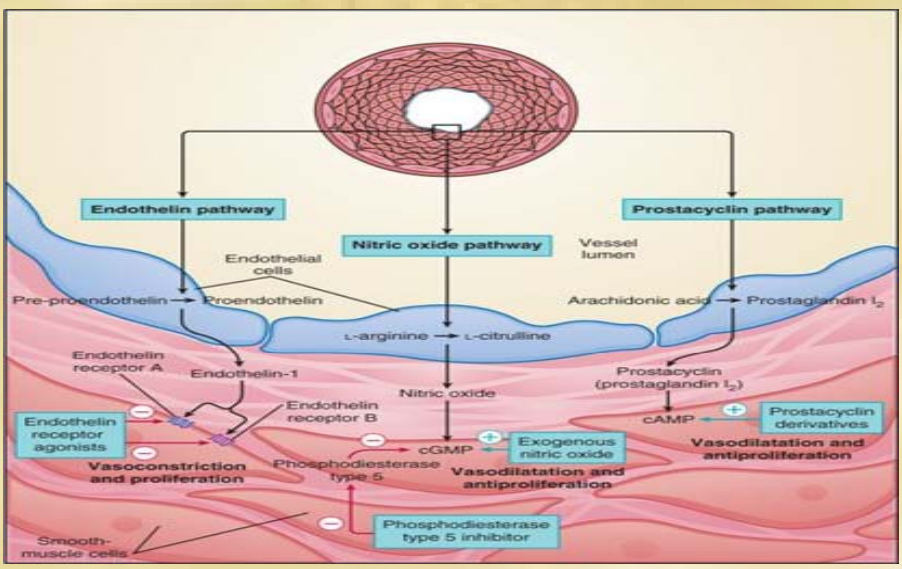


Figure1 Nitric oxide (*NO*) and prostacyclin (*PGI* $_2$) signaling pathways in the regulation of pulmonary vascular tone. NO is synthesized by nitric oxide synthase (*NOS*) from the terminal nitrogen of L-arginine. NO stimulates soluble guanylate cyclase (sGC) to increase intracellular cyclic guanosine monophosphate (*cGMP*). PGI_2 is an arachidonic acid (*AA*) metabolite formed by cyclooxygenase (*COX-1*) and prostacyclin synthase (*PGIS*) in the vascular endothelium. PGI_2 stimulates adenylate cyclase in vascular smooth muscle cells, which increases intracellular cyclic adenosine monophosphate (*cAMP*). Both cGMP and cAMP indirectly decrease free cytosolic calcium, resulting in smooth muscle relaxation. Specific phosphodiesterases hydrolyze cGMP and cAMP, thus regulating the intensity and duration of their vascular effects. Inhibition of these phosphodiesterases with agents, such as sildenafil and milrinone, may enhance pulmonary vasodilation. *GTP*, guanosine triphosphate; *5'GMP*, 5' guanosine monophosphate; *PDE5*, type 5 phosphodiesterase; *ATP*, adenosine triphosphate; *5'AMP*, 5' adenosine monophosphate; *PDE3*, type 3 phosphodiesterase.

Clinical Uses of Inhaled Nitric Oxide In The Neonate



Clinical Uses of Inhaled Nitric Oxide In The Neonate

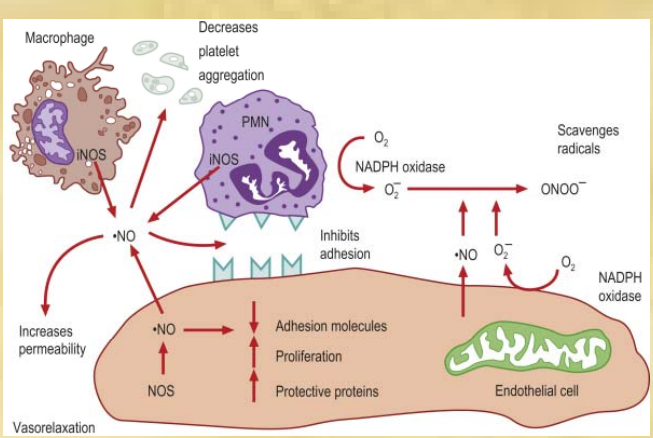


Fig. 24.5. Nitric oxide-mediated protective mechanisms in acute lung injury. Nitric oxide (•NO) from inducible nitric oxide synthase (iNOS) in macrophages and neutrophils and from NOS in endothelial cells stimulates protein leakage, and relaxation of smooth muscle but also decreases platelet aggregation, reduces neutrophil adhesion to endothelium, and scavenges toxic oxygen radicals. Within endothelial cells, •NO stimulates protective heat shock protein expression and endothelial cell proliferation.

Clinical Uses of Inhaled Nitric Oxide
In The Neonate

USE OF NITRIC OXIDE IN TERM INFANTS

Clinical Uses of Inhaled Nitric Oxide
In The Neonate

Persistent Pulmonary Hypertension of the Newborn

- Persistence of fetal pattern circulatory pattern of right to left shunting through the foramen ovale and ductus arterioyus.

- May be primary problem or secondary to pulmonary parenchymal disease or pulmonary nypoplasia.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

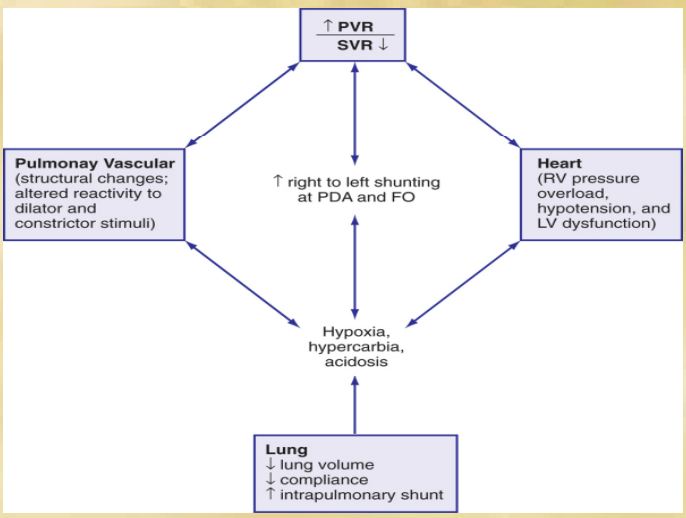
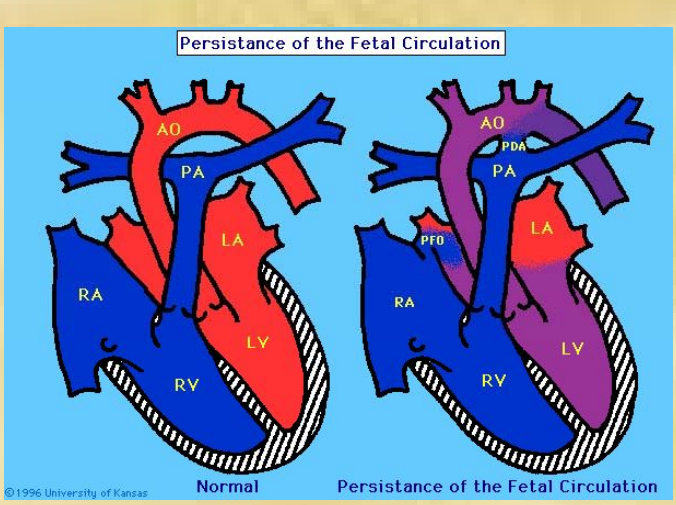


Figure 101-8 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn (PPHN). FO, foramen ovale; LV, left ventricular; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; RV, right ventricular; SVR, systemic vascular resistance. ***(From Kinsella JP, Abman SH: Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. J Pediatr 1995;126:853–864.)***

Clinical Uses of Inhaled Nitric Oxide In The Neonate



Clinical Uses of Inhaled Nitric Oxide In The Neonate

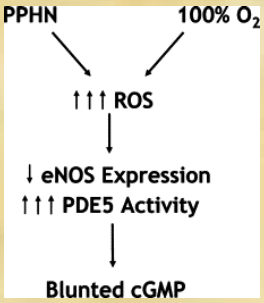


Figure 2 Increased reactive oxygen species (*ROS*), such as superoxide and hydrogen peroxide, produced in the vascular wall of pulmonary vessels affected by persistent pulmonary hypertension of the newborn (*PPHN*). In addition, even brief exposures to hyperoxia elevate cellular levels of ROS in the neonatal pulmonary vasculature. Increased ROS diminish nitric oxide synthase activity and increase type 5 phosphodiesterase (*PDE5*) activity, both of which blunt the normal production of cyclic guanosine monophosphate (*cGMP*). *eNOS*, endothelial nitric oxide synthase

Clinical Uses of Inhaled Nitric Oxide In The Neonate

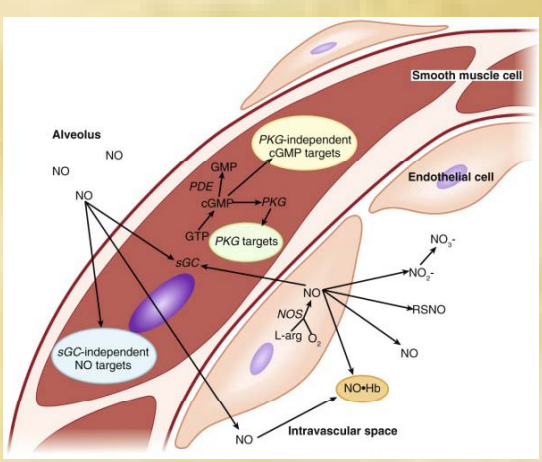


Figure 31-4 Schematic of the nitric oxide (NO) signaling pathway in the lung. NO, formed by endothelial cells or administered by inhalation, diffuses to vascular smooth muscle cells. Numerous targets of NO contribute to the wide variety of effects of this molecule on the cardiovascular system. One of the primary targets for NO is soluble guanylate cyclase (sGC). NO binds to the heme moiety of sGC and stimulates synthesis of the intracellular second messenger cyclic guanosine monophosphate (cGMP). cGMP interacts with a variety of targets, including ion channels, cGMP-regulated phosphodiesterases (PDEs), and cGMP-dependent protein kinases (PKGs). PKGs have been shown to phosphorylate various proteins in vascular smooth muscle cells. cGMP is metabolized to GMP by PDEs. On arrival in the bloodstream, the majority of NO rapidly binds to hemoglobin with high affinity, but small amounts of NO may remain to react with other molecules, including proteins. GTP, guanosine triphosphate; NOS, nitric oxide synthase; RSNO, S-nitrosothiol. *(From Ichinose F, Roberts JD, Zapol WM: Inhaled nitric oxide, a selective pulmonary vasodilator, current uses and therapeutic potential. Circulation 109:3106-3111, 2004, with permission.)*

Clinical Uses of Inhaled Nitric Oxide In The Neonate

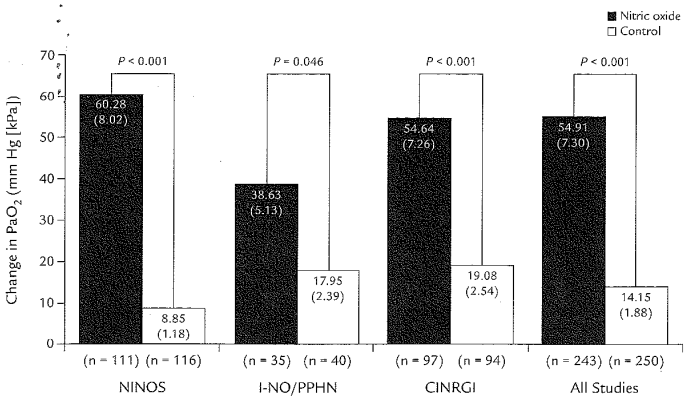


Figure 1. Change from baseline in mean partial pressure of arterial oxygen (PaO_2) after 30 minutes of inhaled nitric oxide treatment. Pairwise *P* values were calculated using the Wilcoxon rank sum test. NINOS = Neonatal Inhaled Nitric Oxide Study[13]; I-NO/PPHN = Inhaled Nitric Oxide/Persistent Pulmonary Hypertension of the Newborn[14]; CINRGI = Clinical Inhaled Nitric Oxide Research Group Initiative.[15]

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Summary of Clinical Results from CINRGI Study

	Placebo	INOmax	P value
ECMO*,†	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

* Extracorporeal membrane oxygenation
† ECMO was the primary end point of this study

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*,†	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation

† Death or need for ECMO was the study's primary end point

Clinical Uses of Inhaled Nitric Oxide In The Neonate

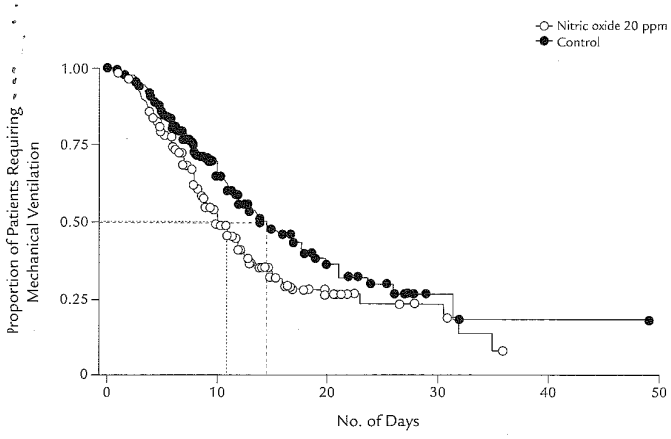
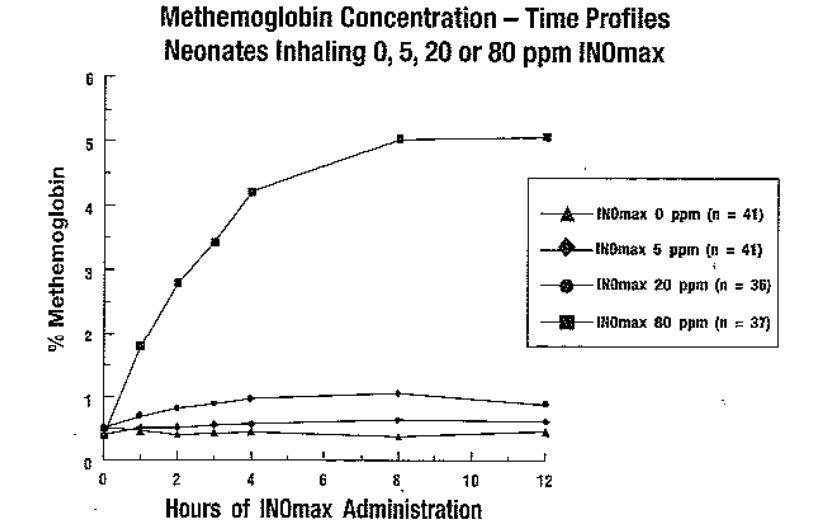


Figure 3. Kaplan-Meier analysis of the time to removal from mechanical ventilation. The broken line at 11 days represents the median duration of mechanical ventilation in the inhaled nitric oxide group, and the broken line at 14 days represents the corresponding value in the control group.

Clinical Uses of Inhaled Nitric Oxide In The Neonate



Clinical Uses of Inhaled Nitric Oxide In The Neonate

Finer, Neil

iNO for respiratory failure in Newborns Cochrane Database for Systemic Reviews 2009.

It is reasonable to use iNO at 20 ppm in term infants with Hypoxic respiratory failure who do not have Diaphragmatic hernia

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Criteria for iNO use

1) No Parenchymal Lung Disease by CXR

- Persistent Hypoxemia
- ECHO Cardiogram to R/O structure Heart Disease and confirm PPHN
- Difference in SaO_2 of P 5%.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Parenchymal Lung Disease on Chest X-ray

1) Respiratory Failure OI> 25
2) Pulmonary Hypertension

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Use of iNO in Non-ECMO Centers

-Be sure of Diagnosis
-Agreement with preferred ECMO center with the ability to transport on iNO
-Predetermined criteria for mandatory transport to ECMO center.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Use of iNO to Prevent Chronic Lung Disease in Preterm Infants

Clinical Uses of Inhaled Nitric Oxide In The Neonate

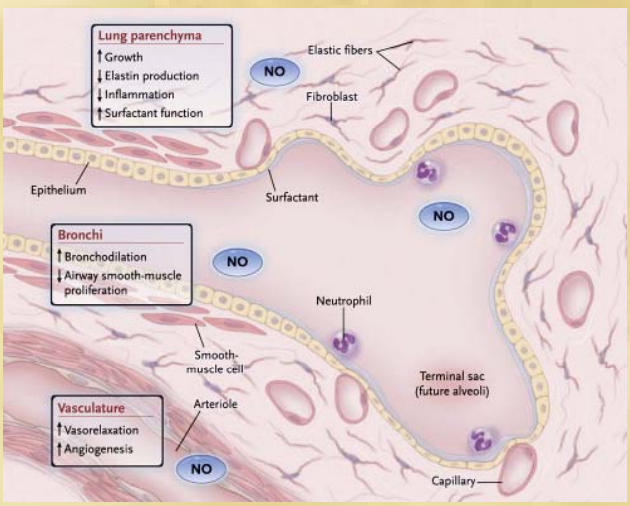


Fig. 2 Potential effects of NO on the developing lung. This figure represents a fetal or preterm lung during the saccular to alveolar stage of development at 25 to 28 weeks of gestation. The potential effects of inducible NO on the developing lung parenchyma, airways, and vasculature are shown. (*From* Martin RJ, Walsh MC. Inhaled nitric oxide for preterm infants—who benefits? N Engl J Med 2005;353:83; with permission. Copyright © 2005, Massachusetts Medical Society.)

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Short Term Benefits of iNO in Preterm Infants

1) Selective Pulmonary Vasodilation
2) Improvement in V/Q Mismatch
3) Improved Oxygenation

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Long Term Benefits of iNO in Preterm Infants

1) Decreased Oxidant Stress
2) Improved Surfactant Function
3) Decreased Airway Resistance
4) Improved Lung Growth

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Trial of Early Use of iNO
- Kisella 1999
- Mercier – 1999
- Srisuparp – 2002
- Van Mears – 2005
- Hascoet – 2005
- Innovo – 2005
- EUNO - 2010

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Trials of Early Use of iNO

- iNO may produce short term improvement in oxygenation
- No long term benefits in survival or seizures without BPD confirmed

Clinical Uses of Inhaled Nitric Oxide In The Neonate

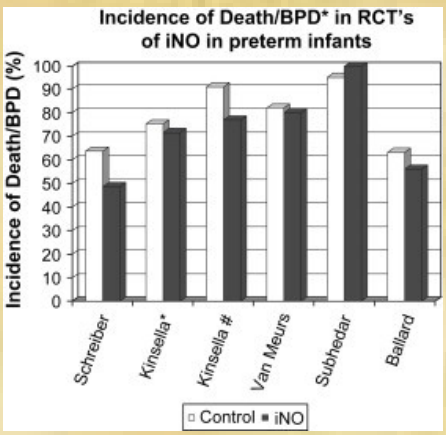


Fig. 3 Effect of inhaled NO on the incidence of death or BPD in RCTs. The trials show a modest benefit with a large number needed to treat (NNT) and pending confirmation from long-term outcome data. Kinsella * refers to the trial by Kinsella and colleagues in 2006. [59] Kinsella # refers to the trial by Kinsella and colleagues in 1999

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Why Different Outcomes from Trials

- Different Hyptheses
- Different Risk Groups
- Different Dose and Exposures

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Original Article

Early Inhaled Nitric Oxide Therapy in Premature Newborns with Respiratory Failure

John P. Kinsella, M.D., Gary R. Cutter, Ph.D., William F. Walsh, M.D., Dale R. Gerstmann, M.D., Carl L. Bose, M.D., Claudia Hart, M.D., Kris C. Sekar, M.D., Richard L. Auten, M.D., Vinod K. Bhutani, M.D., Jeffrey S. Gerdes, M.D., Thomas N. George, M.D., W. Michael Southgate, M.D., Heather Carriedo, M.D., Robert J. Couser, M.D., Mark C. Mammel, M.D., David C. Hall, M.D., Mariann Pappagallo, M.D., Smeeta Sardesai, M.D., John D. Strain, M.D., Monika Baier, Ph.D., and Steven H. Abman, M.D.

N Engl J Med
Volume 355(4):354-364
July 27, 2006

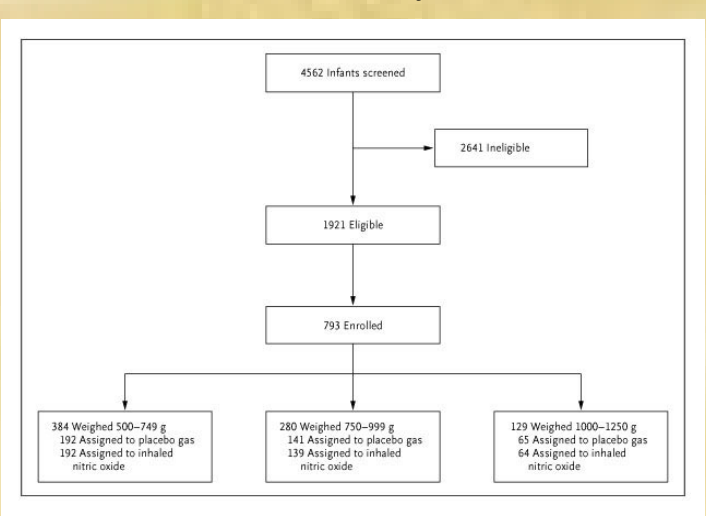
Clinical Uses of Inhaled Nitric Oxide In The Neonate

Study Overview

- In this multicenter, randomized trial of preterm newborns with a birth weight from 500 to 1250 g and with respiratory failure, low-dose inhaled nitric oxide did not significantly reduce death or bronchopulmonary dysplasia overall but reduced this risk in infants with a birth weight of 1000 g or more and reduced the risk of brain injury in the cohort overall
- These results support the potential benefits of low-dose inhaled nitric oxide in preterm infants with respiratory failure

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Enrollment of Study Patients



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Clinical Uses of Inhaled Nitric Oxide In The Neonate

Baseline Characteristics of Patients

Table 1. Baseline Characteristics of Patients.*

Characteristic	Inhaled Nitric Oxide (N=398)	Placebo (N=395)	P Value
Birth weight — g	796±190	788±185	0.54
Birth-weight strata			
500–749 g	642±76	639±71	0.66
750–999 g	851±71	843±71	0.36
1000–1250 g	1129±68	1113±77	0.21
Gestational age — wk	25.6±1.7	25.6±1.8	0.86
Male sex — no. (%)	211 (53.0)	216 (54.7)	0.64
Mother's race or ethnic group — no./total no. (%)†			0.77
White	249/397 (62.7)	234/394 (59.4)	
Black	94/397 (23.7)	98/394 (24.9)	
Hispanic	41/397 (10.3)	48/394 (12.2)	
Other	13/397 (3.3)	14/394 (3.6)	
Inborn — no./total no. (%)	296/397 (74.6)	299/395 (75.7)	0.71
Antenatal corticosteroids — no./total no. (%)	310/395 (78.5)	290/394 (73.6)	0.11
Apgar score — median (interquartile range)			
At 1 min	4 (0–9)	4 (0–9)	0.71
At 5 min	7 (0–9)	7 (1–10)	0.24

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clinical Uses of Inhaled Nitric Oxide In The Neonate

Baseline Characteristics of Patients (cont.)

Maternal complications — no./total no. (%)			
Cesarean section	248/398 (62.3)	276/395 (69.9)	0.02
Chorioamnionitis	76/397 (19.1)	58/394 (14.7)	0.07
Preeclampsia	65/397 (16.4)	64/394 (16.2)	0.95
Multiple gestation	96/397 (24.2)	107/394 (27.2)	0.34
Diabetes‡:	24/397 (6.0)	15/394 (3.8)	0.16
Antepartum hemorrhage	64/397 (16.1)	58/394 (14.7)	0.61
Age at randomization — hr	30.5±13.4	30.1±13.2	0.65
Oxygenation index§	5.4±5.2	5.8±6.7	0.30
F_IO_2	0.4±0.2	0.4±0.2	0.82
Arterial blood gas			
PaO_2 — mm Hg	63.9±25.6	64.3±29.7	0.81
$PaCO_2$ — mm Hg	47.6±13.2	47.4±10.6	0.77
pH	7.3±0.1	7.3±0.1	0.79
Surfactant before randomization — no./total no. (%)	319/398 (80.1)	304/395 (77.0)	0.27
Type of ventilator — no./total no. (%)			0.93
Conventional	280/393 (71.2)	276/389 (71.0)	
High-frequency	113/393 (28.8)	113/389 (29.0)	
Pulmonary hemorrhage before randomization — no.	1	0	
Intracranial hemorrhage — no./total no. (%)			0.41
None	296/392 (75.5)	280/392 (71.4)	
Grade 1 or 2	72/392 (18.4)	86/392 (21.9)	
Grade 3 or 4	24/392 (6.1)	26/392 (6.6)	

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. F_IO_2 denotes the fraction of inspired oxygen, PaO_2 the partial pressure of arterial oxygen, and $PaCO_2$ the partial pressure of arterial carbon dioxide.
† Race or ethnic group was self-reported by a parent or guardian.
‡ Diabetes includes both preexisting and gestational diabetes mellitus.
§ The oxygenation index equals the mean airway pressure multiplied by the F_IO_2 multiplied by 100, with the result divided by the PaO_2.

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Clinical Uses of Inhaled Nitric Oxide In The Neonate

Incidence of Death or Bronchopulmonary Dysplasia at 36 Weeks of Postmenstrual Age

Table 2. Incidence of Death or Bronchopulmonary Dysplasia at 36 Weeks of Postmenstrual Age.

Variable	Inhaled Nitric Oxide (N=398)	Placebo (N=395)	P Value	Relative Risk (95% CI)*
	no./total no. (%)			
All patients				
Death	78/394 (19.8)	98/392 (25.0)	0.08	0.79 (0.61–1.03)
Bronchopulmonary dysplasia	212/326 (65.0)	210/309 (68.0)	0.43	0.96 (0.86–1.09)
Death or bronchopulmonary dysplasia	282/394 (71.6)	295/392 (75.3)	0.24	0.95 (0.87–1.03)
Birth weight of 500–749 g				
Death	55/191 (28.8)	66/189 (34.9)	0.20	0.82 (0.61–1.11)
Bronchopulmonary dysplasia	113/144 (78.5)	100/132 (75.8)	0.59	1.04 (0.91–1.18)
Death or bronchopulmonary dysplasia	162/191 (84.8)	159/189 (84.1)	0.85	1.01 (0.92–1.10)
Birth weight of 750–999 g				
Death	15/138 (10.9)	24/139 (17.3)	0.13	0.63 (0.35–1.15)
Bronchopulmonary dysplasia	82/125 (65.6)	76/120 (63.3)	0.71	1.04 (0.86–1.25)
Death or bronchopulmonary dysplasia	95/138 (68.8)	95/139 (68.3)	0.93	1.01 (0.86–1.18)
Birth weight of 1000–1250 g				
Death	8/65 (12.3)	8/64 (12.5)	0.97	0.98 (0.39–2.46)
Bronchopulmonary dysplasia	17/57 (29.8)	34/57 (59.6)	0.001	0.50 (0.32–0.79)
Death or bronchopulmonary dysplasia	25/65 (38.5)	41/64 (64.1)	0.004	0.60 (0.42–0.86)

* CI denotes confidence interval.

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Clinical Uses of Inhaled Nitric Oxide In The Neonate

Incidence of Primary Outcomes According to Cranial Ultrasonography

Table 3. Incidence of Primary Outcomes According to Cranial Ultrasonography.*

Variable	Inhaled Nitric Oxide	Placebo	P Value	Relative Risk (95% CI)
	no./total no. (%)			
All patients				
Grade 3 or 4 ICH, PVL, or ventriculomegaly	64/366 (17.5)	87/364 (23.9)	0.03	0.73 (0.55–0.98)
Grade 3 or 4 ICH or PVL	61/372 (16.4)	80/366 (21.9)	0.06	0.75 (0.56–1.02)
Grade 3 or 4 ICH	49/398 (12.3)	63/394 (16.0)	0.14	0.77 (0.54–1.09)
PVL	19/365 (5.2)	32/356 (9.0)	0.048	0.58 (0.33–1.00)
Ventriculomegaly	19/364 (5.2)	32/359 (8.9)	0.05	0.58 (0.37–1.01)
Death or grade 3 or 4 ICH	112/394 (28.4)	140/392 (35.7)	0.03	0.80 (0.65–0.98)
Death, grade 3 or 4 ICH, or PVL	120/392 (30.6)	151/391 (38.6)	0.02	0.79 (0.65–0.96)
Birth weight of 500–749 g				
Grade 3 or 4 ICH, PVL, or ventriculomegaly	37/177 (20.9)	38/168 (22.6)	0.70	0.92 (0.62–1.38)
Grade 3 or 4 ICH or PVL	34/179 (19.0)	35/170 (20.6)	0.71	0.92 (0.60–1.41)
Grade 3 or 4 ICH	29/192 (15.1)	27/191 (14.1)	0.79	1.07 (0.66–1.73)
PVL	10/175 (5.7)	14/165 (8.5)	0.32	0.67 (0.31–1.47)
Ventriculomegaly	11/173 (6.4)	13/166 (7.8)	0.60	0.81 (0.37–1.76)
Death or grade 3 or 4 ICH	75/191 (39.3)	83/189 (43.9)	0.36	0.89 (0.70–1.14)
Death, grade 3 or 4 ICH, or PVL	77/191 (40.3)	89/189 (47.1)	0.18	0.86 (0.68–1.08)

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Clinical Uses of Inhaled Nitric Oxide
In The Neonate

Incidence of Primary Outcomes According to Cranial Ultrasonography (cont.)

Birth weight of 750–999 g				
Grade 3 or 4 ICH, PVL, or ventriculomegaly	17/131 (13.0)	36/137 (26.3)	0.006	0.49 (0.29–0.83)
Grade 3 or 4 ICH or PVL	17/129 (13.0)	36/135 (26.7)	0.006	0.49 (0.29–0.83)
Grade 3 or 4 ICH	13/141 (9.2)	27/139 (19.4)	0.02	0.47 (0.26–0.88)
PVL	5/130 (3.8)	14/133 (10.5)	0.04	0.37 (0.14–0.99)
Ventriculomegaly	3/131 (2.3)	12/133 (9.0)	0.02	0.25 (0.07–0.88)
Death or grade 3 or 4 ICH	25/138 (18.1)	42/139 (30.2)	0.02	0.60 (0.39–0.93)
Death, grade 3 or 4 ICH, or PVL	29/137 (21.2)	47/139 (33.8)	0.02	0.63 (0.42–0.93)
Birth weight of 1000–1250 g				
Grade 3 or 4 ICH, PVL, or ventriculomegaly	10/60 (16.7)	13/61 (21.3)	0.52	0.78 (0.37–1.64)
Grade 3 or 4 ICH or PVL	10/62 (16.1)	9/59 (15.3)	0.86	1.07 (0.47–2.46)
Grade 3 or 4 ICH	7/65 (10.8)	9/64 (14.1)	0.57	0.77 (0.30–1.93)
PVL	4/60 (6.7)	4/58 (6.9)	0.96	0.97 (0.25–3.68)
Ventriculomegaly	5/60 (8.3)	7/60 (11.7)	0.54	0.71 (0.24–2.13)
Death or grade 3 or 4 ICH	12/65 (18.5)	15/64 (23.4)	0.49	0.79 (0.40–1.55)
Death, grade 3 or 4 ICH, or PVL	14/64 (21.9)	15/63 (23.8)	0.80	0.92 (0.48–1.74)

* CI denotes confidence interval, ICH intracranial hemorrhage, and PVL periventricular leukomalacia. ICH was defined by the maximum grade at baseline, at follow-up on days 7 to 14, and at 30 days by ultrasonography; ventriculomegaly and PVL were defined by ultrasonography at 30 days.

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Clinical Uses of Inhaled Nitric Oxide
In The Neonate

Incidence of Secondary Outcomes

Table 4. Incidence of Secondary Outcomes.

Variable	Inhaled Nitric Oxide (N=398)	Placebo (N=395)	P Value
	no./total no. (%)		
Air leak	25/398 (6.3)	24/395 (6.1)	0.94
Pulmonary hemorrhage	24/398 (6.0)	26/395 (6.6)	0.75
Symptomatic patent ductus arteriosus			
Medical treatment	215/398 (54.0)	212/395 (53.7)	0.92
Surgical ligation	86/398 (21.6)	86/395 (21.8)	0.96
Necrotizing enterocolitis	53/379 (14.0)	46/369 (12.5)	0.54
Threshold retinopathy*	66/398 (16.6)	60/395 (15.2)	0.59
Postnatal corticosteroids	222/369 (60.2)	204/365 (55.9)	0.24
Sepsis	139/381 (36.5)	118/369 (32.0)	0.19
Medications at 36 wk			
Bronchodilators	62/309 (20.1)	60/298 (20.1)	0.98
Corticosteroids	47/308 (15.3)	37/298 (12.4)	0.31
Diuretics	113/309 (36.6)	113/298 (37.9)	0.73
Medications among survivors			
Bronchodilators	56/298 (18.8)	55/283 (19.4)	0.84
Corticosteroids	43/298 (14.4)	32/283 (11.3)	0.26
Diuretics	105/298 (35.2)	104/283 (36.7)	0.70

* Threshold retinopathy of prematurity was defined as a condition requiring interventional therapy.

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Clinical Uses of Inhaled Nitric Oxide
In The Neonate

Conclusion

- Among premature newborns with respiratory failure, low-dose inhaled nitric oxide did not reduce the overall incidence of bronchopulmonary dysplasia, except among infants with a birth weight of at least 1000 g, but it did reduce the overall risk of brain injury

Clinical Uses of Inhaled Nitric Oxide
In The Neonate

Original Article

Inhaled Nitric Oxide in Preterm Infants Undergoing Mechanical Ventilation

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Study Overview

- In this multicenter, randomized trial of preterm newborns with a birth weight of 1250 g or less who required ventilatory support, the initiation of inhaled nitric oxide between days 7 and 21 of life significantly reduced the risk of death or chronic lung disease and the duration of both hospitalization and supplemental oxygen therapy
- Using a regimen of inhaled nitric oxide therapy different from that in the companion report by Kinsella et al., this group also found inhaled nitric oxide to be beneficial in preterm infants with respiratory failure

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Baseline Characteristics of the Infants

Table 1. Baseline Characteristics of the Infants.*

Characteristic	Inhaled Nitric Oxide (N=294)	Placebo (N=288)	P Value†
Birth weight			
Mean — g	766±161	759±155	0.45
500–799 g — no. (%)	197 (67.0)	197 (68.4)	0.60
800–1250 g — no. (%)	97 (33.0)	91 (31.6)	
Gestational age — wk	26±1.5	26±1.5	0.38
Male sex — no. (%)	155 (52.7)	162 (56.2)	0.37
Mother's race or ethnic group — no. (%)‡			0.22
White	170 (57.8)	145 (50.3)	
Black	76 (25.9)	90 (31.3)	
Hispanic	32 (10.9)	43 (14.9)	
Other	16 (5.4)	10 (3.5)	
Antenatal corticosteroids — no. (%)	243 (82.7)	229 (79.5)	0.23
Surfactant — no. (%)	288 (98.0)	277 (96.2)	0.25
Vitamin A — no. (%)	154 (52.4)	160 (55.6)	0.58
Age at entry			
Median (interquartile range) — days	16 (12–19)	16 (13–19)	0.68
7–14 days at entry — no. (%)	112 (38.1)	115 (39.9)	0.71

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Baseline Characteristics of the Infants (cont.)

Respiratory severity score at entry — no. (%)§			0.60
<3.5	162 (55.1)	149 (51.7)	
3.5 to <10	120 (40.8)	126 (43.8)	
≥10	12 (4.1)	13 (4.5)	
Clinical complications — no. (%)¶			
Pneumothorax or pneumomediastinum	34 (11.6)	32 (11.1)	0.76
Patent ductus arteriosus	192 (65.3)	194 (67.4)	0.84
Necrotizing enterocolitis	12 (4.1)	11 (3.8)	0.83
Sepsis	70 (23.8)	58 (20.1)	0.36
Grade 3 or 4 intraventricular hemorrhage	35 (11.9)	45 (15.6)	0.13
Type of ventilation — no. (%)			0.66
Conventional	202 (68.7)	191 (66.3)	
High frequency	65 (22.1)	74 (25.7)	
Nasal continuous positive airway pressure	27 (9.2)	23 (8.0)	

* Plus–minus values are means ±SD.
† P values correspond to multiple outputation analysis.
‡ Race or ethnic group was self-reported by the parents of the patient.
§ The respiratory severity score was calculated as the fraction of inspired oxygen multiplied by the mean airway pressure (in centimeters of water). The median value for infants in this trial was 3.5, which represents less severe disease.
¶ Patent ductus arteriosus was reported only if echocardiography was performed and treatment with either indomethacin or surgical closure was provided. Necrotizing enterocolitis was diagnosed by the presence of pneumatosis, hepatobiliary gas, or pneumoperitoneum on radiography, plus one or more of the following symptoms: bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in the stool not secondary to a fissure. Sepsis was diagnosed by a positive culture of blood or cerebrospinal fluid.

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Incidence of the Primary Outcome

Table 2. Incidence of the Primary Outcome.

Outcome	Inhaled Nitric Oxide	Placebo	P Value	Relative Benefit (95% CI)*
	no./total no. (%)			
Overall population			0.04	1.23 (1.01–1.51)
Survival without chronic lung disease	129/294 (43.9)	106/288 (36.8)		
Death or survival with chronic lung disease	165/294 (56.1)	182/288 (63.2)		
Chronic lung disease	149/294 (50.7)	164/288 (56.9)		
Death	16/294 (5.4)	18/288 (6.3)		
Birth weight of 500–799 g			0.14	1.20 (0.94–1.54)
Survival without chronic lung disease	85/197 (43.1)	74/197 (37.6)		
Death or survival with chronic lung disease	112/197 (56.9)	123/197 (62.4)		
Chronic lung disease	99/197 (50.3)	108/197 (54.8)		
Death	13/197 (6.6)	15/197 (7.6)		1.01 (0.96–1.07)
Birth weight of 800–1250 g			0.14	1.30 (0.91–1.87)
Survival without chronic lung disease	44/97 (45.4)	32/91 (35.2)		
Death or survival with chronic lung disease	53/97 (54.6)	59/91 (64.8)		
Chronic lung disease	50/97 (51.5)	56/91 (61.5)		
Death	3/97 (3.1)	3/91 (3.3)		1.00 (0.95–1.06)

* CI denotes confidence interval.

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Outcome According to the Severity of Disease at 40 and 44 Weeks of Postmenstrual Age

Table 3. Outcome According to the Severity of Disease at 40 and 44 Weeks of Postmenstrual Age.*

Outcome	500–799 g		800–1250 g		All Infants		P Value†
	Nitric Oxide (N=197)	Placebo (N=197)	Nitric Oxide (N=97)	Placebo (N=91)	Nitric Oxide (N=294)	Placebo (N=288)	
	number (percent)						
Severity of disease at 40 wk							0.01
Discharged	82 (41.6)	60 (30.5)	43 (44.3)	38 (41.8)	125 (42.5)	98 (34.0)	
Hospitalization without support‡	45 (22.8)	44 (22.3)	21 (21.6)	12 (13.2)	66 (22.4)	56 (19.4)	
Hospitalization with oxygen only	40 (20.3)	55 (27.9)	26 (26.8)	29 (31.9)	66 (22.4)	84 (29.2)	
Hospitalization with mechanical ventilation	15 (7.6)	21 (10.7)	3 (3.1)	9 (9.9)	18 (6.1)	30 (10.4)	
Death	15 (7.6)	16 (8.1)	4 (4.1)	3 (3.3)	19 (6.5)	19 (6.6)	
Unknown	0	1 (0.5)	0	0	0	1 (0.3)	
Severity of disease at 44 wk							0.03
Discharged	151 (76.6)	129 (65.5)	82 (84.5)	70 (76.9)	233 (79.3)	199 (69.1)	
Hospitalization without support‡	6 (3.0)	15 (7.6)	2 (2.1)	4 (4.4)	8 (2.7)	19 (6.6)	
Hospitalization with oxygen only	19 (9.6)	26 (13.2)	8 (8.2)	9 (9.9)	27 (9.2)	35 (12.2)	
Hospitalization with mechanical ventilation	5 (2.5)	8 (4.1)	1 (1.0)	4 (4.4)	6 (2.0)	12 (4.2)	
Death	16 (8.1)	16 (8.1)	4 (4.1)	4 (4.4)	20 (6.8)	20 (6.9)	
Unknown	0	3 (1.5)	0	0	0	3 (1.0)	

* Percentages may not total 100 because of rounding.
† P values reflect the comparison of status of respiratory disease between nitric oxide and placebo with the use of a Monte Carlo simulation of the exact Wilcoxon two-sample test. All P values are based on multiple outputation analysis. Discharged infants were discharged to home and included some infants discharged with supplemental oxygen. The status of one infant at 40 weeks and three infants at 44 weeks was unknown.
‡ This category refers to hospitalization without ventilatory support or supplemental oxygen.

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Incidence of Clinical Complications after Study Entry

Table 4. Incidence of Clinical Complications after Study Entry.

Variable	Inhaled Nitric Oxide (N=294)	Placebo (N=288)	Relative Risk (95% CI)*	P Value
	no. (%)			
Sepsis	121 (41.2)	118 (41.0)	0.98 (0.80–1.20)	0.91
Necrotizing enterocolitis	23 (7.8)	19 (6.6)	1.17 (0.64–2.13)	0.63
Necrotizing enterocolitis requiring surgery	10 (3.4)	8 (2.8)	1.20 (0.46–3.13)	0.84
Patent ductus arteriosus treated	54 (18.4)	55 (19.1)	0.96 (0.68–1.35)	0.85
Retinopathy of prematurity	246 (83.7)	236 (81.9)	1.00 (0.93–1.07)	1.00
Retinopathy of prematurity requiring surgery	72 (24.5)	68 (23.6)	0.97 (0.72–1.31)	0.95
Neurologic evolution†	13 (5.0)	10 (4.1)	1.21 (0.53–2.76)	0.67

* CI denotes confidence interval.
† Evolution of a neurologic lesion on ultrasonography of the head was defined as the occurrence of a new grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, or hydrocephalus requiring a shunt during or after administration of study gas, when there was either no or only grade 1 or 2 intraventricular hemorrhage before study entry (as occurred among 259 infants receiving inhaled nitric oxide and 243 infants receiving placebo). Retinopathy of prematurity was defined as stage 1 to 4 disease by ophthalmologic examination. Treatment of patent ductus arteriosus was defined as the administration of indomethacin or surgical ligation.

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Post Hoc Subgroup Analyses of Survival without Chronic Lung Disease at 36 Weeks of Postmenstrual Age

Table 5. Post Hoc Subgroup Analyses of Survival without Chronic Lung Disease at 36 Weeks of Postmenstrual Age.

Variable	Inhaled Nitric Oxide (N=294)	Placebo (N=288)	Relative Benefit (95% CI)*	P Value†
	no./total no. (%)			
Age at entry				0.006
7–14 days			1.81 (1.27–2.59)	
Survival without chronic lung disease	55/112 (49.1)	32/115 (27.8)		
Death	11/112 (9.8)	13/115 (11.3)		
15–21 days			0.99 (0.77–1.27)	
Survival without chronic lung disease	74/182 (40.7)	74/173 (42.8)		
Death	12/182 (6.6)	10/173 (5.8)		
Severity score at entry				0.20
<3.5			1.26 (1.00–1.58)	
Survival without chronic lung disease	92/162 (56.8)	69/149 (46.3)		
Death	8/162 (4.9)	9/149 (6.0)		
≥3.5			1.10 (0.74–1.64)	
Survival without chronic lung disease	37/132 (28.0)	37/139 (26.6)		
Death	15/132 (11.4)	14/139 (10.1)		

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Post Hoc Subgroup Analyses of Survival without Chronic Lung Disease at 36 Weeks of Postmenstrual Age (cont.)

Survival without chronic lung disease				0.05‡
Race or ethnic group				
White	59/170 (34.7)	50/145 (34.5)	1.04 (0.76–1.43)	
Black	43/76 (56.6)	32/90 (35.6)	1.66 (1.16–2.37)	
Hispanic	21/32 (65.6)	17/43 (39.5)	1.62 (1.04–2.53)	
Other	6/16 (37.5)	7/10 (70.0)	0.57 (0.27–1.20)	
Age of 7–14 days at entry				
White	24/60 (40.0)	16/52 (30.8)	1.37 (0.81–2.32)	
Nonwhite	31/52 (59.6)	16/63 (25.4)	2.32 (1.43–3.77)	
Age of 15–21 days at entry				
White	35/110 (31.8)	34/93 (36.6)	0.89 (0.60–1.33)	
Nonwhite	39/72 (54.2)	40/80 (50.0)	1.13 (0.83–1.54)	
Severity score <3.5 at entry				
White	38/82 (46.3)	28/67 (41.8)	1.14 (0.78–1.67)	
Nonwhite	54/80 (67.5)	41/82 (50.0)	1.37 (1.05–1.80)	
Severity score ≥3.5 at entry				
White	21/88 (23.9)	22/78 (28.2)	0.88 (0.52–1.50)	
Nonwhite	16/44 (36.4)	15/61 (24.6)	1.52 (0.84–2.76)	

* CI denotes confidence interval.
† Interaction terms for subgroup analyses were tested in a multiple logistic-regression model.
‡ The P value is for the comparison between white infants and nonwhite infants.

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Conclusion

- Inhaled nitric oxide therapy improves the pulmonary outcome for premature infants who are at risk for bronchopulmonary dysplasia when it is started between 7 and 21 days of age and has no apparent short-term adverse effects

Clinical Uses of Inhaled Nitric Oxide In The Neonate

(Continued)

	Trial (*N* = 793)			Detailed-Outcomes Cohort (*N* = 652)			Non–Detailed-Outcomes Cohort (*N* = 141)	
	iNO (*n* = 398)	Placebo (*n* = 395)	Total	iNO (*n* = 332)	Placebo (*n* = 320)	Total	Total	*P*[a]
Gender, % female	47	45.3	46.2	48.2	46.9	47.6	39.7	0.09
Race, %								0.002
Black	23.7	25.1	24.4	22.9	22.2	22.6	32.9	
White	62.7	59.2	61	61.8	60	60.9	61.4	
Hispanic	10.3	12.2	11.2	11.5	13.8	12.6	5	
Asian/other	3.3	3.5	3.4	3.9	4.1	4	0.7	

[a] *P* values are for comparison between totals in detailed-outcomes and non–detailed-outcomes subjects.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

	Trial (*N* = 793)			Detailed-Outcomes Cohort (*N* = 652)			Non–Detailed-Outcomes Cohort (*N* = 141)	
	iNO (*n* = 398)	Placebo (*n* = 395)	Total	iNO (*n* = 332)	Placebo (*n* = 320)	Total	Total	*P*[a]
Birth weight, mean (SD), g	796 (190)	788 (185)	792 (187)	797 (190)	791 (186)	794 (188)	780 (184)	0.4
Birth weight strata, *n* (%)								
500–749 g	192 (48.2)	192 (48.6)	384 (48.4)	159 (47.9)	155 (48.4)	314 (48.2)	70 (49.7)	
750–999 g	141 (35.4)	139 (35.2)	280 (35.3)	118 (35.5)	113 (35.3)	231 (35.4)	49 (34.8)	
1000–1250 g	65 (16.3)	64 (16.2)	129 (16.3)	55 (16.6)	52 (16.3)	107 (16.4)	22 (15.6)	
Gestational age, mean (SD), wk	25.6 (1.7)	25.6 (1.8)	25.6 (1.8)	25.6 (1.7)	25.7 (1.9)	25.7 (1.8)	25.5 (1.6)	0.56

[a] *P* values are for comparison between totals in detailed-outcomes and non–detailed-outcomes subjects.

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1-y Corrected Age Survivors			Neurodevelopmental Evaluation Completed			Neurodevelopmental Evaluation Missing, Total (*n* = 135)	*P*[a]	Total (*n* = 455)
	iNO (*n* = 305)	Placebo (*n* = 285)	Total (*n* = 590)	iNO (*n* = 237)	Placebo (*n* = 218)			
Birth weight, (mean, SD), g	813 (183)	817 (188)	815 (185)	813 (181)	814 (184)	814 (182)	817 (197)	0.77
Birth weight strata, *n* (%)								0.04
500–749 g	129 (42.3)	121 (42.5)	250 (42.4)	98 (41.4)	87 (39.9)	185 (40.7)	65 (48.2)	
750–999 g	125 (41.0)	109 (38.2)	234 (39.6)	102 (43.0)	91 (41.7)	193 (42.4)	41 (30.4)	
1000–1250 g	51 (16.7)	55 (19.3)	106 (18.0)	37 (15.6)	40 (18.4)	77 (16.9)	29 (21.5)	

a P values are for comparison between 1-year corrected age survivors who completed neurodevelopmental evaluation and survivors missing neurodevelopmental evaluation.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

(Continued)

	Trial (*N* = 793)			Detailed-Outcomes Cohort (*N* = 652)			Non–Detailed-Outcomes Cohort (*N* = 141)	
	iNO (*n* = 398)	Placebo (*n* = 395)	Total	iNO (*n* = 332)	Placebo (*n* = 320)	Total	Total	*P*[a]
Inborn, *n* (%)	296 (74.6)	299 (75.7)	595 (75.1)	240 (72.3)	233 (72.8)	473 (72.6)	122 (87.1)	0.0003
Baseline OI, median (IQR)	4.0 (2.7–6.0)	4.0 (2.7–6.1)	4.0 (2.7–6.1)	4.1 (2.8–6.2)	4.1 (2.7–6.4)	4.1 (2.8–6.3)	3.5 (2.4–5.4)	0.008
Surfactant before randomization, *n* (%)	319 (80.2)	306 (77.5)	625 (78.8)	272 (81.9)	244 (76.3)	516 (79.1)	109 (77.3)	0.63
Baseline ICH, *n* (%)								
None	297 (75.8)	280 (71.4)	577 (73.6)	248 (75.8)	225 (71.0)	473 (73.5)	104 (74.3)	
Grades 1–2	71 (18.1)	86 (21.9)	157 (20.0)	57 (17.4)	68 (21.5)	125 (19.4)	32 (22.9)	
Grades 3–4	24 (6.1)	26 (6.6)	50 (6.4)	22 (6.7)	24 (7.6)	46 (7.1)	4 (2.9)	0.06

[a] *P* values are for comparison between totals in detailed-outcomes and non–detailed-outcomes subjects.

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	All			500–749 g			750–999 g			1000–1250 g		
	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*
Death at 1 y corrected age, *n* (%)	80 (20.8)	98 (25.5)	0.12	57 (30.5)	66 (35.3)	0.32	15 (10.8)	24 (18.1)	0.09	8 (13.8)	8 (12.5)	0.83
Death or on oxygen at 1 y corrected age, *n* (%)	97 (25.3)	110 (28.7)	0.29	70 (37.4)	70 (37.4)	0.99	19 (13.7)	29 (21.8)	0.08	8 (13.8)	11 (17.2)	0.61
Death or NDI at 1 y corrected age, *n* (%)	164 (42.4)	171 (44.5)	0.55	102 (54.3)	96 (51.3)	0.57	45 (32.1)	59 (44.4)	0.04	17 (28.8)	16 (25.0)	0.63
Death, on oxygen, or NDI at 1 y corrected age, *n* (%)	170 (43.9)	175 (45.6)	0.65	107 (56.9)	98 (52.4)	0.38	46 (32.9)	60 (45.1)	0.04	17 (28.8)	17 (26.6)	0.78

NDI includes any of the following: cerebral palsy; blind, severe hearing loss; MDI < 70; or PDI < 70. Unimpaired includes

Clinical Uses of Inhaled Nitric Oxide In The Neonate

(Continued)

	All			500–749 g			750–999 g			1000–1250 g		
	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*
Subjects receiving supplemental home oxygen prior to 1 y corrected age, *n* (%)	179 (71.9)	166 (71.9)	0.99	84 (79.3)	69 (73.4)	0.33	74 (72.6)	65 (72.2)	0.96	21 (51.2)	32 (68.1)	0.11
Subjects on oxygen at 1 y corrected age, *n* (%)	17 (6.5)	12 (5.0)	0.47	13 (11.7)	4 (4.0)	0.04	4 (3.7)	5 (5.3)	0.74	0 (0)	3 (6.4)	0.24
Duration of supplemental home oxygen, median (IQR), d	90 (36–182)	90 (49–192)	0.62	107 (51–222)	109 (62–229)	0.45	90 (31–158)	84 (46–181)	0.86	70 (31–110)	64 (37–176)	0.88
NDI at 1 y corrected age, *n* (%)	84 (35.4)	73 (33.5)	0.66	45 (45.9)	30 (34.5)	0.11	30 (29.4)	35 (38.5)	0.18	9 (24.3)	8 (20.0)	0.65
Unimpaired at 1 y corrected age, *n* (%)	91 (38.4)	80 (36.7)	0.71	28 (28.6)	28 (32.2)	0.59	41 (40.2)	30 (33.0)	0.3	22 (59		

NDI includes any of the following: cerebral palsy; blind, severe hearing loss; MDI < 70; or PDI < 70. Unimpaired includes

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(Continued)

	1-y Corrected Age Survivors		Neurodevelopmental Evaluation Completed			Neurodevelopmental Evaluation Missing, Total (*n* = 135)	*P*[a]	Total (*n* = 455)
	iNO (*n* = 305)	Placebo (*n* = 285)	Total (*n* = 590)	iNO (*n* = 237)	Placebo (*n* = 218)			
Inborn, *n* (%)	235 (77.1)	225 (79.0)	460 (78.0)	195 (82.3)	177 (81.2)	372 (81.8)	88 (65.2)	<.0001
Baseline OI, median (IQR)	3.7 (2.7–5.5)	3.9 (2.7–5.7)	3.8 (2.7–5.6)	4.0 (2.7–5.6)	4.0 (2.8–5.7)	4.0 (2.8–5.6)	3.3 (2.4–5.5)	0.01
Surfactant before randomization, *n* (%)	247 (81.0)	220 (77.2)	467 (79.2)	192 (81.0)	171 (78.4)	363 (79.8)	104 (77.0)	0.55
Baseline ICH, *n* (%)								0.02
None	240 (79.7)	216 (76.1)	456 (78.0)	189 (81.1)	172 (79.3)	361 (80.2)	95 (70.4)	
Grades 1–2	47 (15.6)	56 (19.7)	103 (17.6)	33 (14.2)	35 (16.1)	68 (15.1)	35 (25.9)	
Grades 3–4	14 (4.7)	12 (4.2)	26 (4.4)	11 (4.7)	10 (4.6)	21 (4.7)	5 (3.7)	

a P values are for comparison between 1-year corrected age survivors who completed neurodevelopmental evaluation and survivors missing neurodevelopmental evaluation.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

(Continued)

	1-y Corrected Age Survivors		Neurodevelopmental Evaluation Completed			Neurodevelopmental Evaluation Missing, Total (*n* = 135)	*P*[a]	Total (*n* = 455)
	iNO (*n* = 305)	Placebo (*n* = 285)	Total (*n* = 590)	iNO (*n* = 237)	Placebo (*n* = 218)			
Gestational age, mean (SD), wk	25.8 (1.7)	26.0 (1.8)	25.9 (1.8)	25.8 (1.7)	26.0 (1.8)	25.9 (1.8)	25.9 (1.9)	0.84
Gender, % female	45.3	51.6	48.3	46.4	50.9	48.6	47.4	0.85
Race, %								0.003
Black	22.3	23.5	22.9	19.8	19.3	19.6	34.1	
White	63.6	61.4	62.5	67.5	64.7	66.2	50.4	
Hispanic	10.5	11.2	10.9	8.9	11.9	10.3	12.6	
Asian and other	3.6	3.9	3.7	3.8	4.1	4	2.9	

a P values are for comparison between 1-year corrected age survivors who completed neurodevelopmental evaluation and survivors missing neurodevelopmental evaluation.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

(Continued)

	All			500–749 g			750–999 g			1000–1250 g		
	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*
Study hospital												
MV duration, median (IQR), d	36 (15–53)	34 (11–55)	0.52	42 (29–63)	41 (20–64)	0.36	35 (19–52)	32 (13–52)	0.45	13 (5–23)	14 (6–37)	0.32
LOS, median (IQR), d												
Total	87 (58–108)	84 (55–107)	0.37	95 (62–119)	90 (28–111)	0.04	88 (71–106)	85 (66–109)	0.85	64 (48–74)	67 (51–87)	0.08
Survivors	92 (74–112)	94 (74–113)	0.97	107 (89–124)	102 (86–119)	0.22	90 (77–107)	95 (73–113)	0.8	65 (51–75)	70 (59–89)	0.07
Nonsurvivors	12 (7–27)	13 (5–30)	0.78	15 (8–42)	11 (3–28)	0.03	7 (1–10)	16 (8–48)	0.01	10 (6–13)	11 (5–22)	0.72
Study hospital disposition, *n* (%)			0.48			0.21			0.74			0.24
Home without paid help	191 (72.9)	169 (71.3)		83 (75.5)	70 (71.4)		75 (71.4)	64 (69.6)		33 (70.2)	35 (74.5)	
Home with professional help	20 (7.6)	17 (7.2)		9 (8.2)	3 (3.1)		8 (7.6)	9 (9.8)		3 (6.4)	5 (10.6)	
Intermediate care or rehabilitation facility	14 (5.4)	21 (8.9)		7 (6.4)	10 (10.2)		5 (4.8)	7 (7.6)		2 (4.3)	4 (8.5)	
Transfer to secondary hospital	37 (14.1)	30 (12.6)		11 (10.0)	15 (15.3)		17 (16.2)	12 (13.0)		9 (19.2)	3 (6.4)	
LOS at secondary hospital, median (IQR), d	28 (14–53)	29 (19–54)	0.96	40 (22–54)	35 (19–56)	0.92	27 (14–52)	28 (17–31)	0.84	21 (15–42)	19 (7–56)	0.61

Study hospital LOS and duration of MV were obtained from the trial clinical data collection (*n* = 793, *n* = 398 in the iNO group, and *n* = 395 in the placebo group). Study hospital costs were obtained from analysis of detailed hospital bills (*n* = 631, *n* = 319 in the iNO group, and *n* = 312 in the placebo group). Data on postdischarge resource use were collected via telephone interview and at the in-person evaluation at 1 year of corrected age. Postdischarge resource use and cost values were calculated per hospital survivor.

[a] Costs are presented in thousands of 2008 US dollars.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

(Continued)

	All			500–749 g			750–999 g			1000–1250 g		
	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*
Study hospital												
Outpatient physician visits per subject in first 12 mo, median (IQR)	14 (9–20)	14 (9–21)	0.94	13 (9–20)	13 (9–19)	0.76	15 (10–20)	14 (10–21)	0.98	13 (8–22)	15 (9–21)	0.78
Subjects with ED visits in first 12 mo, *n* (%)	136 (53.8)	109 (48.2)	0.23	59 (54.6)	45 (48.4)	0.38	52 (51.0)	40 (45.5)	0.45	25 (58.1)	24 (53.3)	0.65
Subjects readmitted to the hospital in first 12 mo, *n* (%)	116 (45.8)	97 (42.9)	0.52	59 (54.6)	42 (45.2)	0.18	42 (41.2)	34 (38.6)	0.72	15 (34.9)	21 (46.7)	0.26
LOS per readmission, median (IQR), d	3 (1–6)	3 (2–6)	0.55	3 (1–6)	2 (1–5)	0.79	3 (1–6)	4 (2–8)	0.12	3 (2–7)	3 (2–4)	0.69
ICU use during readmission, *n* (% of rehospitalized subjects)	40 (34.5)	32 (33.0)	0.82	21 (35.6)	16 (38.1)	0.8	14 (33.3)	11 (32.4)	0.93	5 (33.3)	5 (23.8)	0.71
MV during readmission, *n* (% of rehospitalized subjects)	25 (21.6)	18 (18.6)	0.59	12 (20.3)	8 (19.0)	0.87	10 (23.8)	7 (20.6)	0.74	3 (20.0)	3 (14.3)	0.68

Study hospital LOS and duration of MV were obtained from the trial clinical data collection (*n* = 793, *n* = 398 in the iNO group, and *n* = 395 in the placebo group). Study hospital costs were obtained from analysis of detailed hospital bills (*n* = 631, *n* = 319 in the iNO group, and *n* = 312 in the placebo group). Data on postdischarge resource use were collected via telephone interview and at the in-person evaluation at 1 year of corrected age. Postdischarge resource use and cost values were calculated per hospital survivor.

[a] Costs are presented in thousands of 2008 US dollars.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

(Continued)

	All			500–749 g			750–999 g			1000–1250 g		
	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*
Study hospital												
Costs, median (IQR)[a]												
Birth hospital different from study hospital (*n* = 169)	0.7 (0.5–0.9)	0.8 (0.5–1.3)	0.16	0.6 (0.5–0.7)	0.6 (0.4–1.1)	0.97	0.7 (0.4–0.8)	0.8 (0.5–1.5)	0.07	1.0 (0.7–1.2)	1.1 (0.8–1.3)	0.37
Study hospital												
All (*n* = 631)	188.4 (108.1–292.6)	181.1 (90.8–289.2)	0.39	240.4 (110.0–345.1)	197.1 (74.8–304.4)	0.08	178.3 (121.9–271.5)	191.5 (109.0–289.0)	0.99	128.0 (72.6–167.1)	124.1 (86.7–222.1)	0.37
Survivors (*n* = 494)	217.7 (140.4–304.0)	215.3 (145.9–311.2)	0.7	260.6 (190.5–365.1)	265.7 (186.4–329.1)	0.66	194.6 (139.4–282.1)	199.4 (136.1–294.0)	0.88	133.4 (80.1–172.4)	145.9 (95.7–229.7)	0.24
Nonsurvivors (*n* = 137)	51.6 (28.9–92.0)	49.1 (24.1–97.9)	0.64	61.0 (41.1–125.4)	45.3 (18.7–99.1)	0.06	26.6 (12.9–50.3)	61.8 (30.9–109.0)	0.03	35.9 (28.9–38.9)	51.4 (20.3–86.7)	0.37
Secondary hospital or other medical facility prior to discharge home (*n* = 102)	40.8 (33.0–94.2)	44.7 (24.5–82.4)	0.46	58.8 (27.2–104.6)	44.8 (23.1–113.0)	0.61	40.8 (33.0–87.1)	49.4 (25.8–70.6)	0.65	42.4 (29.9–58.8)	39.4 (25.8–44.7)	0.55
Total postnatal hospitalization	195.0 (122.6–305.1)	195.0 (97.3–294.7)	0.35	243.5 (112.8–358.8)	216.5 (79.7–312.2)	0.1	193.0 (138.9–282.8)	197.8 (130.8–290.9)	0.99	134.0 (90.5–186.8)	125.0 (90.0–229.5)	0.86

Study hospital LOS and duration of MV were obtained from the trial clinical data collection (*n* = 793, *n* = 398 in the iNO group, and *n* = 395 in the placebo group). Study hospital costs were obtained from analysis of detailed hospital bills (*n* = 631, *n* = 319 in the iNO group, and *n* = 312 in the placebo group). Data on postdischarge resource use were collected via telephone interview and at the in-person evaluation at 1 year of corrected age. Postdischarge resource use and cost values were calculated per hospital survivor.

[a] Costs are presented in thousands of 2008 US dollars.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

(Continued)

	All			500–749 g			750–999 g			1000–1250 g		
	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*	iNO	Placebo	*P*
Study hospital												
Total costs after postnatal hospitalization	21.9 (12.0–43.1)	21.1 (12.7–40.0)	0.96	25.2 (13.9–46.7)	21.1 (12.4–37.5)	0.13	22.5 (11.8–43.6)	22.5 (14.5–37.6)	0.72	13.7 (9.7–33.0)	20.0 (12.3–46.1)	0.09
Total costs from birth to 1 y corrected age												
All (*n* = 544)	235.8 (130.4–333.8)	198.3 (99.1–335.9)	0.19	270.1 (103.8–376.7)	211.0 (68.3–337.5)	0.04	231.2 (159.1–315.9)	221.6 (133.3–350.1)	0.95	159.9 (103.0–214.2)	144.8 (102.6–262.3)	0.57
Survivors (*n* = 407)	260.3 (179.4–355.6)	265.7 (180.5–365.9)	0.87	314.8 (253.8–407.2)	304.6 (228.8–391.0)	0.49	238.4 (178.5–334.1)	251.4 (185.1–364.3)	0.71	169.5 (118.8–222.5)	172.1 (123.5–325.4)	0.39
Nonsurvivors (*n* = 137)	52.4 (29.9–92.0)	49.5 (24.5–98.3)	0.65	61.2 (41.1–125.4)	45.3 (18.7–99.1)	0.07	26.6 (13.2–50.7)	62.3 (30.9–109.4)	0.03	36.5 (29.9–38.9)	51.4 (21.0–87.3)	0.37

Study hospital LOS and duration of MV were obtained from the trial clinical data collection (*n* = 793, *n* = 398 in the iNO group, and *n* = 395 in the placebo group). Study hospital costs were obtained from analysis of detailed hospital bills (*n* = 631, *n* = 319 in the iNO group, and *n* = 312 in the placebo group). Data on postdischarge resource use were collected via telephone interview and at the in-person evaluation at 1 year of corrected age. Postdischarge resource use and cost values were calculated per hospital survivor.

[a] Costs are presented in thousands of 2008 US dollars.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

Nitric Oxide

- Soluable gas produced by Endothelial cells, Macrophages and some neurons.

- Acts in a Paracrine manner through induction of Cyclic guanosine monophosphate (CGMP).

Clinical Uses of Inhaled Nitric Oxide In The Neonate

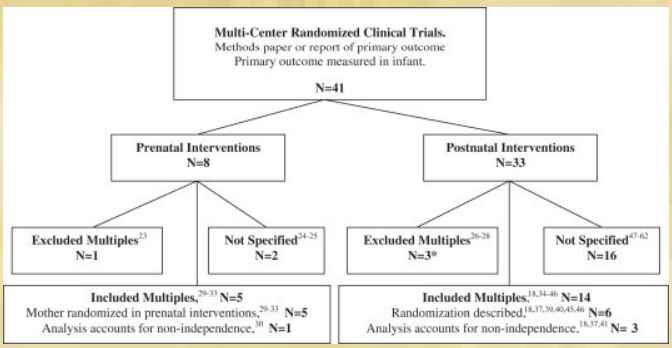


Figure Results of systematic review. The majority of studies excluded multiples or did not specify whether they were enrolled. Only the minority of studies enrolling multiples used statistics that accounted for the nonindependence of their outcomes. *Of the postnatal intervention trials that excluded multiples, 2 excluded all infants from a multiple gestation and 1 only included the first-born multiple.

Clinical Uses of Inhaled Nitric Oxide In The Neonate

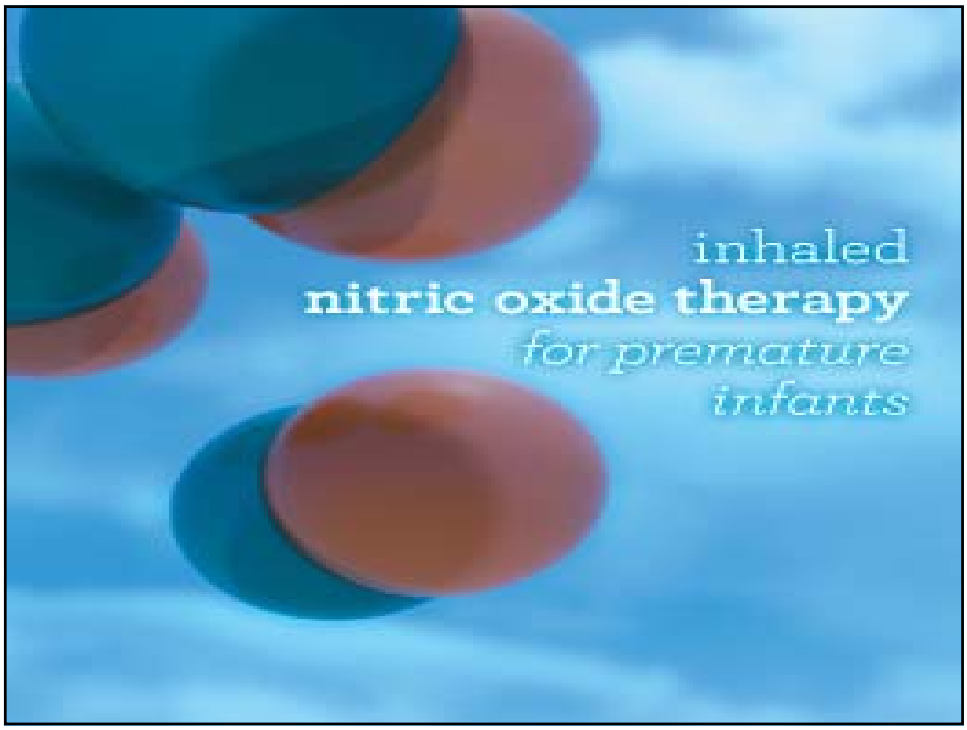
Nitric Oxide

-Plays important role in modulating vascular and cellular components of inflamation.

-Potent vasodilators
-Reduces platelet Aggregation
-Inherits mass cell inflamation

Clinical Uses of Inhaled
Nitric Oxide In The Neonate

Nitric Oxide
- Half life is seconds so it only acts on cells in close proximity to where it was formed.



SUNDAY, OCTOBER 24, 2010

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP
Co-Moderator (BOT Member) – James Kirk, DO, FACOP

10:30 am – 11:00 am

Neonatal Dermatology

Melinda F. Greenfield, DO

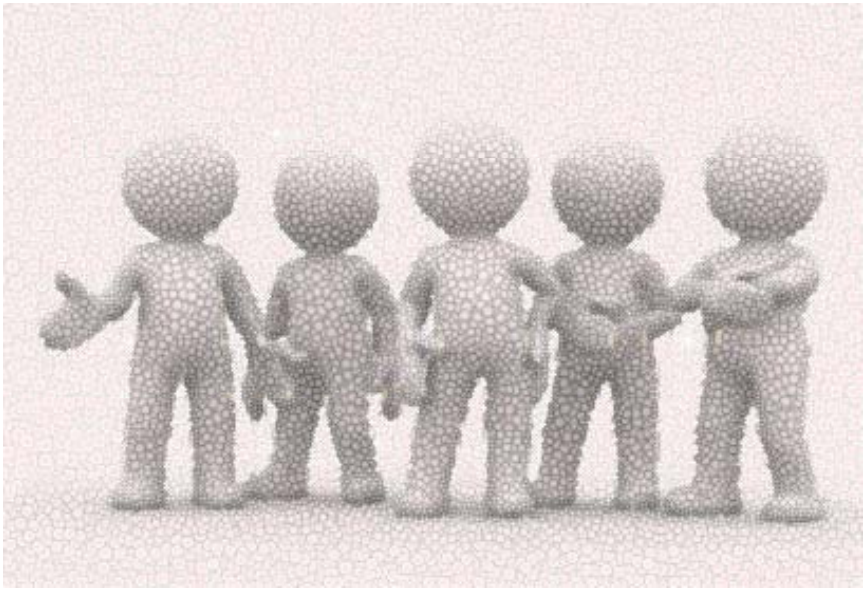
Objective: Upon completion of this lecture, the participant will be able to discuss differential diagnosis in infants with vesicles and pustules, including: herpes, varicella, transient neonatal pustular melanosis, neonatal acne, erythema toxicum neonatorum, and scabies.

NEONATAL DERMATOLOGY

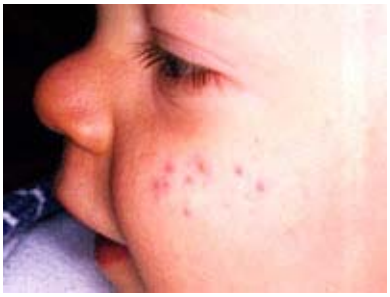
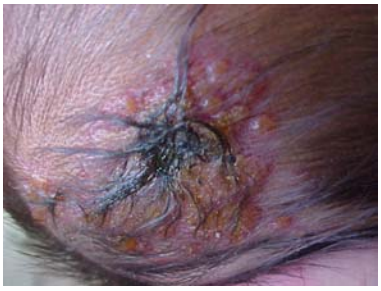
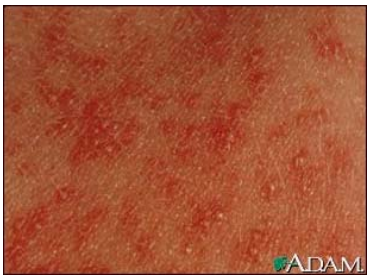
Melinda F. Greenfield, DO
Albany Dermatology Clinic
Albany, Georgia

Objectives

- Discuss differential diagnosis in infants with vesicles and pustules, including:
  - Herpes
  - Varicella
  - Transient neonatal pustular melanosis
  - Neonatal acne
  - Erythema toxicum neonatorum
  - Scabies
  - Etc.



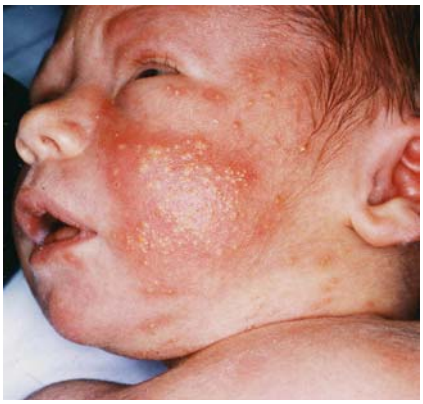
Evaluation of the neonate with pustules and vesicles

Pustules and vesicles-D/D

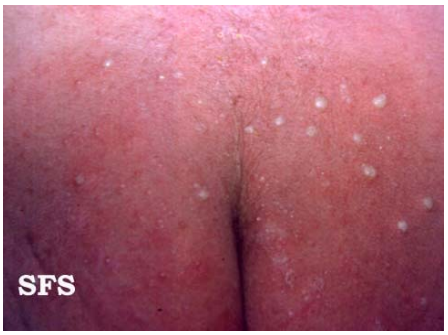
- HSV
- Erythema toxicum neonatorum
- Transient neonatal pustular melanosis
- Scabies
- Candidiasis
- Others……

2 day old with rash



- Rash started 24 hours after birth
- Yellow pustules on an erythematous base
- Lesions seen on face and trunk
- Lesions change hourly
- No constitutional symptoms

Erythema Toxicum Neonatorum

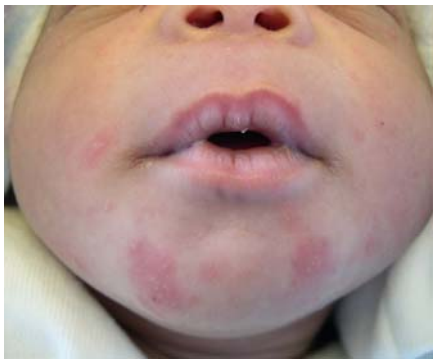


- ETN has been recognized for centuries
- Originally said to be ‘nature’s method of cleansing the child of the impure blood of the mother’
- Incidence up to 72% of neonates

Morgan AJ, Steen CJ, Schwartz RA, Janniger CK. Erythema Toxicum Neonatorum Revisited. Cutis. 2009;83;13-16

Erythema Toxicum Neonatorum

- No racial, ethnic, sexual or seasonal predilection
- Higher incidence in infants that are term, weighing more than 2500g



Erythema Toxicum Neonatorum

- Etiology is unknown but thought to be related to allergies due to the eosinophilic infiltrates
- Studies have found no relationship to family history of atopy
- Keitel and Yadav considered ETN “a transient adjustment reaction of the newborn skin to mechanical or thermal stimulation”

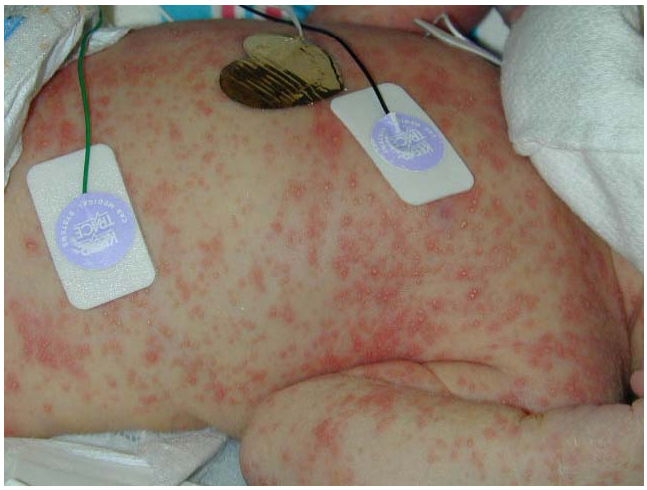
ETN

- A 2005 study, Marchini et al, looked at neonates with ETN using microbial cultures and scanning and transmission electron microscopy
- They found microorganisms (staph) localized to the follicular epithelium and internalized into surrounding immune cells
- Concluded that ETN is a cutaneous immune reaction to “an acute, transitory attack of the commensal microflora” that penetrate the newborn skin via hair follicles

Clinical Manifestations

- Self-limited
- Begins within 2 days of birth, resolves 6 days
- Can be papular or pustular
- Typically seen on face, trunk and thighs, sparing palms, soles and genitals-probably related to location of hair follicles
- Pustules are 2-4mm, composed of >50% eos

Erythema Toxicum Neonatorum



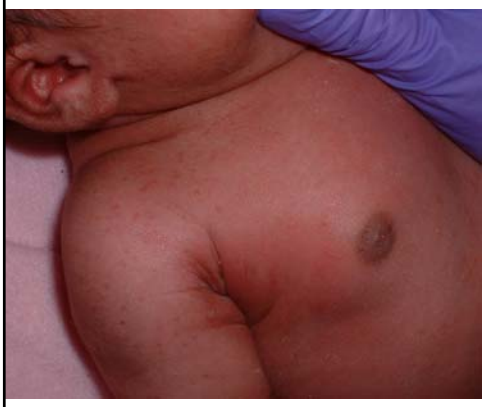
D/D ETN

- Acne neonatorum
- Candidiasis
- Infantile acropustulosis
- Incontinentia pigmenti
- Milaria crystallina
- Miliaria rubra
- Varicella/HSV
- Sepsis
- Transient neonatal pustular melanosis

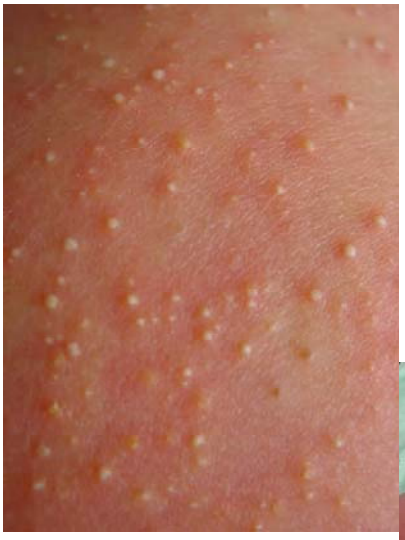
Treatment

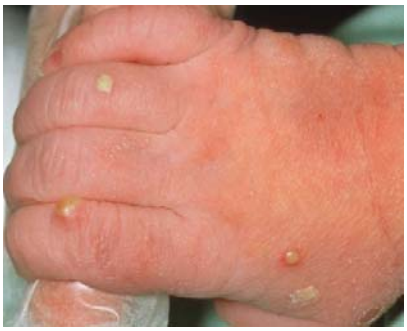
- Antihistamines as needed, however the rash is asymptomatic to the infant
- Reassurance to parents is usually all that is needed

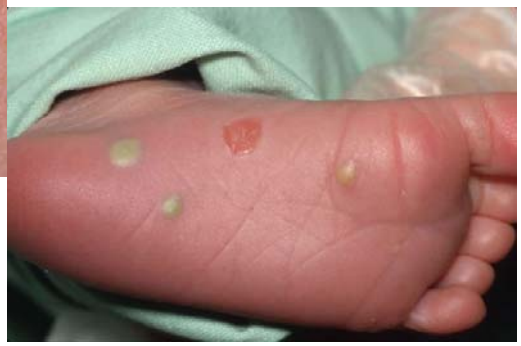
Newborn with rash



- 4 day old AA infant with 2 mm pustules and vesicles noted on face, trunk, palms and soles
- Developed on first day of life
- The lesions rupture leaving an area of discoloration behind



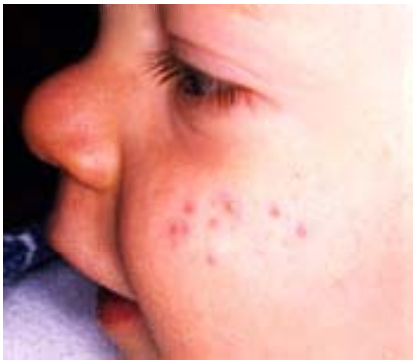




Transient Neonatal Pustular Melanosis

- Benign idiopathic condition
- Present at birth
- Resolve within 48 hours
- Lesions seen on face, neck, trunk, palms and soles
- Incidence: 0.6% cauc, 4.4% AA infants
- More common in term infants
- Self-limiting
- No treatment is necessary

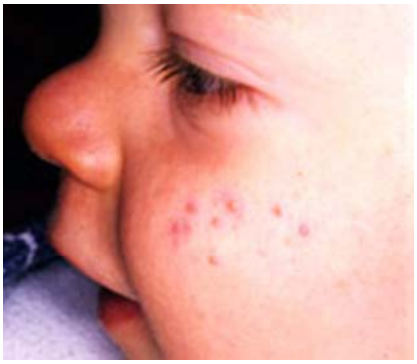
Infant with rash on face



- Lesions on face since 2 weeks of age
- More lesions are developing
- Does not seem to bother child but parents are very unhappy
- Mom tx with otc hydrocortisone cream

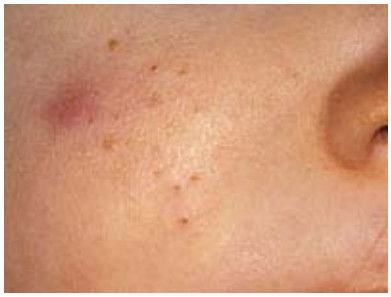
Benign Cephalic Pustulosis

- Aka neonatal acne
- Has the appearance of acne but comedonal lesions are absent
- Yeast based folliculitis triggered by *Malassezia sympodialis* or *furfur*
- Seen in first 2-3 weeks of life
- Lesions are found on the face, neck, scalp and torso
- No treatment is necessary, but ketoconazole 2% can be used



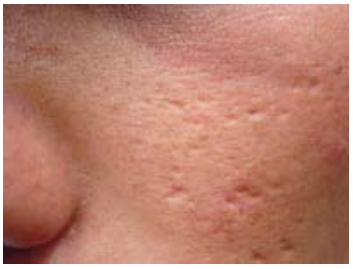
Piggott CD, Eichenfield LF. Overcoming the challenges of pediatric acne. Practical Dermatology 2010;17-18

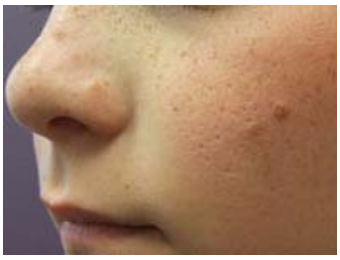
Infantile Acne



- True infantile acne affects the cheeks, occasionally the forehead and chin
- Associated with comedones, papules and pustules
- 6 months to 3 years
- More common in boys

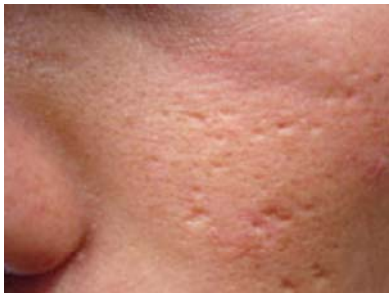
Infantile Acne





- Thought to have a genetic component
- Most cases are mild and resolve within a few months
- Severe cases can result in scarring
- Treatments include topical retinoids, benzoyl peroxide, and antibiotics

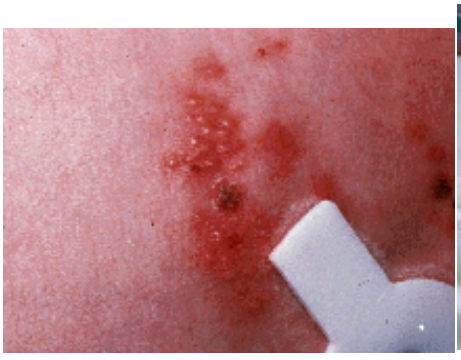
Infantile Acne

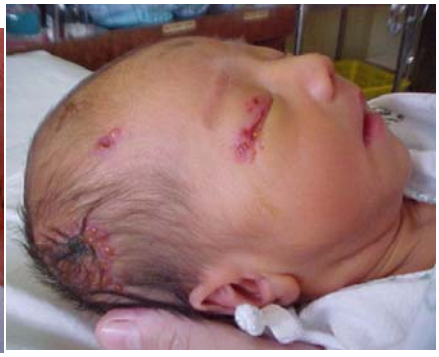


- Rare, severe cases have been treated with isotretinoin
- In a limited study conducted by Barnes and Eichenfield , isotretinoin used within a range of 0.2mg-1.5mg/kg/day was found to be safe and effective
- This would be considered 'very off-label' use

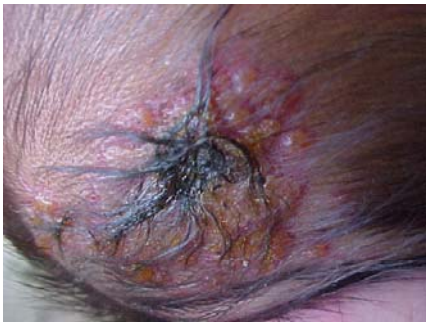
Barnes CJ, Eichenfield LF, et al. A practical approach for the use of oral isotretinoin for infantile acne. Pediatric Dermatology 2005;22;166-169

Newborn with vesicles



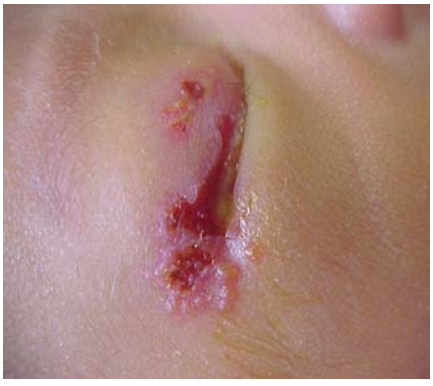


Newborn with vesicles



- Vesicles were noted on face, scalp and trunk of a newborn infant
- What is your biggest concern for this infant?

Neonatal HSV infection

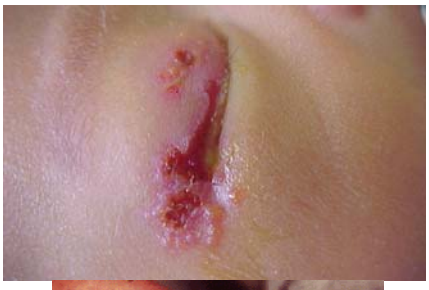


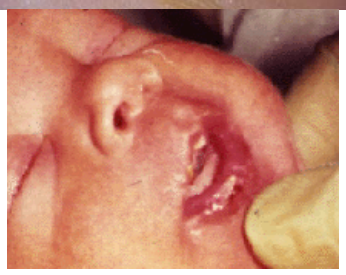
- Neonatal HSV occurs in 1: 2500-5000 deliveries
- 70% due to HSV-2, 30% HSV-1
- Usually seen in first or second week of life
- Neonates have highest risk of developing encephalitis and dissemination

Neonatal HSV

- 80% are born to mothers who do not know they have an HSV infection
- 85% are transmitted during delivery through contact with lesions on cervix or vaginal secretions
- 3 associated syndromes:
  - ✓skin, eye & mouth disease
  - ✓CNS disease
  - ✓disseminated disease

Skin, eye & mouth disease





- Most recognizable form
- Can be seen anywhere but typically in areas of trauma, like the scalp
- Low mortality if it does not progress to CNS
- 90% recurrence rate
- Can result in delayed development

CNS HSV

- Presents by 3rd week of life
- Only 60% will have skin lesions
- Untreated, has 50% mortality
- Prompt treatment, 18% mortality
- Diagnosis must be entertained in any infant with s&s of encephalitis (seizures, apnea, bradycardia, cranial nerve abnormalities)

CNS HSV

- CSF findings are non-specific
- Prompt initiation of therapy must be started while diagnosis is being pursued
- 2/3 (of survivors) will have neurologic impairment even if treatment is given

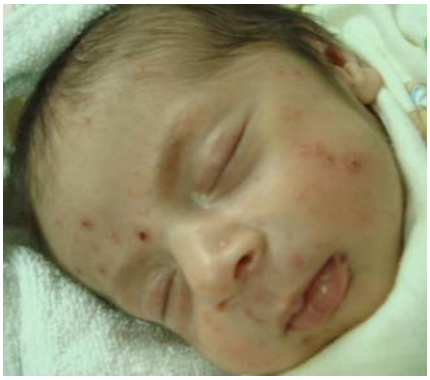
Disseminated HSV

- Usually presents in first week of life
- All organs are susceptible
- Cutaneous lesions may not be present
- Diagnosis should be considered in any infant who has a clinical picture of sepsis and does not respond to antibiotics or who has both pneumonitis and hepatitis
- Without treatment mortality>80%
- With treatment 50-60%

Factors that increase risk of neonatal HSV disease

- Primary HSV infection (risk is 10-20x greater)
- Especially if acquired late in pregnancy
- Membranes ruptured>4 hours
- Prematurity
- Trauma (fetal scalp monitors)

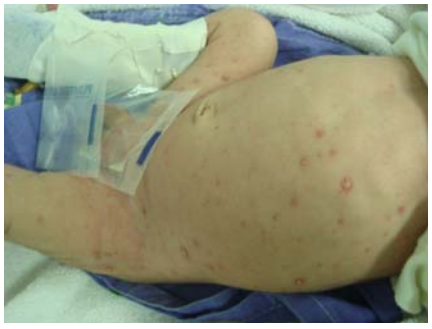
Newborn with vesicular rash



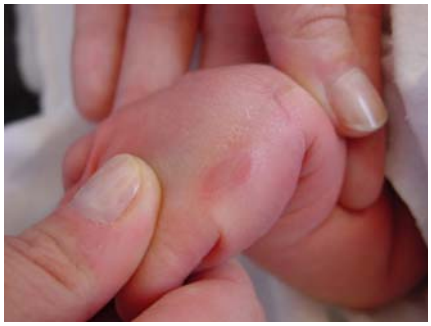
- Rash developed 1-2 weeks after birth
- Mother had similar rash at end of her pregnancy but her rash was very mild and she never told her doctor about it

Neonatal Varicella

- Usually acquired from maternal infection during last 3 weeks of pregnancy
- 20% mortality rate if mother has lesions 4 days before to 2 days after delivery



Blisters at Birth

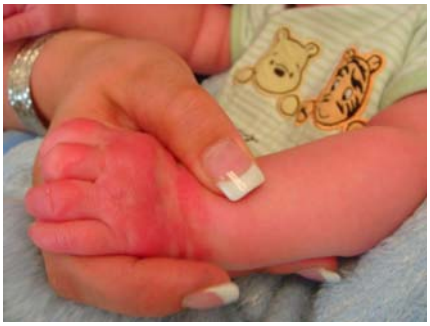


- This blister was present at birth to an otherwise healthy term infant

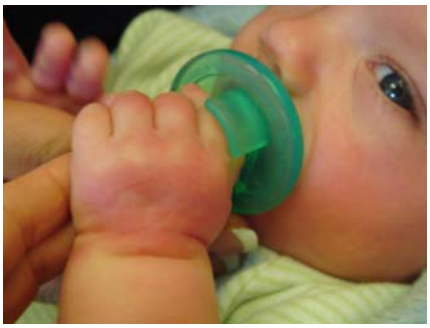
Sucking blister

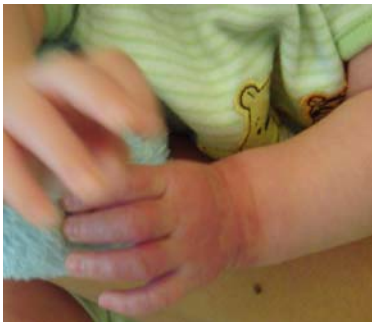
- Present at birth
- Dorsal hand and wrist
- Infant tends to have excessive sucking activity
- No treatment necessary

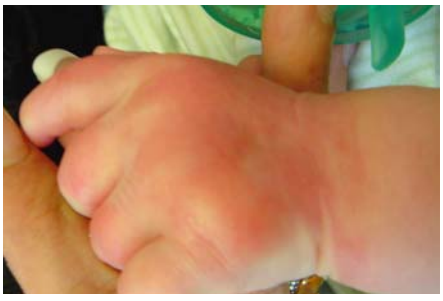
Blisters on hand



- 1 month old developed large blisters on bilateral hands
- No constitutional symptoms
- Twin died in utero
- Born 6 weeks premature







Blisters on hand

- Mother describes area as rapidly developing blisters overnight after noticing some initial redness before bed
- Went to pediatrician who sent her to burn center in Augusta
- Was accused of burning the baby- hot water immersion of hands, due to areas of sparing
- Child services and police were called

Blisters on hands

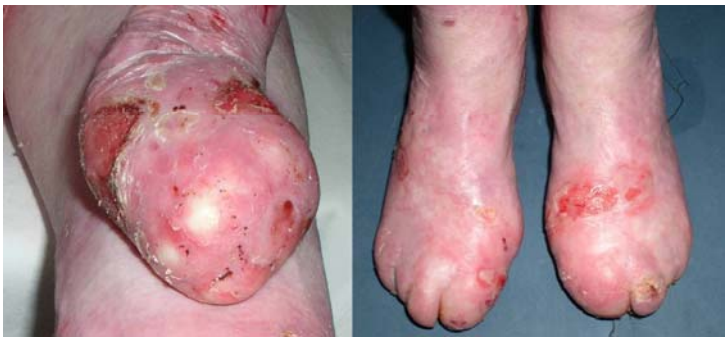
- Mom came to us in desperation, fearful that baby would be taken away
- Biopsy obtained of intact, erythematous skin
- No blisters were present
- Biopsy with direct immunofluorescence showed Epidermolysis bullosa

Epidermolysis Bullosa

- Group of inherited diseases characterized by blistering lesions on skin, mucosa
- Usually occur at sites of friction/trauma
- Usually occurs at birth or shortly after
- Males and females equally affected
- Autosomal dominant and recessive forms
- 3 major types based upon layer of involvement within the skin

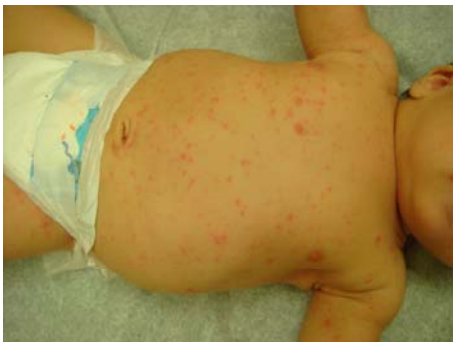
Types of EB

Type of EB	Site of blister formation within skin
EB Simplex	Epidermis (keratinocytes)
Junctional EB	Lamina lucida within the basement membrane zone (between epid/ dermis)
Dystrophic EB	Lamina densa and upper dermis

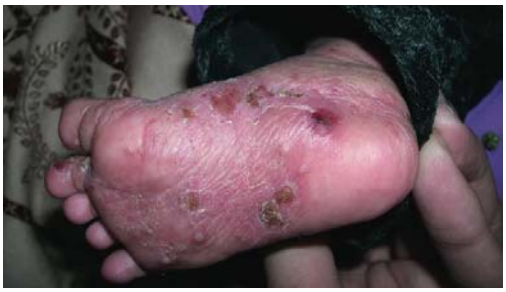


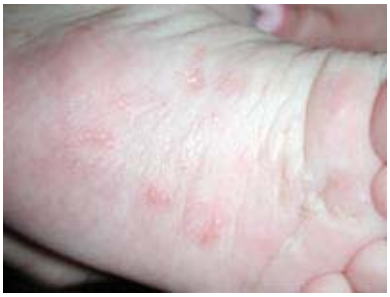
Epidermolysis Bullosa

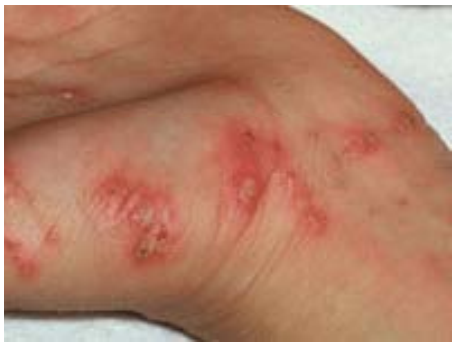
Pustular rash with poor feeding

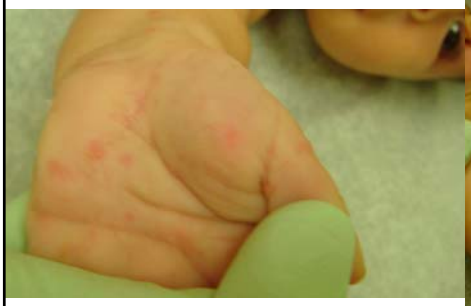


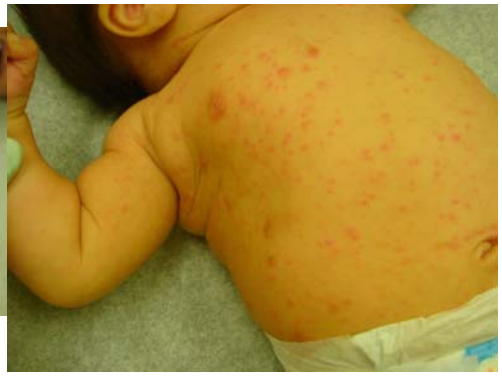
- Infant with several week history of pustules and vesicles on body hands/feet
- Poor feeding/weight gain has been noted

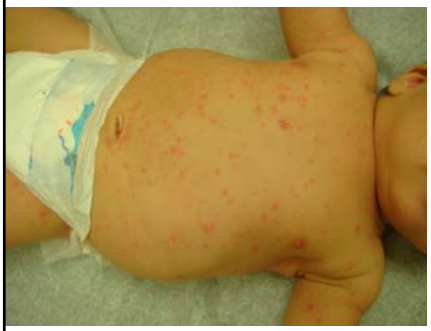


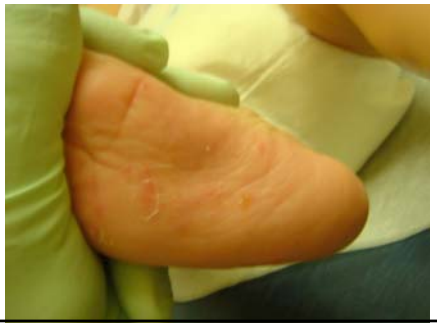




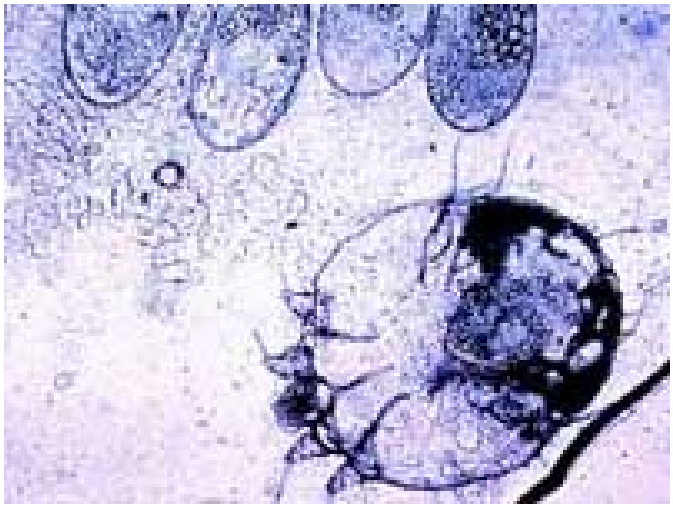








Scabies

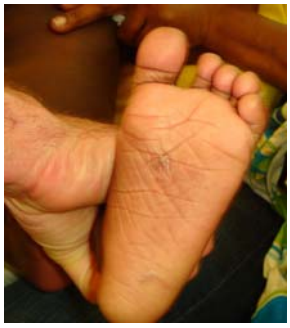


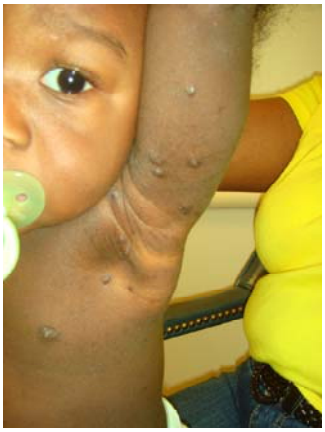
Scabies

- 300 million cases/year worldwide
- Transmitted skin to skin or via fomites
- Can take up to 10 weeks to show signs, even though patient is contagious
- Typical infestation is 10-12 adult mites
- Rarely seen on face and scalp except for infants/ elderly
- Blisters and pustules on palms and soles are characteristic of scabies in infants

Scabies

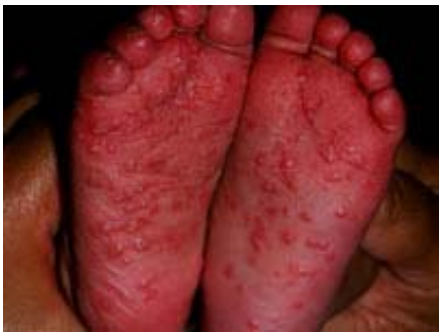
- Pruritic nodules in axillae or groin are a common finding of long-standing scabies



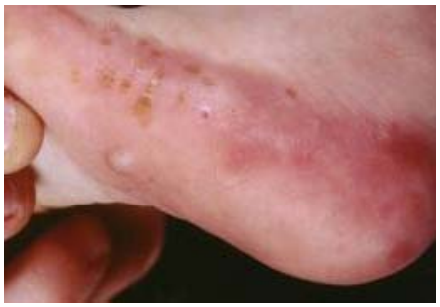


Infant with itchy hands and feet

- Infant with few week history of red papules on hands and feet, slowly evolving to vesicles and pustules
- Lesions are pruritic
- No one else in house itching



Acropustulosis of infancy

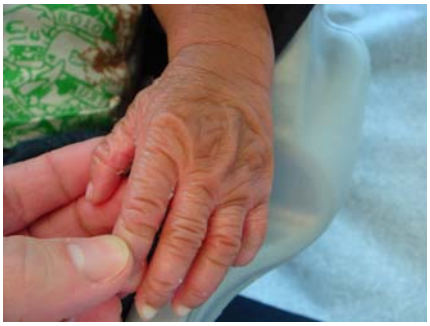
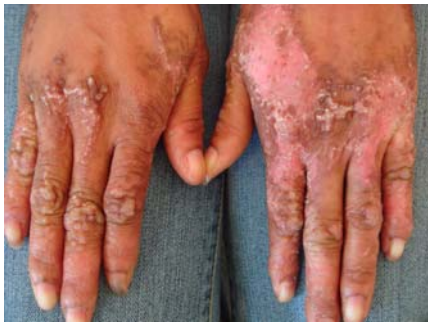


- Seen in first 2-3 years of life
- Can last months-years
- Sometimes preceded by scabies-may be an allergic rxn to the mite
- Tends to wax and wane over time

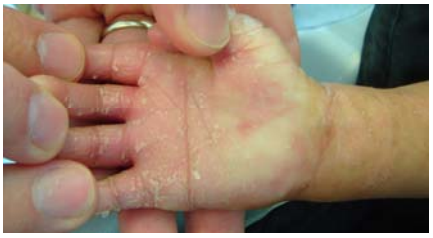
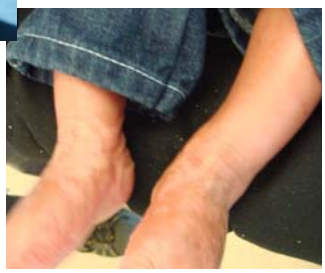
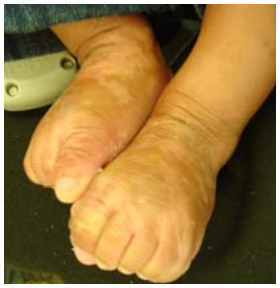
Acropustulosis of Infancy

- Children tend to be irritable and uncomfortable
- Bouts last 7-15 days, recur in 2-4 week intervals
- Intensity of attacks diminish over time
- Seen mostly in African American males
- Treatment: high potency steroids/dapsone

Make The Diagnosis

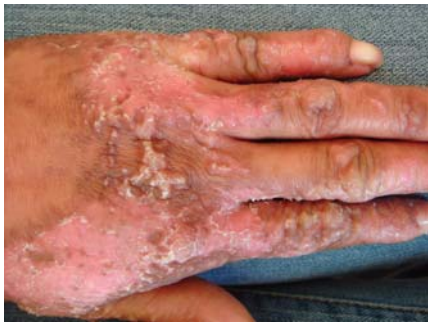



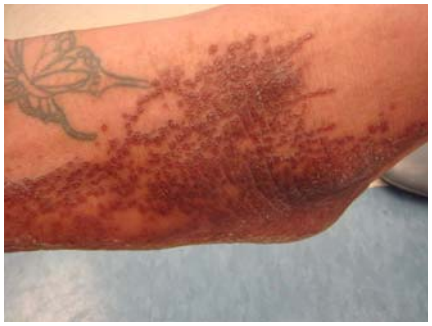
Infant

Mom

STARFISH KERATOSIS

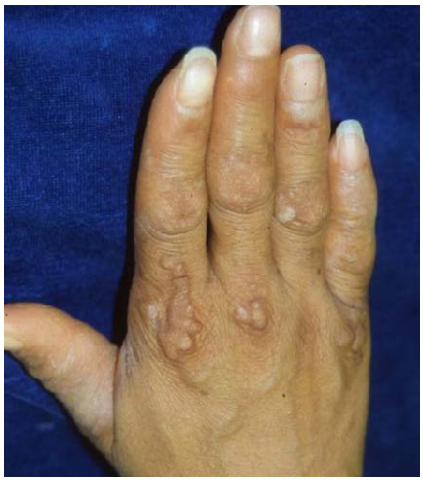


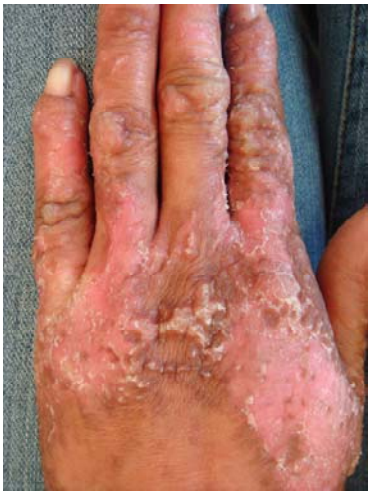


Mutilating Keratoderma (Vohwinkel)

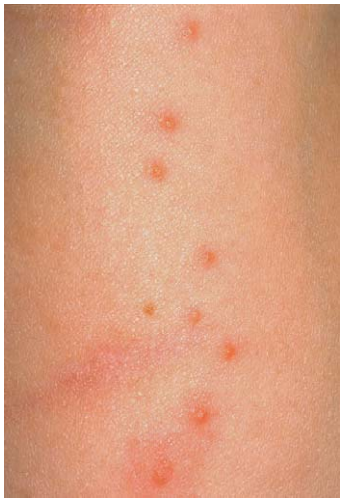
- Classic example of severe, diffuse, hereditary palmoplantar keratoderma
- Present in early childhood with redness of palms and soles, which gradually thicken and develop a waxy, yellowish appearance
- Vohwinkel syndrome is autosomal dominant and associated with ‘starfish’-shaped thickenings over knuckles, tight bands around fingers which can result in amputation and deafness

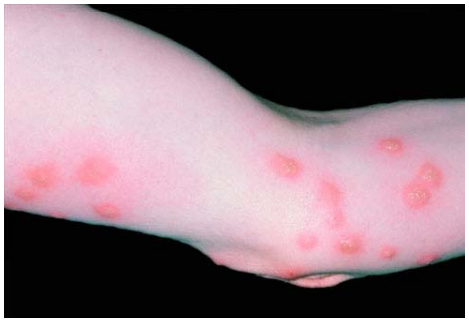
Starfish Keratosis





Rash After Vacation





BED BUGS!!!

Bedbugs

- Orkin has reported an increase in bed bug treatments. Up to 5,800 in 2009 from 250 in 2007
- Other sources estimate infestations are up 5000% since 2000
- They have treated properties in 48/50 states, all except Alaska and Montana
- One pest control company stated that Cincinnati was the most infested city, while another one gave New York the #1 spot

Bed Bugs-Prevention

- Check your mattress, if you see bed bugs, ask to be moved to another room
- Keep luggage off the floor and use the luggage rack
- Don't put clothing in the dressers or lay on the floor
- Wash all clothes in warm water upon returning home, otherwise you can infest your house
- Search sites like bedbugregistry.com to check for contaminated hotels
- Extermination can cost hundreds to thousands of dollars!!

Bedbugs

- The organisms: *Cimex lectularis* in the USA and *Cimex hemipterus* outside the USA
- The lesions can become severely inflamed or secondarily infected
- Bed bugs feed on human blood but don't transmit disease in the USA
- In Brazil they transmit *Trypanosoma cruzi*, the organism responsible for Chagas disease

Guess What Luxury NYC Hotel May Have Bed Bugs?

References

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SUNDAY, OCTOBER 24, 2010

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP
Co-Moderator (BOT Member) – James Kirk, DO, FACOP

11:30 am – 12:30 pm

Fetal Therapy: Here and Now - aka What's Crazy, Sexy and Cool

Garrett Lam, MD

Objective: Upon completion of this lecture, the participant will be able to identify specific fetal issues potentially amenable to fetal therapy, understand the moral dynamic that overlies fetal therapy procedures, and determine what characteristics make up a true fetal therapy center.

SUNDAY, OCTOBER 24, 2010

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP
Co-Moderator (BOT Member) – James Kirk, DO, FACOP

2:00 pm – 3:00 pm

Newborn Jaundice: Alerts, Evidence and Practice

Vinod K. Bhutani, MD

Objrctive: Upon completion of this lecture, the participant will be able to review the impact of 2009 AAP Expert Panel *Guidelines for Management of Jaundice*, review the clinical consequences of unmonitored and untreated newborn jaundice, and understand the vital role of lactation support for a safe experience with newborn jaundice.

Case Discussions: Five cases will be presented to highlight alert, evidence and guideline: Review a clinical case of newborn jaundice that progresses, identify the potential area of lapses in care that could lead to adverse outcome, and apply this analysis to a systems approach for a safer approach to newborn jaundice.

Newborn Jaundice: Evidence and Experience

Vinod K. Bhutani, MD, FAAP
Lucile Packard Children's Hospital,
Stanford University School of Medicine

Lucile Packard Children's Hospital AT STANFORD

We will review

- Management of jaundice in term and late preterm infants
  - I. Biology of hyperbilirubinemia
  - II. Clinical consequences
  - III. Current evidence
  - IV. Current recommendations
  - V. Clinical Interventions

I have no financial disclosures or conflicts of interest

A clinical case of

- A 5 day old well baby with TSB of 19 mg/dL
  - Repeat bilirubin in 24 hours
  - Place infant in sunlight
  - Supplement with formula
  - Start home phototherapy
  - Admit for urgent phototherapy
  - Call NICU, prepare for an exchange

A societal case of

- "My 13 year old son was a late preterm baby at 37 weeks"
- "He was yellow; the docs did not want to worry me"
- "His first bilirubin was 28 at age 6 days."

- Intervention
- Outcome:
  - Age 3 years
  - Age 7 years
  - Age 13 years

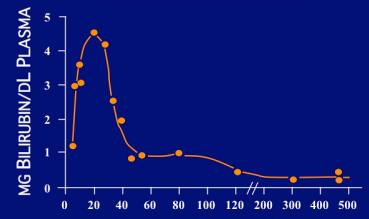
Phase 1

- Management of jaundice in term and late preterm infants
  - Biology of hyperbilirubinemia

The message of

The biology of

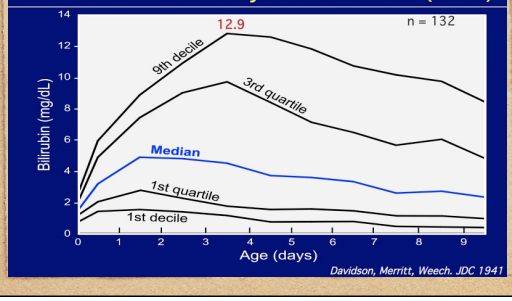
Neonatal Bilirubin Profile in RHESUS MONKEYS



STANFORD SCHOOL OF MEDICINE

The biology of

Pattern and Distribution of Day-specific Serum Bilirubin Levels in Healthy Term Newborns (1941)

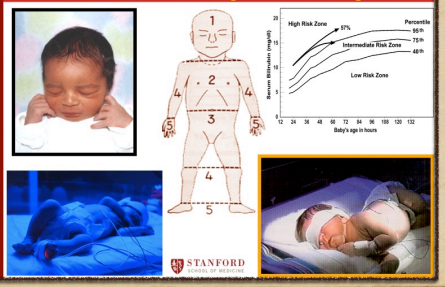


Davidson, Merritt, Weech. JDC 1941

The biology of

Newborn Jaundice: Diagnosis, Management

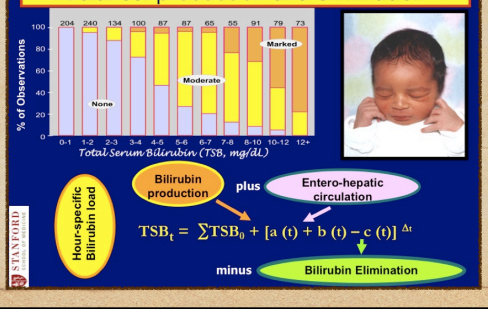
COMPOSITE VIEW



STANFORD SCHOOL OF MEDICINE

The biology of

Balance: production and elimination



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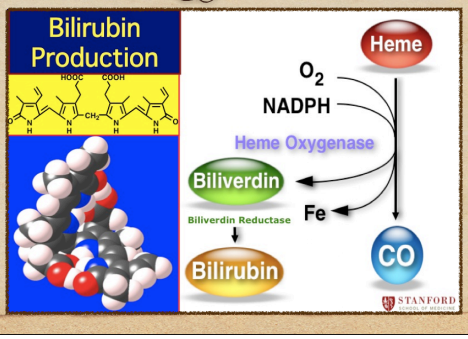
The biology of

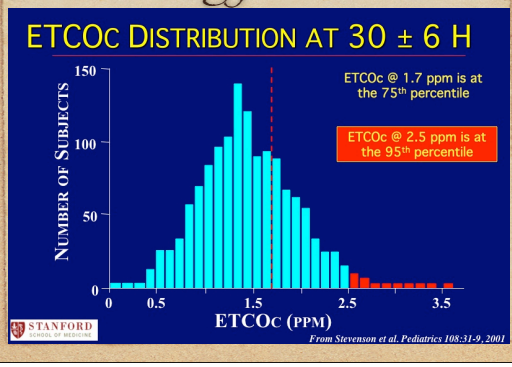
Bilirubin Production



STANFORD SCHOOL OF MEDICINE

The biology of

ETCOc DISTRIBUTION AT 30 ± 6 H

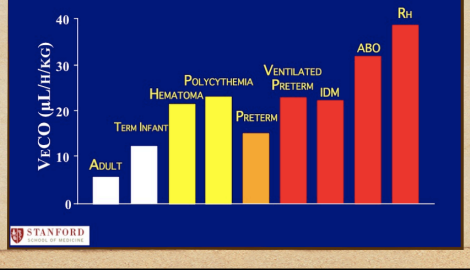


STANFORD SCHOOL OF MEDICINE

From Stevenson et al. Pediatrics 108:31-9, 2001

The biology of

Neonatal conditions with increased bilirubin production



STANFORD SCHOOL OF MEDICINE

The biology of

Desegregation of unbound bilirubin: Review of Law of mass action

$$UB = \frac{k_1 \cdot a\text{TSB}}{k_2 \cdot [\text{Albumin} - (\alpha\text{TBC})]} \cong \frac{\text{TSB}}{K \cdot a}$$

$$\frac{k_2}{k_1} = K$$

UB = Unbound or Free Bilirubin
k_1=Dissociation rate constant
k_2 =Association rate constant
K = Equilibrium (association) Constant
TSB = Total bilirubin concentration
α = Fraction of bilirubin albumin bound ≈1
a = Albumin – (αTBC)

The biology of

Relationship between TSB, UB and serum albumin (A)

At a given TSB, UB is inversely proportional to albumin (A) and its intrinsic ability to bind bilirubin (K).

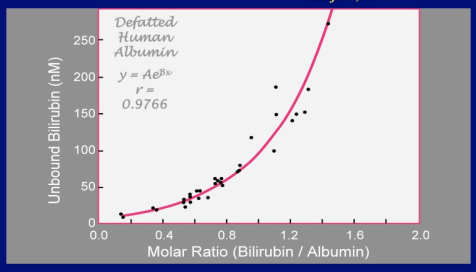
$$UB = \frac{TSB}{(A \sim TSB) \times K}$$

Given the same UB and K, an infant with an albumin level of 4 gm/dL will have a TSB twice as high as a newborn with 2 gm/dL albumin. However, the "driving force" (UB) sending bilirubin to tissue sites will be nearly identical. In other words, given identical values K, an infant with a TSB of 15 mg/dL and albumin of 2 gm/dL will have nearly the same risk for bilirubin toxicity as an infant with TSB 30 mg/dL and albumin of 4 gm/dL.

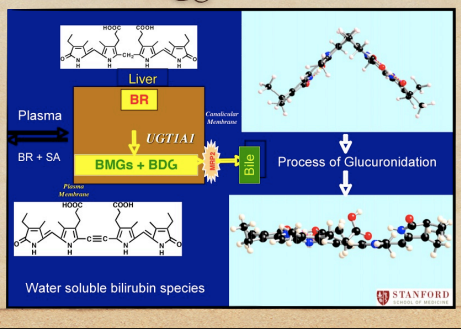
The biology of

Unbound Bilirubin by the Peroxidase Technique

Ahlfors, 1996



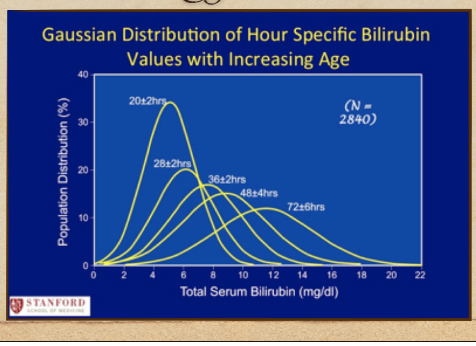
The biology of



STANFORD SCHOOL OF MEDICINE

The biology of

Gaussian Distribution of Hour Specific Bilirubin Values with Increasing Age



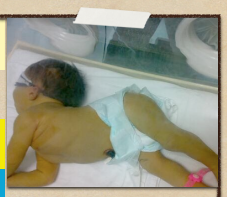
STANFORD SCHOOL OF MEDICINE

Phase II

- Management of jaundice in term and late preterm infants
  - Clinical Consequences

The worry of

Newborn Jaundice	>80%
Bilirubin >95th %ile	8 to 11%
Bilirubin >342 µmol/L	2,000/100,000
Use of Phototherapy	4-8,000/100,000
Exchange Transfusion	50-70/100,000
Bilirubin >513 µmol/L	25-60/100,000



Acute Kernicterus: 5-10/100,000 live-births

The worry of

Collaborative Perinatal Project - 1959 to 1966

A Seven-Year Neurological Follow-up of:

54,795 Total live births

41,324 Excluding multiple births, BW < 2500g, Unk BW, No SB levels, Died < 1 yr, Only black or white race

41,324 90% >37 wks GA, 70% bottle fed,

40,993	(99.2%) peak SB	<20mg/dl	0.3% Rx ExTx
323	(0.8%) peak SB	≥20mg/dl	53.0% Rx Ex Tx
66	(0.16%) peak SB	≥25mg/dl	± 85% Rx Ex Tx

The worry of

Collaborative Perinatal Project (cont'd)

Number of Infants by Bilirubin Category with Abnormal Seven Year Neurologic Exam *

uM/L	mg/dl	Number	%
≤ 171	< 10.0	1090	3.7
171-255	10-14.9	116	4.0
256-341	15-19.8	43	4.9
≥ 342	≥ 20	12	4.5

P (trend, unadjusted) 0.06

Adjusted odds ratio (OR) per bilirubin category 1.10

95% confidence interval..... 0.98, 1.23

**1261 / 34299 (3.7%) of those examined*

The worry of

Collaborative Perinatal Project (cont'd)

Number of Infants by Bilirubin Category with Abnormal or Suspicious 7 Year Neurologic *

uM/L	mg/dl	Number	%
< 171	<10.0	4346	14.9
	10-14.9	472	16.9
	15-19.8	157	18.0
≥ 342	≥ 20.0	60	22.4

P (trend, unadjusted) ..... <0.001

Adjusted odds ratio per bilirubin category 1.12

95% confidence limits 1.06, 1.20

5035 / 34299 (14.7%) of those examined

The worry of

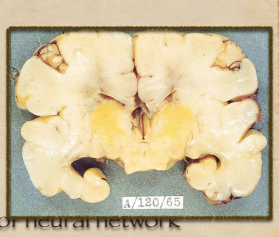
Collaborative Perinatal Project Outcome

Association of abnormal or suspicious neurologic findings with stepwise increase in peak serum bilirubin levels

	Probability
Gait abnormalities	<0.001
Awkwardness	<0.001
Equivocal Babinski	<0.001
Failure at fine stereognosis	0.008
Questionable hypotonia	0.005 to 0.07
Gaze abnormalities	0.001 to 0.05
Vasomotor abnormalities	0.005
Abnormal abdominal reflexes	0.008
Abnormal cremasteric reflexes	0.001

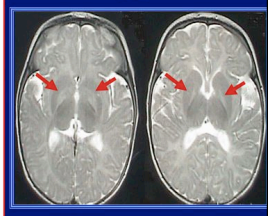
The injury of

- Globus Pallidus
  - Classic
- VIII nerve
  - Isolated
- Global
  - Perturbation of neural network integrity



Kernicterus: An Adverse Outcome of Untreated Severe Hyperbilirubinemia

- Post-icteric Sequelae
  - Athetoid Cerebral Palsy
    - Hypertonia and/or hypotonia
    - Chore-athetosis
    - Sensori-neural hearing impairment
    - Upward gaze abnormalities
    - Enamel dysplasia of deciduous teeth
    - Other cranial lesions
    - Cerebellar involvement
    - Hippocampal involvement



MRI evidence of Kernicterus

Perturbations of developmental events on neuronal integrity

- Evidence of altered neurogenesis, loss of dendrites and axons, with changes of neurite patterning and deficient synaptic wiring emerge over time:
  - a) mental retardation during childhood
  - b) schizophrenia
  - c) dementia during early adulthood
- Other perinatal conditions that have similar long-term impact, include: 1. sepsis/inflammation; 2. hypoxia/ischemia; 3. iron deficiency.

Does bilirubin impair maturation of neuronal network activity?

- Clinical Reports of "minimal cerebral damage" in infants who did not sustain kernicterus: Gervais and Day, 1951
- "Minimal Cerebral Damage" in infants with prolonged exposure to bilirubin and low bilirubin binding: Boggs and Johnson, 1981.
- In vivo model of kernicterus (Gunn rat model): Cerebellar hypoplasia with reductions in the volume and number of neurons were detected.
- Newborn Autopsy: Neuronal necrosis of pyramidal cell layer of hippocampus with kernicteric changes.

Perturbations in developmental sequence can cause neurodevelopmental disorders

- Axonal elongation: for proper formation of neural circuits are dependent on growth cones
- Growth cones: can suffer retraction or collapse promoting mild to severe alterations of neuronal arborization.
- Dendritic spines: abnormalities in number, size, and morphology

Summary of in vitro studies that UCB:

- reduce viability of proliferating neural precursors
- decrease neurogenesis: no effect on astrogliogenesis
- increase cellular dysfunction (differentiating cell)
- decrease dendritic and axonal branches with 3-9 days of in vitro exposure
- leads to a smaller neuron growth cone area
- decrease density of dendritic spines and synapses

Early bilirubin exposure of developing neurons: neuritic atrophy, cell death, decreased neuronal arborization, arrested neuritic growth and neuritic hypoplasia [Brites et al, 2009]

Clinical Impact

- Neuro-developmental consequences of moderate hyperbilirubinemia are impacted by bilirubin's ability to promote alterations in neurogenesis, neuritogenesis, and synaptogenesis.
- Such deleterious role of UCB in neuronal differentiation, development, and plasticity may compromise the performance of the brain in later life, including learning disability.

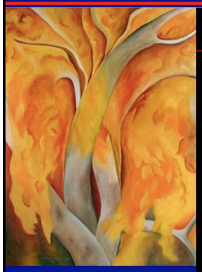
Phase III

- Management of jaundice in term and late preterm infants
  - Current evidence
    - Reviewed 2004 (AAP, AHRQ, CDC)
    - Ongoing Review

The identification of

- Infants with significant hyperbilirubinemia
  - due to hemolysis
  - associated with hypoalbuminemia
  - late preterm and preterm infants
  - with concurrent sepsis
  - with G6PD deficiency

Limitations of Visual Assessment of Jaundice in a Diverse Newborn Population



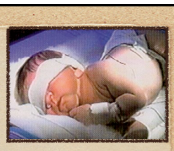
Shades of Yellow

Predischarge Visual Assessment of Jaundice

- Nurses' assessment of jaundice extent (n=522) was only moderately correlated with total bilirubin concentration and was similar in black and non-black infants (p=0.13).
- The correlation was particularly weak among infants <38 wks GA compared with infants ≥38 wks GA (p=0.05).
- Jaundice extent had poor overall accuracy for predicting risk of significant hyperbilirubinemia (c-statistic = 0.65).
- Complete absence of jaundice had high sensitivity (95%) and excellent negative predictive value (99%) for ruling out the development of significant hyperbilirubinemia.

Keren et al: ADC, 2009

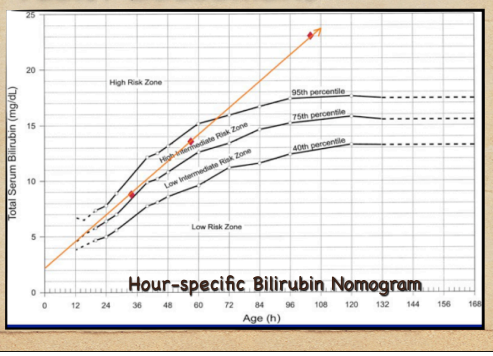
The use of



- Total bilirubin
- Clinical risk factors: BIND score
- Bilirubin-albumin ratio
- Unbound bilirubin (bilirubin binding)
- Auditory brainstem response
- Magnetic resonance imaging (post).

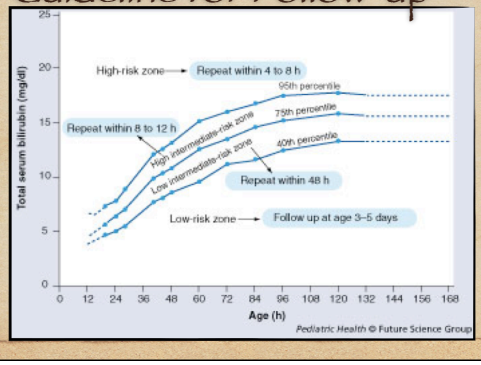
Bhutani, Keren and Johnson. Contemporary Pediatrics. 2005

Risk Assessment

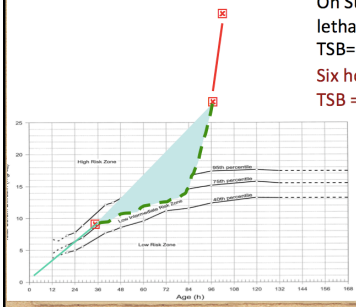


Hour-specific Bilirubin Nomogram

Guideline for Follow-up



Unpredictable Rate of Bilirubin rise (?)



On Sunday evening, she is for lethargy and poor feeding.
TSB= 28.9 mg/dL
Six hours later, in the NICU, TSB = 46.1 mg/dL.

Term AA female, screened at age 34 hours, discharged on Friday with a follow-up made for Monday am: TSB at 75th percentile.

National Incidence of G6PD deficiency

PRESENCE OF G6PD DEFICIENCY IN U.S. MILITARY PERSONNEL BY SEX AND SELF-REPORTED ETHNICITY

Ethnicity	Deficient[a] Female	Male	Total
American Indian/ Alaskan	112 (0.9)	492 (0.8)	604 (0.8)
Asian	465 (0.9)	1,658 (4.3)	2,123 (3.6)
African American	2,763 (4.1)	8,513 (12.2)	11,276 (10.2)
Hispanic	842 (1.2)	4,462 (2.0)	5,304 (1.9)
Caucasian	4,018 (0.0)	38,108 (0.3)	42,126 (0.3)
Unknown/other	228 (1.8)	1,641 (3.0)	1,869 (2.9)

[a] Number tested (percent deficient).

Chinnaswamy, Military Med 2008; 173: 9-905

Clinical and Bilirubin-based Risk Assessment?

Clinical risk factors for bilirubin neurotoxicity

- Prematurity
- Iso-immune hemolytic anemia
- G6PD deficiency
- Significant lethargy
- Sepsis
- Acidosis
- Asphyxia
- Temperature instability
- Albumin <3.0 g/dL

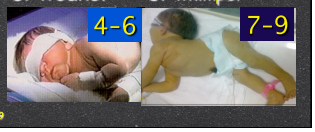
AAP Guidelines: To initiate intensive phototherapy

Risk for BIND	TSB at age 48 hours	TSB at age >96 hours
High (risk factors and 35-376/7 wk)	188 (μmol/L) 11 mg/dL	257 (μmol/L) 15 mg/dL
Moderate (35-376/7 wk)	222 (μmol/L) 13 mg/dL	308 (μmol/L) 18 mg/dL
Low (healthy term)	257 (μmol/L) 15 mg/dL	359 (μmol/L) 21 mg/dL

Based on a technical review for AHRQ: Ip et al: ahrq.gov

ABE: BIND Score ≥4 (A: awake; S: sleep)

Signs	Mild (1)	Mod. (2)	Severe (3)
Mental	A: agitated S: poor arousal	A: irritable S: lethargic	A: seizures S: semi-coma
Tone	A: hypertonia S: hypotonia	A: arching S: limp	A: ophithotonos S: flaccid
Cry	A: shrill S: weak	A: high pitch S: weaker	A: inconsolable S: whimper
Score	1-3*		



*Mild+referred AABR = 4

Johnson and Bhutani, Journal of Perinatology. 2009

Theoretical Bilirubin-Albumin Ratios and the Stability of this Binding

B:A Ratio	Stable Binding	Displaceable Bilirubin	Bilirubin displaced
B: A [mg/g] (molar ratio)	< 5.3 (molar >0.63)	5.3 to 6.9 (>0.63 to <0.8)	≥ 7.0 (molar: >0.80)
TSB to Serum Albumin of 3.2 g	17 mg/dl	17 to 22	22 mg/dl
TSB to Serum Albumin of 3.6 g	19 mg/dl	19 to 25	25 mg/dl
TSB to Serum Albumin of 4.3 g	23 mg/dl	23 to 30	30 mg/dl

Bhutani VK, Keren R and Johnson L. Acute Bilirubin Encephalopathy, Contemp. Ped. 2005

Phase IV

- Management of jaundice in term and late preterm infants
  - Current Recommendation
    - 2004 AAP recommendations
    - BiliTool.org
    - AAP Expert Panel Report: 2009

EXPERT AAP PANEL RECOMMENDS

- We recommend universal predischarge bilirubin screening using total serum bilirubin or transcutaneous bilirubin measurements which help to reduce risk of subsequent severe hyperbilirubinemia.
- We recognize that the quality of evidence for recommending universal predischarge screening.... is limited and, in the absence of higher level of evidence, our recommendations, therefore, be based on expert opinion.

Maisels, Bhutani, Bogen, Newman, Stark and Watchko, Pediatrics: 2009

Phase V

- Management of jaundice in term and late preterm infants
  - Current Interventions
    - Enteral feeds
    - Phototherapy
    - Exchange transfusion
    - Chemoprevention

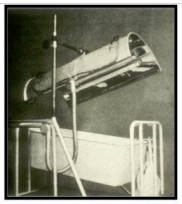
GOALS

- To reduce the incidence of exchange transfusion
- To prevent the need for an exchange transfusion

Vinod K. Bhutani for COFN 4/10/10

PIONEERING REPORTS

Cremer *et al*: 1958
Franklin *et al*:1958
Berezin *et al*: 1960
Berezin *et al*: 1960
Ferreira *et al*: 1960
Ferreira *et al*: 1960
Ferreira *et al*: 1960
Mellone *et al*: 1960
Peluffo *et al*: 1962
Lucey *et al*: 1968
and more: to date



PHOTOTHERAPY

SINGLE
DOUBLE
MULTIPLE
INTENSIVE
✓ **EFFECTIVE**

Vinod K. Bhutani for COFN 4/10/10

NICHD PIVOTAL RCT (1974)

Birthweight	<2000g		2000-2499		>2500g	
Study group	P	C	P	C	P	C
Total (n)	462	460	70	71	140	136
Exchange (n)	22	110	3	18	14	23
% Exchange	4.8*	23.9	4.3*	25.4	10.0	16.9
P value	<.001		<.001		NS	

P = Phototherapy with daylight fluorescent bulbs for 96 hours based on pre-set bilirubin thresholds adjusted for birthweight. C = Control.

Brown AK, Kim MH, Wu PY, Bryla DA. Efficacy of phototherapy in prevention and management of neonatal hyperbilirubinemia. Pediatrics. 1985 Feb;75(2 Pt 2):393-400.

Vinod K. Bhutani for COFN 4/10/10

PREPARATION OF A CHECKLIST:

TECHNICAL TOPICS

- LIGHT WAVELENGTH
- LIGHT IRRADIANCE
- BODY SURFACE EXPOSED TO LIGHT
- RATE OF RESPONSE
- SAFETY MEASURES
- GAPS IN KNOWLEDGE
- EVIDENCE FOR RECOMMENDATIONS

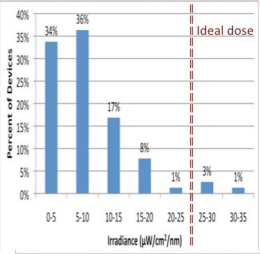
TIMELINESS OF TREATMENT

Parameter	Recommendation	Implementation
Timeliness of implementation	Urgent or "crash-cart" intervention for excessive TSB	Conduct procedures while on treatment
Continuity of therapy	Briefly interrupt for feeding, bonding, nursing care	After confirmation of bilirubin decline
Efficacy of intervention	Periodically measure rate of response in TSB reduction	Degree of TSB decline
Duration of therapy	Discontinue at desired TSB; be aware of rebound.	Serial TSB based on rate of decline

GAPS IN KNOWLEDGE

- Are there clinical devices to concurrently measure the actual wave-length and irradiance of a phototherapy light source?
- Can we predict the efficiency of phototherapy with comparative testing models such as *in vivo or bench-top modifications?*
- Whether home phototherapy can be implemented as safely?
- Are there short- and long-term consequences for infants with combined conjugated and unconjugated hyperbilirubinemia?
- Does initiation of phototherapy reduce the risk of bilirubin neurotoxicity in a timely and effective manner?

Identified Gaps in Optimization of Intervention



1. **Light emission:** Intensity and blue-green spectral output predicts effectiveness of treatment. Level B
2. **Effectiveness:** Clinical effectiveness should be known before/during use [>30 μW/cm^2/nm]. Level B
3. **Interference:** Maximal body surface should be illuminated. Level B
4. **Device Performance:** ***urgent need for affordable evidence-based, sturdy and safe technologies.***

Cline et al 2010. Audit of devices used in Nigeria (n=77). Evidence basis for standard of care: AAP2004.

Summary

- Management of jaundice in term and late preterm infants
  - Lessons Learned
    - Health outcomes
    - Societal outcomes

The Lessons From

125 cases of Kernicterus in America (1989-2003): Analysis by I.O.M. Matrix

Patient Centeredness	Safety	Effective Care	Timeliness
Experience of services	Diagnosis of kernicterus	Preventive care provided	Access
Patient-Provider Partnerships	Treatment safety	Acute care and chronic care effectiveness	Getting the right care in a timely manner
Trustworthy Care	Environment and facilities	Procedures used	Continuity of care

David Haus
1995-2008

Conclusion: need for a systems-approach to prevent severe Hyperbilirubinemia

Identification: A Matter of Safety

Medical Interventions

- Decrease entero-hepatic circulation
  - Increase enteral milk intake
  - Promote breast feeding and milk transfer
  - Supplement enteral intake
- Phototherapy
- Exchange transfusion
- Chemoprevention

Prevention	Analogy	Incidence
Jaundice screening and lactation support	use of a safety belt	For all infants
Use of effective phototherapy (hospital)	use of emergency procedures	Less than 1 in 50
Prepare for an exchange transfusion	a crash landing	A rare event

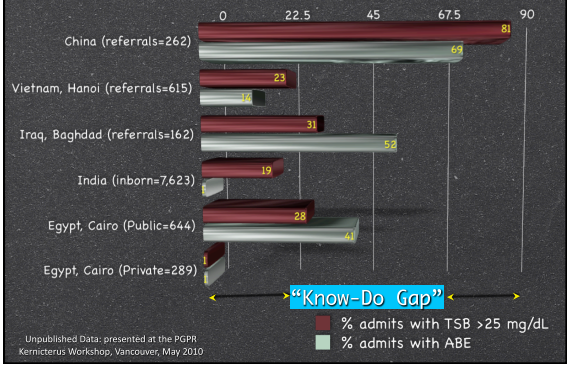
Lessons Learned

Outcomes: Successful Provider Strategies

POST IMPLEMENTATION OF 2004 AAP GUIDELINES AT BIRTHING FACILITIES	USA Rate /100,000 live births 116 national hospitals (HCA: 2004-8)**		CALIFORNIA Rate/100,000 live births CPQCC: 2007-8 (126 sites) Knauer et al (PAS, 2010)
	PRE- SCREENING	Systems approach	
Total live-births	129,345	899,472	1,120,114
TSB ≥25 mg/dL	52	29.5	17.9
TSB ≥25 - 29.9 mg/dL	43	26.5	14
TSB ≥30 mg/dL	9	3	4
Exchange Transfusion	x	x	4
Mortality	0	0	0

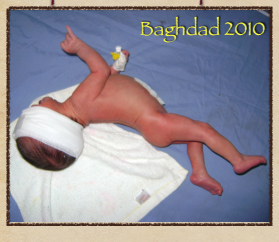
** Pediatrics. 2010. Reduction of Severe Hyperbilirubinemia after Institution of Predischarge Bilirubin Screening. Mah MP et al

A Global Snap-shot: Percent Infants with TSB >25 mg/dL or Acute Bilirubin Encephalopathy



Unpublished Data: presented at the PGPR Kernicterus Workshop, Vancouver, May 2010

Newborn jaundice and its potential sequelae



Newborn Jaundice	Universal Bilirubin Screening
Bilrubin >95th %ile	Evaluate and Treat
Bilirubin >20 mg/dL	Effective Phototherapy
Use of Phototherapy	TSB Rate of rise >0.2mg/dL/hour
Exchange Transfusion	"A Crash-Landing"
Bilirubin >30mg/dL	A "Never-Event"

Screen and Prevent
Aviation Safety Standards

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10. Newman TB, Liljestrand P, Escobar GJ. Infants with bilirubin levels of 30 mg/dl or more in a large managed care organization. *Pediatrics* 2003; 111(6 Part 1): 1303–1311.

Contact

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Pilot Kernicterus Registry

SUNDAY, OCTOBER 24, 2010

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP
Co-Moderator (BOT Member) – James Kirk, DO, FACOP

3:00 pm – 4:00 pm

Apnea and Bradycardia

Shannon Jenkins, DO

Objective: Upon completion of this lecture, the participant will be able to gain a better understanding of Apnea of prematurity and review the current literature on how long of a desaturation may be harmful.

Apnea and Intermittent Hypoxia in Preterm Infants

Shannon Jenkins, D.O.
Medical Director
Eastern Idaho Regional Medical Center

Objectives

- What is apnea?
- Classical Teaching about "short apnea"
- What is intermittent hypoxia
- New Studies on Neurodevelopment
- What can be done about intermittent hypoxia
- Limitations of current research

Fetal Breathing Patterns

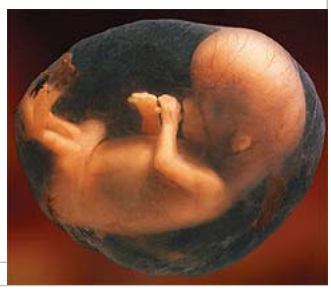
- Start at the 10th week of gestation
- At 19 weeks breath 6% of the time
- At 26 weeks breath 14% of the time
- At 30 weeks breath greater than 50% of the time
  - Miller 2006

Fetal Breathing Patterns

- In NORMAL third trimester pregnancy
  - No fetal breathing in 8% of 30 minute observation periods (BPP)
  - Episodic breathing common
  - During active labor active breathing seen in less than 10 % of babies
    - Richardson 2004

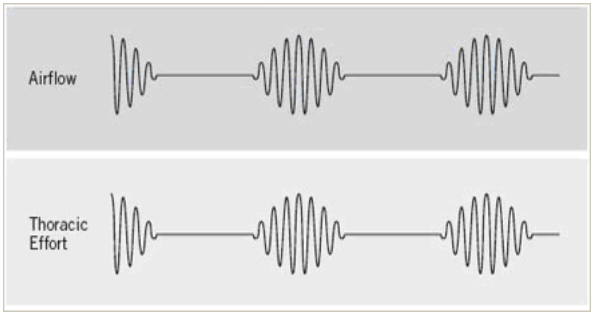
Fetal Breathing Patterns

- Decreased fetal breathing (apnea)
  - Active labor
  - Hypoxemia with acidemia
  - Maternal tobacco use – (increased apnea)
  - Maternal Hypoglycemia



Periodic Breathing

- Breathing for 10-15 seconds then apnea for 5-10 seconds



Periodic Breathing

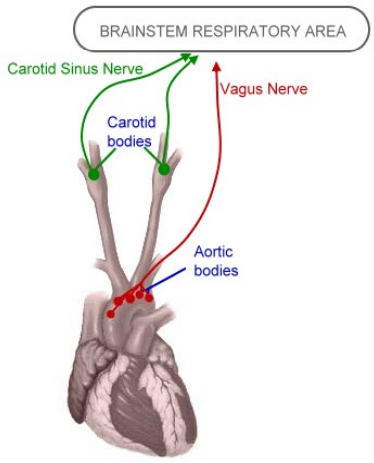
- Increased at higher altitudes
- Net effect may be hypoventilation
  - Rigatto and Brady 1972
- More frequent in premature infants but persists into infancy
  - Hoppenbrouwers 1977

Periodic Breathing

- Periodic breathing is classically thought to have an excellent prognosis
  - Barrington and Finer 1990
- Current hypothesis is that its caused by an imbalance in the peripheral chemoreceptor
  - Barrington and Finer 1990

Chemoreceptors

- Receptors
- Arterial side
  - Oxygen
  - CO2
  - PH

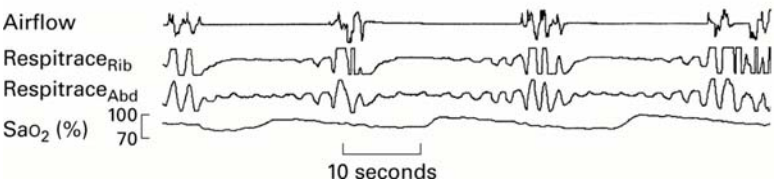


Classical Apnea

- Absence of airflow and breathing for more than 20 seconds

- Significant
  - 1) longer than 20 seconds
  - 2) associated with bradycardia
  - 3) associated with color change (desaturation)
    - Martin RJ, Fanaroff AA 1998

Classical Apnea



- Incidence of apnea inversely related to GA
  - Henderson-Smart 1981
- Usually random and episodic
  - Daily 1969

Classical Apnea

- Apnea typically starts first day of life
  - Finer 1991, Henderson-Smart 1981
- Apnea of Prematurity (AOP)
  - 40% Central
  - 10% Obstructive
  - 50% Mixed
    - Butcher-Puech 1985, Martin 1986
- Obstructive apnea mostly on first day of life
  - Barrington and Finer 1991

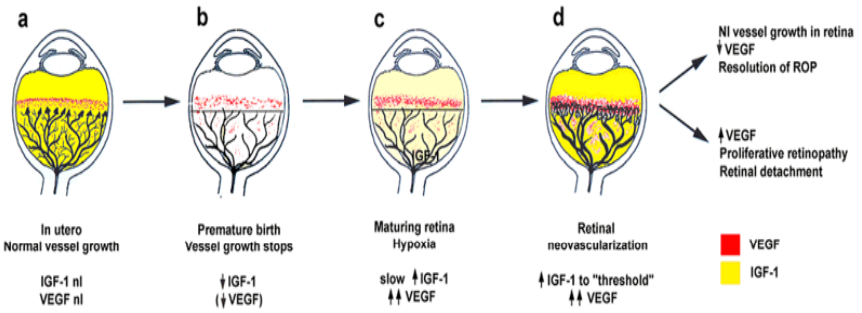
Apnea

- Apnea with bradycardia typically resolves at 38 weeks, but can go 42 to 44 weeks
  - Silvestri 1994
- Severe apnea can last up to 6 months of age
  - Silvestri 1994

Apnea and Adverse Outcomes

- Increased apnea events associated with decreased neurodevelopmental outcomes
  - Tudehope 1986, Kitchen 1981, Cheung 1999
- Cerebral ischemia found with bradycardia (<80) and apnea (>20 seconds)
  - Perlman and Volpe 1985
- Apnea associated with increased ROP
  - Shohat 1983, Primhak 1981, Kim 2004

Apnea and Adverse Outcomes



Lutty, Mol Vis 2006; **12:532**

Apnea

- Is apnea without bradycardia significant?
- What is more significant bradycardia, apnea or desaturation?

Bradycardia and Desaturations without Apnea

- Many Names
  - "Events"
  - Self resolved desaturations
  - Intermittent Hypoxia (IH)
  - Non-significant apnea
  - "Cardiorespiratory events"

Intermittent hypoxia – Dangerous?

- "Prevailing data suggest persisting cardiorespiratory events should not be considered sinister and are neither predictive of SIDS or significant neurodevelopmental handicap."
  - Martin and Fanaroff 1998
- "…apnea without bradycardia is not significant apnea"
  - Avery 2005, Others …

Intermittent Hypoxia

- Repeated episodes of hypoxia interspersed with normoxia
- Pro-inflammatory
  - CRP, other inflammatory cytokines
  - Associated with re-oxygenation, excess free radicals
    - Hunt 1999

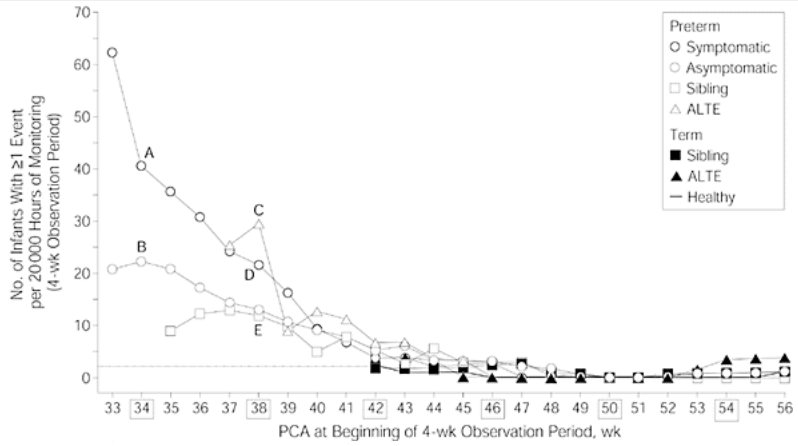
Intermittent Hypoxia

- Even mild levels of IH adversely impacts neurodevelopment
  - Kinane 2004
- Chronic IH decreases cognitive development and academic achievement in prematurity above that seen in prematurity alone
  - Gottlieb 2004

Intermittent Hypoxia

- Chronic IH studies decreases left ventricular cardiac function (Animal study)
  - Scharf 2010
- 34% of IH (prolonged) has no apnea or bradycardia
  - Poets 1995
- 21% of desats and 36% of brady's recorded
  - Diebold 2008

IH After Discharge



- Ramanathan R et al. JAMA 2001

How long is too long?

- The answer is ….
- However, even short, "non-significant events" may actually be harmful
  - Lower oxygen saturation assoc. with increased mortality (SUPPORT Trial)
    - NEJM Finer 2010
- What can be done about preventing apnea and IH?

Caffeine and Theophylline

- Unknown mechanism of action
- Possible increased responsiveness of the peripheral chemoreceptor
- Possible increased central nervous system excitation
- Possible increased muscle performance
  - Henderson-Smart 2004

Caffeine

- Caffeine (Methylxanthines)
  - Significantly reduce or eliminate apnea and bradycardia in premature infants
    - Apnea
    - Respiratory pauses, periodic breathing
- Not adequate studies to document effect on IH
  - Either in the NICU or after discharge
    - Hunt 2010

Caffeine

- Prophylaxis appears to decrease ventilation length
  - Schmidt 2005
- Prophylaxis appears to decrease length of oxygen use
  - Schmidt 2006
- Decreases neurodevelopmental disability at 18 to 21 months
  - Tin 2007

Caffeine and CAP trial

- Caffeine for Apnea (CAP)
  - 1860 infants 500 to 1,250 grams at birth
  - Randomized to placebo or caffeine
  - Discontinued when treatment no longer necessary
- Aim
  - Define AOP treatment ***without*** methylxanthines
  - Define long term morbidity of methylxanthines

CAP Trial

- Early Findings
  - Decreased days on ventilator
  - Decreased days on oxygen
  - No increased morbidity
- 18 to 21 month follow-up
  - Cognitive delay reduced in caffeine group
  - Increased survival in caffeine group
  - Decreased CP in caffeine group

CAP Trial

- Benefits May Vary in Subgroups
  - Infants on respiratory support have more benefit
  - Earlier initiation of caffeine shows greater reduction in ventilation

CAP trial

- More days of placebo treatment associated with increased CP
  - Speculation this was from increased untreated apnea
  - Caffeine mitigated this risk
    - PAS Vancouver, May 2010

What We Know

- Apnea and IH are associated with adverse outcomes
- Even short "non-significant" apnea can be harmful
- Babies who have less of these events have better outcomes

What We Don't Know

- What is adequate treatment for IH?
  - In the NICU and after discharge
- Does long term prophylaxis of all preterm babies have benefit?
- How much is too much and how long is too long?

Future Studies Needed

- Caffeine vs no caffeine until 44 weeks GA
- Caffeine and ROP
- IH and ROP
- Better identification methods of IH

DECAF Trial - Hunt 2010

- Planned study
  - Continue caffeine until 44 week PMA
  - Compared to discontinuing caffeine before discharge
  - Test developmental outcome at 18 months
- Aim – determine whether caffiene's effects on IH explain developmental outcome

Finish!

- Questions?

SUNDAY, OCTOBER 24, 2010

PERINATAL / NEONATAL

Moderator – Holly Payne, DO, MS, FACOP
Co-Moderator (BOT Member) – James Kirk, DO, FACOP

4:00 pm – 5:00 pm

Assessing Limits of Viability

Carl Backes, DO, FACOP, FAAP

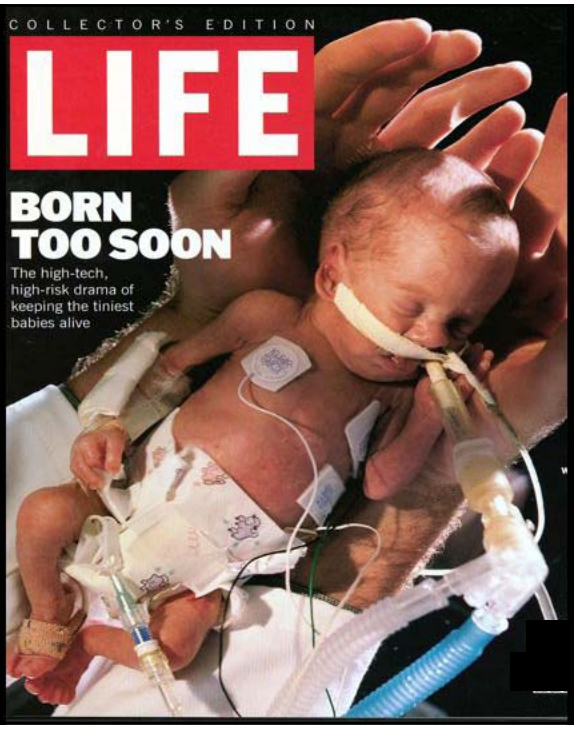
Objective: Upon completion of this lecture, the participant will be able to present national and international survival of the extreme preterm infant, discuss morbidity of extreme problem infants, and discuss changing attitudes of extreme preterm resuscitation.

Mortality and Morbidity at the Limits of Viability: Defining the "Gray Zone"

The Columbus Experience

Carl R. Backes, D.O.
Professor of Pediatrics at Oho University College of Osteopathic Medicine
Assistant Professor of Pediatrics at The Ohio State University
Director- Neonatal Special Care Unit -Nationwide Children's Hospital/ Doctors Hospital

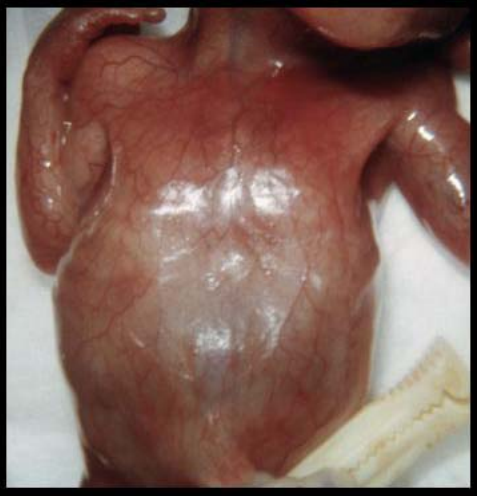
NATIONWIDE CHILDREN'S HOSPITAL℠



Complex medical, social, ethical, resource utilization issues

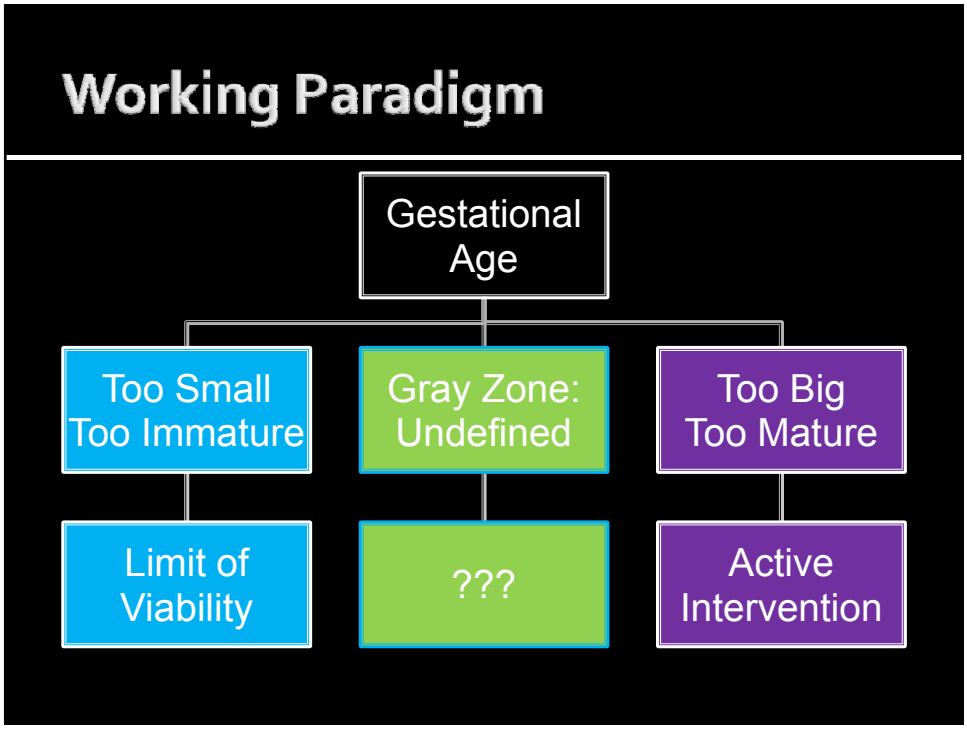
Goals in Approach to Care

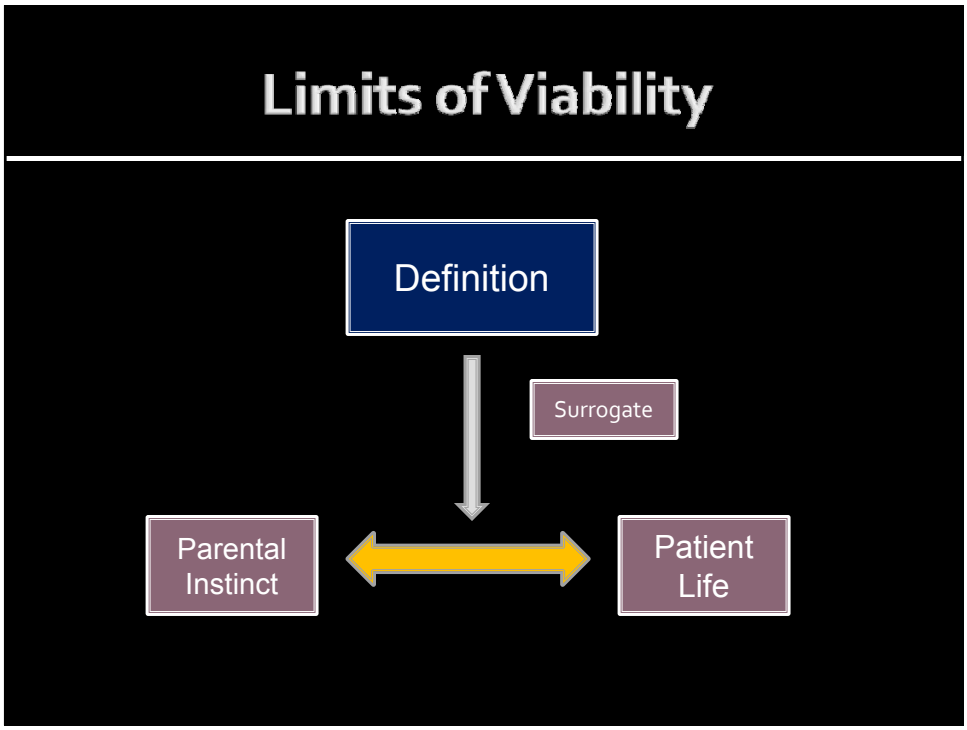
Minimize both undertreatment and overtreatment of the extremely premature infant



Goals of Presentation

- Controversial Topic
- Review National and Regional Data: Mortality and Morbidity
- To Discuss the "Columbus Culture" and Impact on Internal Data
- Suggest Possible Paradigm


Working Paradigm
Gestational Age
Too Small Too Immature
Gray Zone: Undefined
Too Big Too Mature
Limit of Viability
???
Active Intervention


Limits of Viability
Definition
Surrogate
Parental Instinct
Patient Life

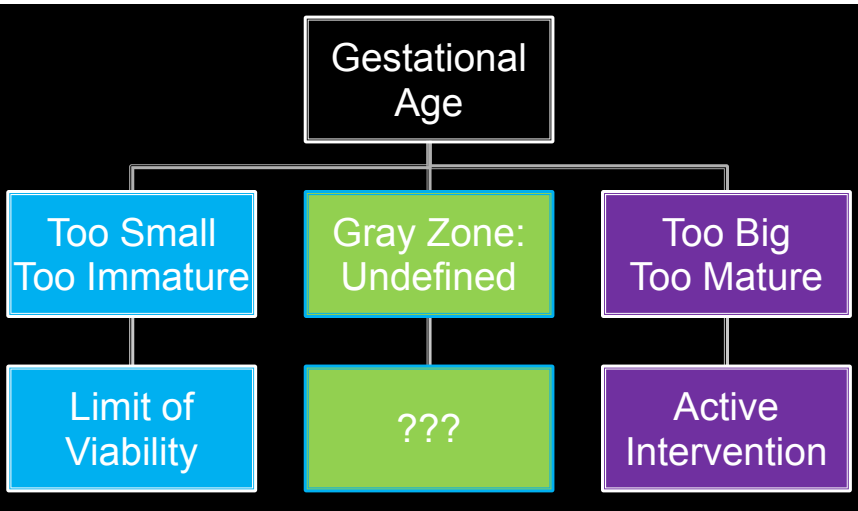
Governing Bodies

- The **World Health Organization** (WHO) places **25 weeks** of gestational age as potential lower limit of viability

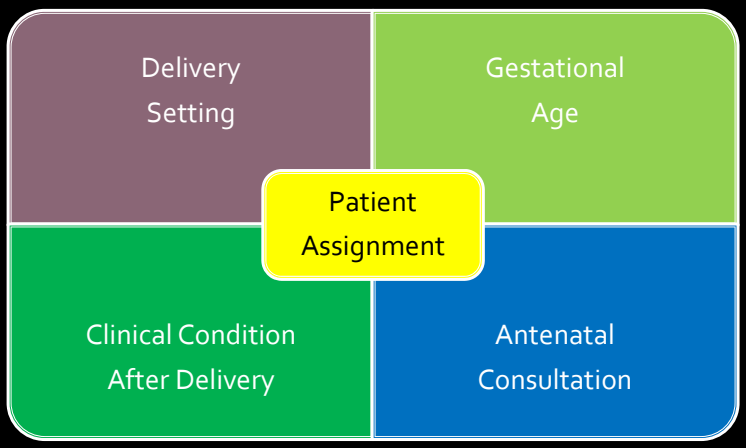
- The **European Association of Perinatal Medicine** (EAPM): lower limits of viability " from **24 completed weeks** gestation onward…"

- The **American Academy of Pediatrics** (AAP) suggests non-initiation of resuscitation for newborns of less than **23 weeks** gestational age and/or **400 grams** in birthweight is appropriate

Working Paradigm



Limits of Viability
Patient "Assignment"



Gestational Age
How Reliable are the Dates?

- 8 week US: +/- 3 days
- 12 week US: +/- 5 days
- 2nd trimester US: +/- 12 days
- 3rd trimester US: +/- 19 days

Evans et al, AJOG, 2008

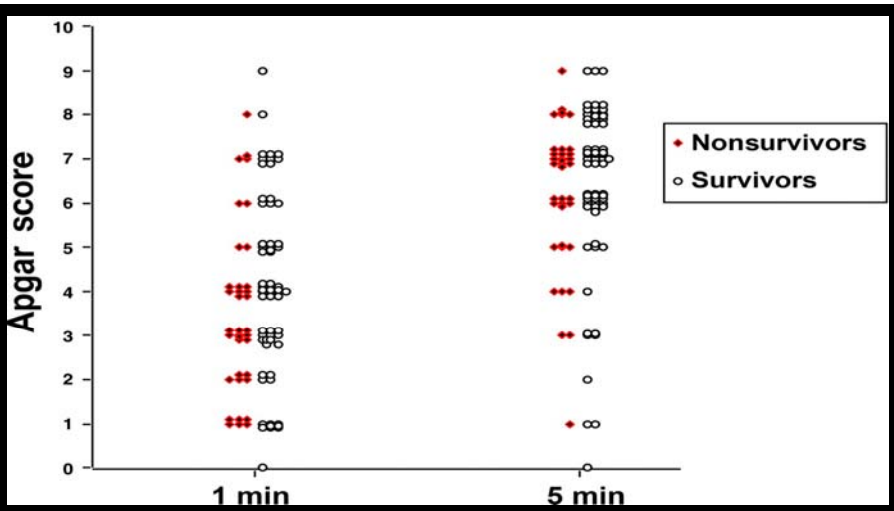
1st: CRL
2nd: BPD, HC, Femur length, abd circumfrence

Antenatal Consultation

- **Gestational Age**
- **Additional Factors**
  - Antenatal Steroids
  - Female Sex
  - Singleton Gestation
  - Increased Birth Weight (100g increments)

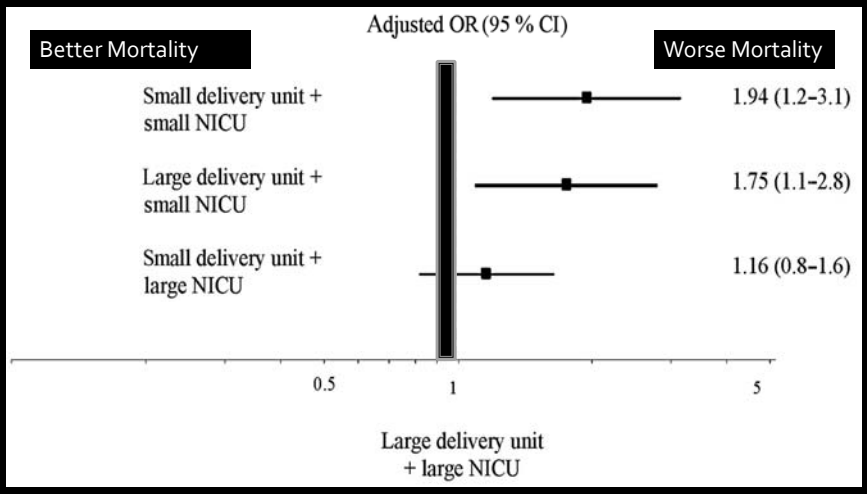
Tyson et al, NEJM, 2007

Clinical Condition



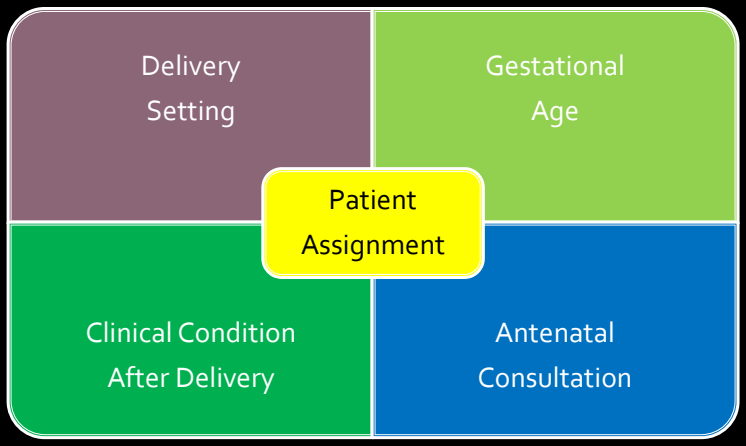
Singh et al, Pediatrics, 2007

Delivery Setting



Bartels et al, Pediatrics, 2006

Limits of Viability Patient "Assignment"



Mortality

International, National and Regional Data

Limits of Viability: Gestational Age at Which a Newborn had 50/50 Chance of Survival*

1940's	-	32-33 weeks
1960's	-	30-31 weeks
1980's	-	26-27 weeks
2007	-	24 weeks

Data from past decade suggest *lower limit* of viability is now 22-23 weeks

* North America

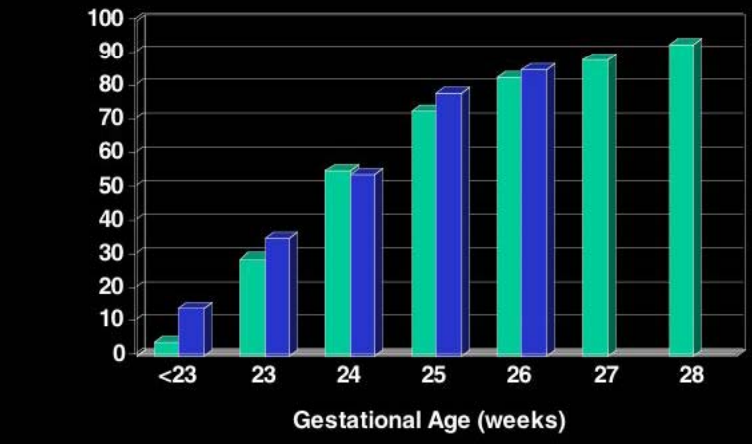
Major sources of data

- Vermont Oxford Network
  - 557 participating NICU's, 86% US
  - 42937 infants 500-1500 g in 2005
  - Data on >50% all infants <1500 g born in US each year
  - No post-discharge followup
- NICHD
  - 12 academic NICUs
  - 2478 infants < 1000 g born 93-94; 1480 survivors at 18 mos
  - 78% 18-22 mo followup
  - (also mortality data for 4438 infants ≤ 26 wks born 95-96 in 14 centers)
- EPICure Study
  - All 276 delivery units UK/Ireland
  - All 1185 liveborn infants <26wks gestation born March-Dec 1995
  - 811 survived to NICU admit, 308 survivors at 30 months
  - 92% 30 month and 78 % 6 year followup

Major sources of data

- NICHD
  - 20 Academic NICU's
  - 9575 infants
  - Gestational age 22-28 weeks
  - Birth weight 401-1500 grams
  - Born 1-1-03 to 12-31-07

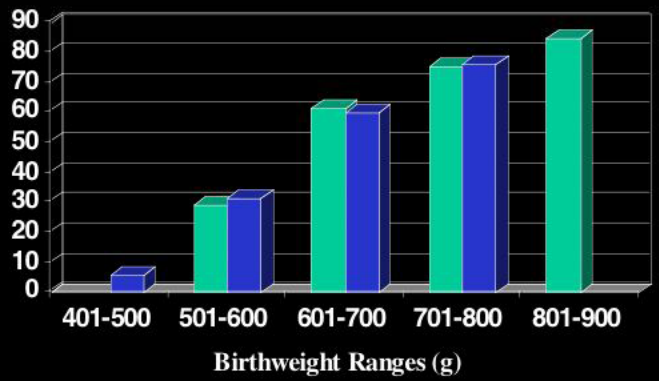
Percent Survival by Gestational Age



Vermont Oxford Database, 2000 Liveborn, 501-1500 gm BW; n=42937
NICHD, 95-96, Liveborn, 401-1500 gm BW; n=4438

Pediatrics 05

Percent Survival by Birth Weight



Vermont Oxford 2000 ; n=42937
Hack et al, 90-96; n=4932

Pediatrics, 2005

Outcomes by Gestational Age NICHD 9575 infants 22-28 weeks gestation 401-1500 grams

NICHD Pediatrics 2010

22 weeks

22 weeks (421 infants)

- Intervention
  - Survival to discharge 6%
  - Death < 12 hours 85%
  - Antenatal steroids 13%
  - Cesarean Section 7%
  - Delivery room intubation 19%
  - Surfactant therapy 17%
  - Mechanical ventilation @ 24 hours 96%
  - CPAP @ 24 hours 0%

NICHD Pediatrics 2010

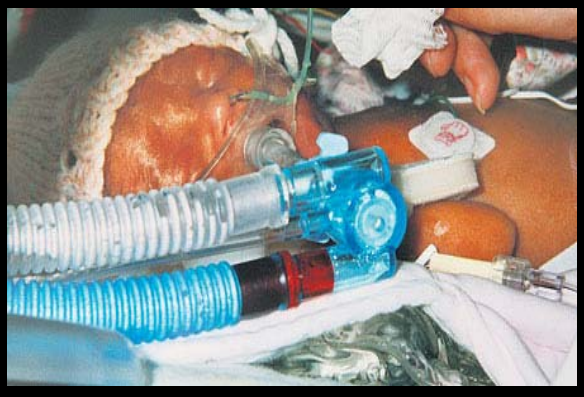
23 weeks

23 weeks (871 infants)

- Intervention
  - Survival to discharge 26%
  - Death < 12 hours 43%
  - Antenatal steroids 53%
  - Cesarean Section 24%
  - Delivery room intubation 68%
  - Surfactant therapy 63%
  - Mechanical ventilation @ 24 hours 94%
  - CPAP @ 24 hours 3%

NICHD Pediatrics 2010

24 weeks

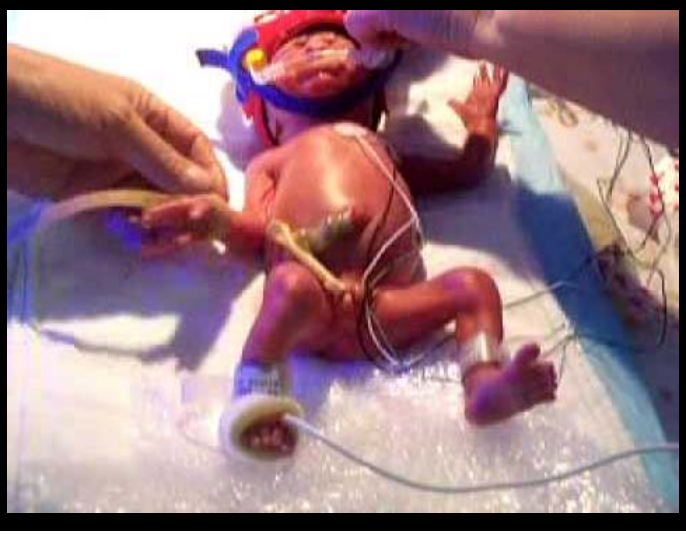


24 weeks (1370 infants)

- Intervention
  - Survival to discharge 55%
  - Death < 12 hours 11%
  - Antenatal steroids 85%
  - Cesarean Section 60%
  - Delivery room intubation 87%
  - Surfactant therapy 90%
  - Mechanical ventilation @ 24 hours 89%
  - CPAP @ 24 hours 8%

NICHD Pediatrics 2010

28 weeks



28 weeks (2001 infants)

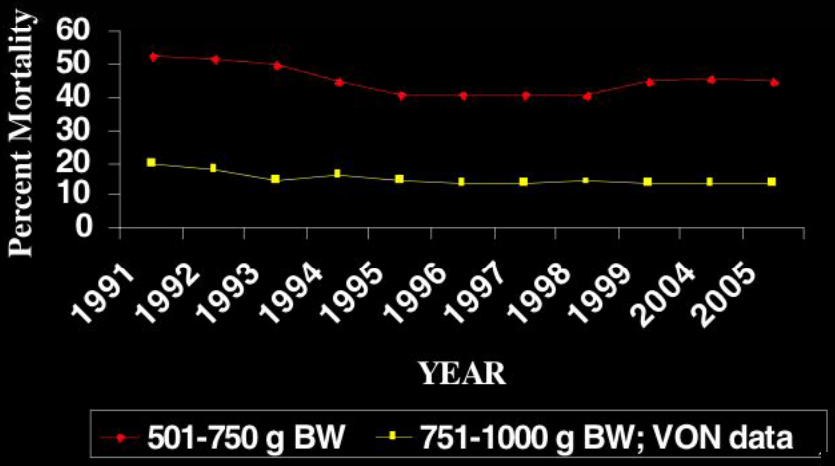
- Intervention
  - Survival to discharge 92%
  - Death < 12 hours 1-2%
  - Antenatal steroids 87%
  - Cesarean Section 68%
  - Delivery room intubation 47%
  - Surfactant therapy 65%
  - Mechanical ventilation @ 24 hours 40%
  - CPAP @ 24 hours 38%

NICHD Pediatrics 2010

International Comparison of Infant Survival

Itabashi et al, Pediatrics, 2009

Mortality 1991-2006 for ELBW Infants: No improvement past decade



Neonatal Morbidity and Outcome Data

Difficulties

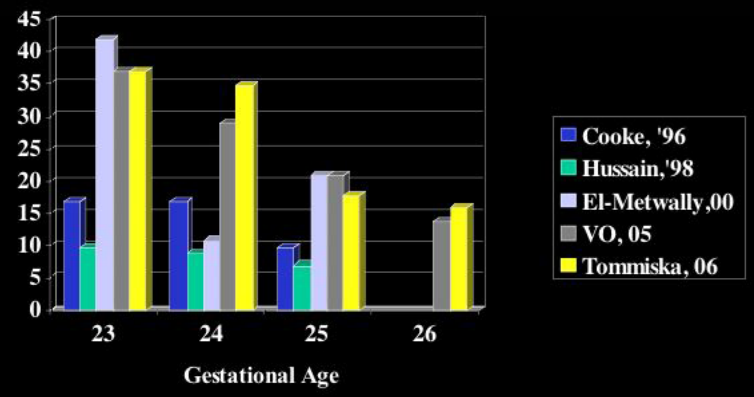
- Lack of universally acceptable definition of "quality of life" has resulted in difficulties in interpreting long-term neurodevelopmental outcomes
- Outdated findings: changes in clinical practice outpace timeframe which long-term data can be collected and published

Morbidity in Survivors

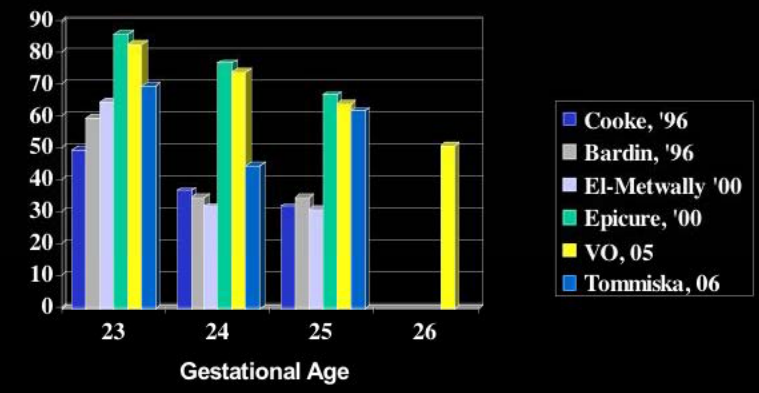
Caveats

- Moving target
- *Very* little data with stratification by small weight and gestational age groups
- Variances in definitions of morbidities
- Do early morbidities predict very late outcome or quality of life?

Percent Severe Head Ultrasound Abnormalities by Gestational Age

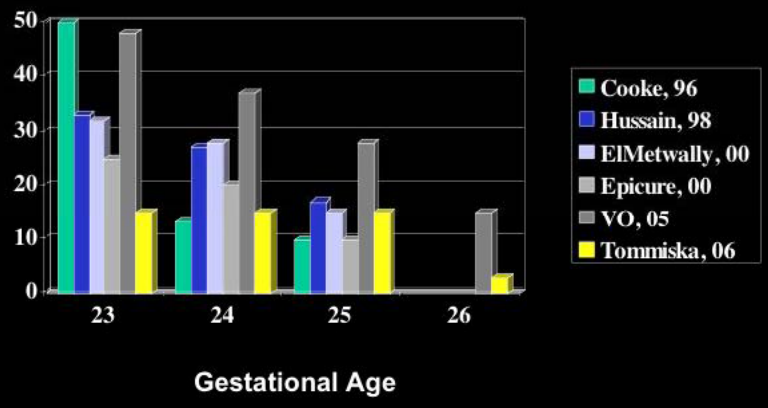


Percent Bronchopulmonary Dysplasia by Gestational Age at Birth



FiO_2 at 36 wks

Percent Severe Retinopathy of Prematurity by Gestational Age



Complications by Gestational Age- NICHD

9575 infants

22-28 weeks gestation

401-1500 grams

NICHD Pediatrics 2010

22 weeks (421 infants)

Early onset sepsis	6%
Late onset sepsis	58%
ROP	96%
ROP treatment	50%
Survival with morbidity	100%
Median length of hospitalization	20.1 weeks
NEC	
Medical	67%
Surgical	33%
PDA	
Indocin	82%
Surgical Tx	50%
IVH- Grade IV	30%
BPD Severe	56%

NICHD Pediatrics 2010

23 weeks (871 infants)

Early onset sepsis	4%
Late onset sepsis	62%
ROP	88%
ROP treatment	40%
Survival with morbidity	92%
Median length of hospitalization	18.3 weeks
NEC	
Medical	31%
Surgical	69%
PDA	
Indocin	73%
Surgical Tx	43%
IVH- Grade IV	21%
BPD Severe	39%

NICHD Pediatrics 2010

24 weeks (1370 infants)

Early onset sepsis	4%
Late onset sepsis	55%
ROP	89%
ROP treatment	35%
Survival with morbidity	91%
Median length of hospitalization	16.7 weeks
NEC	
Medical	39%
Surgical	61%
PDA	
Indocin	76%
Surgical Tx	40%
IVH- Grade IV	14%
BPD Severe	37%

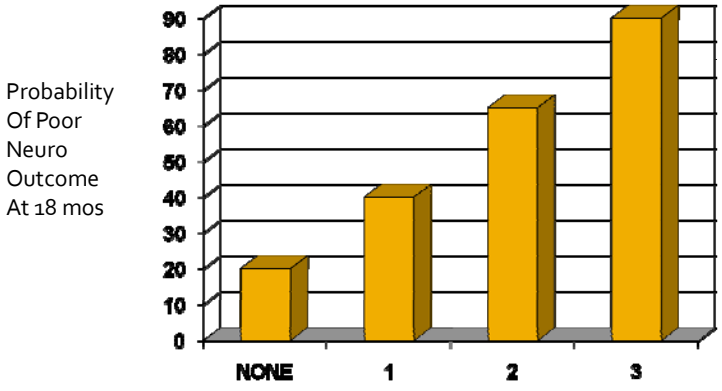
NICHD Pediatrics 2010

28 weeks (2001 infants)

Early onset sepsis	1%
Late onset sepsis	20%
ROP	32%
ROP treatment	2%
Survival with morbidity	43%
Median length of hospitalization	9.0 weeks
NEC	
Medical	38%
Surgical	42%
PDA	
Indocin	67%
Surgical Tx	12%
IVH- Grade IV	3%
BPD Severe	8%

NICHD Pediatrics 2010

Impact of BPD, Brain Injury, and ROP on 18 Month Outcome of ELBW

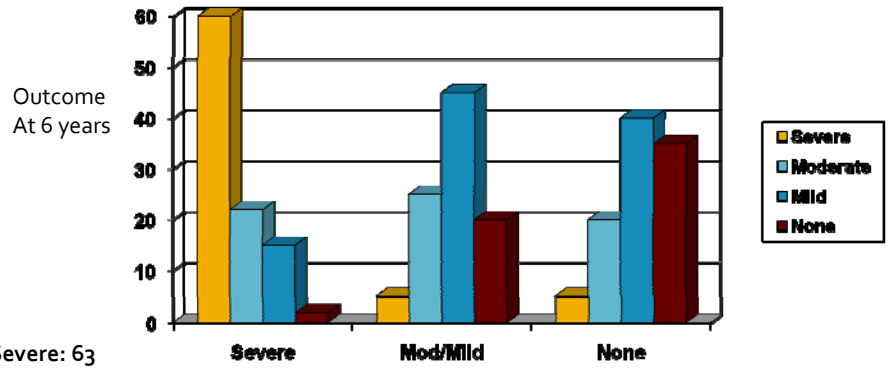


Neonatal Morbidities: ROP, BPD, and HUS Grade 3 or 4 or PVL

We do not know if 18 mos outcomes translates into long-term outcomes; Developmental Pediatricians, 80% agreement, Kaufmanns Assessment Battery for Children; Poor Outcome < 2.5 S.D. from age-matched controls

Schmidt et al, Pediatrics, 03

Disability at 30 mos and 6 years in ELBW neonates born at <26 weeks



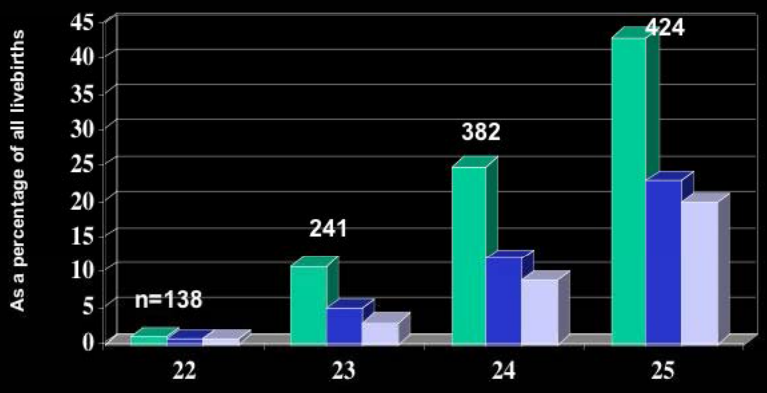
Severe: 63
Mild/Mod: 82
None: 92

Disability at 30 mos CGA

However, long-term neuro-developmental outcomes (> 6 years) DO NOT correlate well with these predictors, as maternal education and home environment are more important than all the other factors except severe brain injury (Vohr et al, 1999) 7 developmental peds, kaufman assessment battery for children, severe >3 S.D., mod, mild; 80% agreement

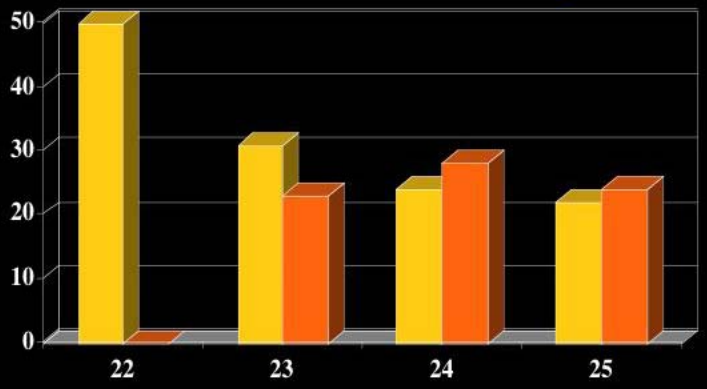
Marlow et at NEJM 2005

Survival to D/C & Survival Without Moderate-Severe Disability



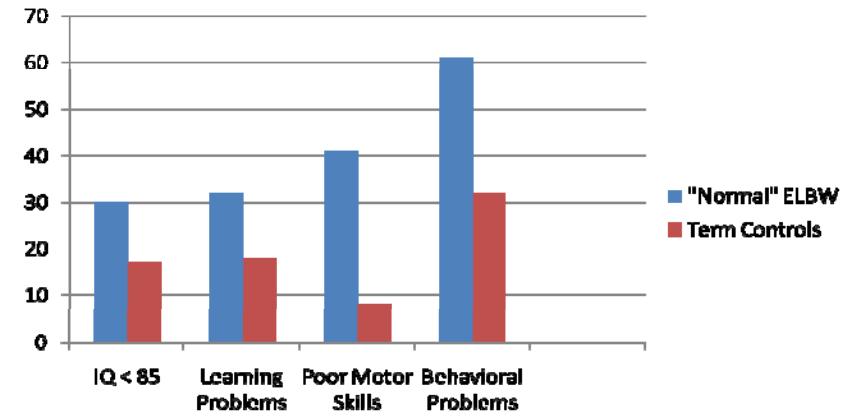
Epicure Study Group, 2000, 2005

Incidence of Neurodevelopmental Handicap at 30 Months in Infants Who Survived to Discharge



Epicure Study Group, 2000

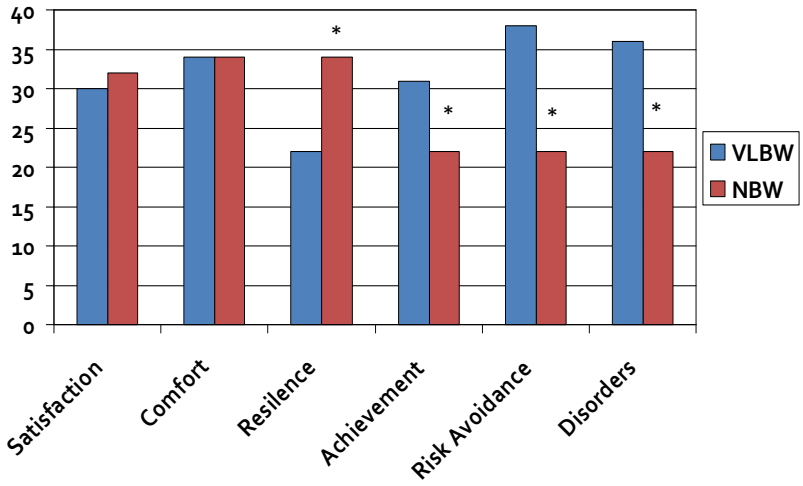
ELBW and School Age



Study between 1992-1995, and evaluated at 8-9 years of age;
"Normal" refers to infants who are ELBW and at discharge, had
no neurosensory abnormality In same study, for every 100 children
studied, 24 more children with ELBW had IQ <85, 38 * special services,
43* functional limitation As compared with children with normal birth weight

Johnson, et al, JAMA, 2005

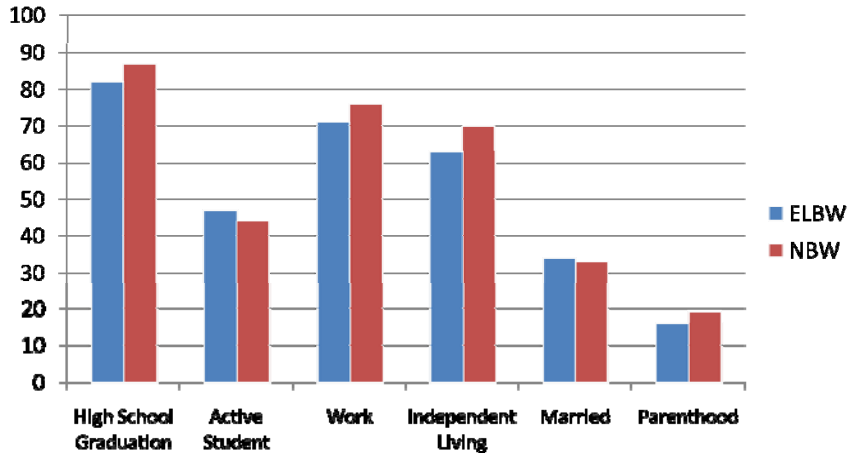
Adolescent Perceptions in VLBW infants



Adolescent graduated who are clearly handicapped by most "normal" standards self-report a score on their quality of life that is often higher than self-reported scores for "normal" nonhandicapped teens. Study did not report on the number of NICU graduates that were so impaired that they cannot self-report. Are these children/families more flexible than we who are not required to adapt to hardship can anticipate

Hack et al, JP, 2007

Transition to Adulthood



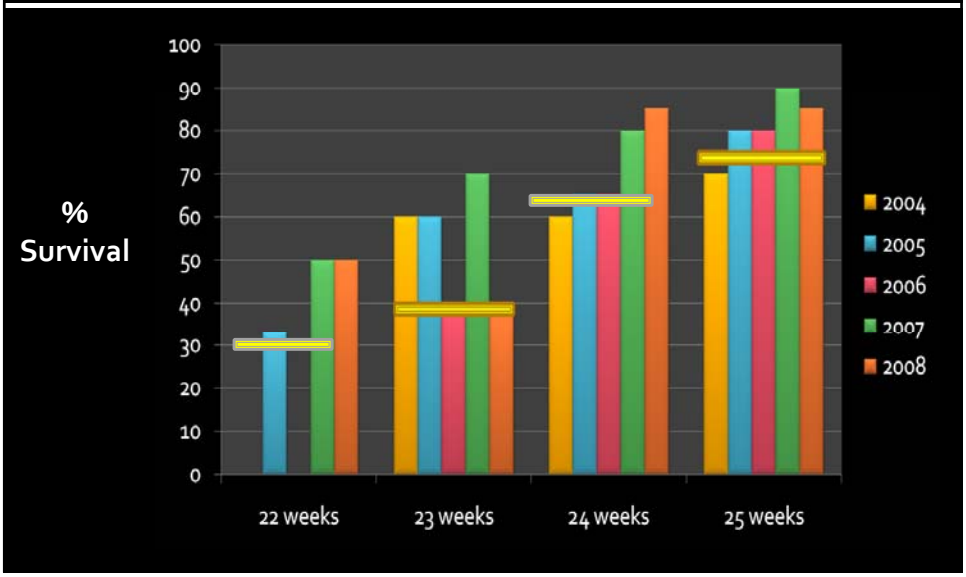
Prospective, longitudinal population based study between 1977-1982. 166/145. Assess 22-25 years. Markers of successful transition to adultood. Contrary to much of literature, a significant majority of ELBW infants make a successful transition from adolescence to adulthood. Lifespan perspective, recovery evident not until adulthood

Saigal, NEJM, 2008

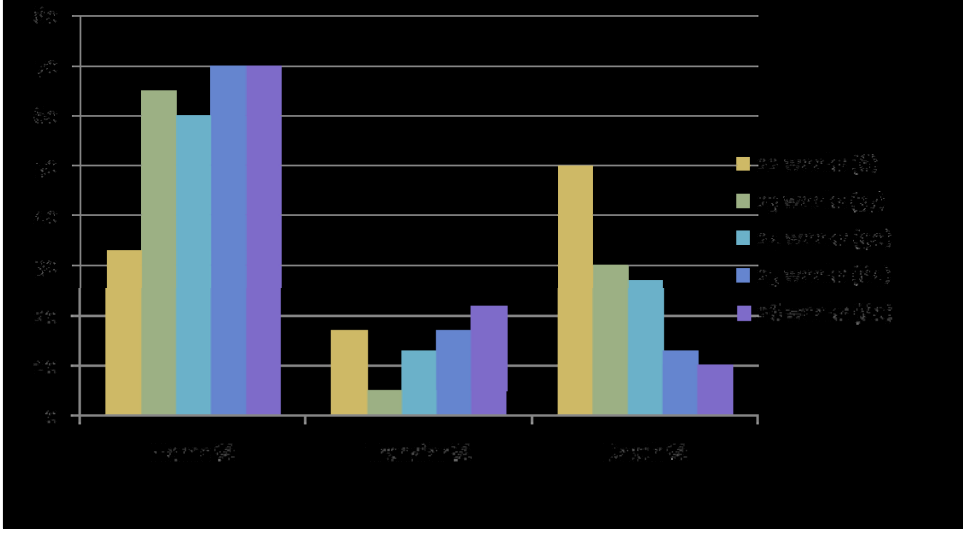
Problems in Predicting Long-Term Outcome

- Adverse *short and medium* term neurodevelopmental outcomes in ELBW infants correlate with early neonatal morbidities
- However, *later* neurodevelopmental outcomes do not correlate very well with these predictors; *maternal education & home environment* are more important than all factors except severe brain injury

Nationwide Children's Hospital Neonatal Network Data 2004-2008



Small Baby Pod Data



Small Baby Protocol <27 weeks NCH NICU First Week of Life

Respiratory

- Surfactant
- O2 Saturation alarm 85-93%
- Suctioning only as needed
- Extubation ASAP to bCPAP
- Caffeine
- Vitamin A

Skin

- Giraffe Omnibed- 80% relative humidity
- Avoid sticks
- UAC/UVC/PICC
- No tape, routine baths, routine weight
- Omiderm skin breakdown

Development

- IVH- avoid blood pressure fluctuations
- Head- midline position
- Kangaroo care after 72 hours

PDA

- Treatment- indocin, ibuprofen, ligation

Cardiovascular

- MAP-> 25 mmHg- Avoid rapid changes
- Monitor urine output and perfusion
- Treat
  - Saline bolus slow 10ml/kg
  - Dopamine 3-5 micrograms/kg/min
- Initial fluid rate 100-120 ml/kg/ day
- Blood out – consider PRBC replacement
- Avoid bladder bladder

Nutrition

- IV + Dextrose containing fluids
  + Sodium after 2-3 days
  + Protein- ASAP
  + Intralipids
- Trophic Feeds
  + as soon as feasible- usually day 3
  -10-20 ml/kg/ day without advancing
  + breast milk
  + no glycerin suppositories

Neurologic/ Pain

- Head ultrasound day 7-14
- Head circumference 7 and weekly
- Pain control

Laboratory

- Limit lab draws

Infection

- Hand washing
- Omiderm skin breakdown
- Line care
- Prophylaxes-fluconazole

Family

- Keep informed

Plan of Care

- Team approach

Bottom Line: Best Survival Estimate From Internal Data

- 22 weeks – 30%
- 23 weeks –60%
- 24 weeks– 80%
- 25 weeks—>90%

Live Births

Bottom Line: Best Intact Survival Estimate (Internal AND National Data)

- 22 weeks-- <5%
- 23 weeks--<10-15%
- 24 weeks --20-25%
- 25 weeks –30-40%

Who decides regarding intervention in the "Gray Zone"?

The AAP and ACOG all have issues statements (1997, 2002, 2008) supporting the primary of ***parental decisions*** for infants at the limits of viability


USA TODAY

NO. 1 IN THE USA

Who decides whether a baby lives or dies

Key Texas case weighs parents' right to refuse care against hospital's desire to save 'preemies'

Cover story

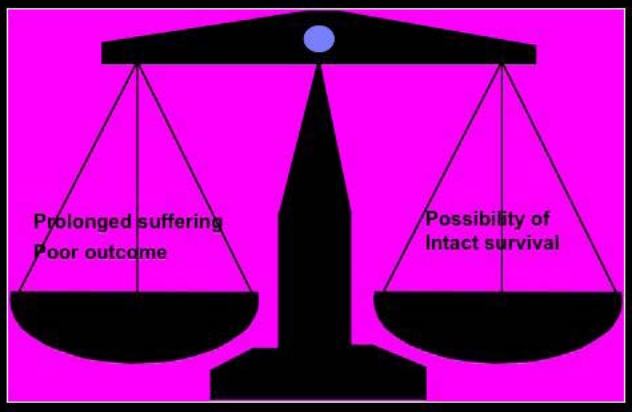
Choices in decision making

- Delegate all decision-making responsibilities to physician
  - Parental role discounted
- Defer all decisions making to parents
  - Physician is a technician
  - Guilt/overwhelm parents
- Collaborate with parents in the decision making process
  - *Independent obligations* of parents and physicians to act in child's best interest

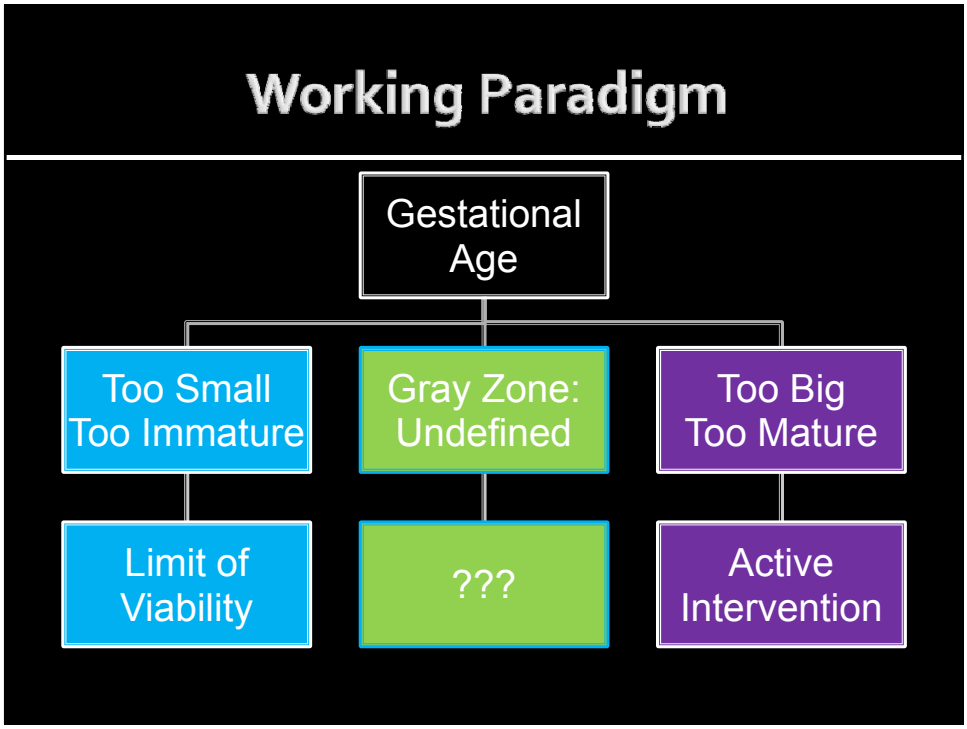
What Should We do

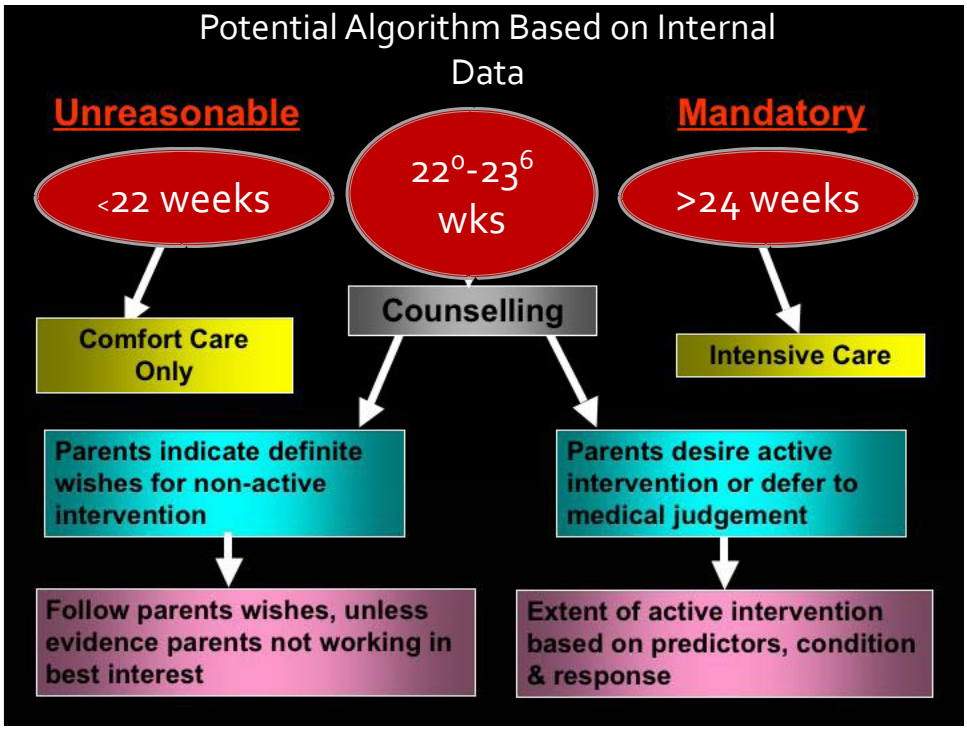
- Understand our role as the physician in the decision process for the ELBW infant
- Advocate for the resources for reliable, up-to-date data regarding burden, benefit and costs of treatment
- Commit to presenting this information to parents as accurately and objectively as possible

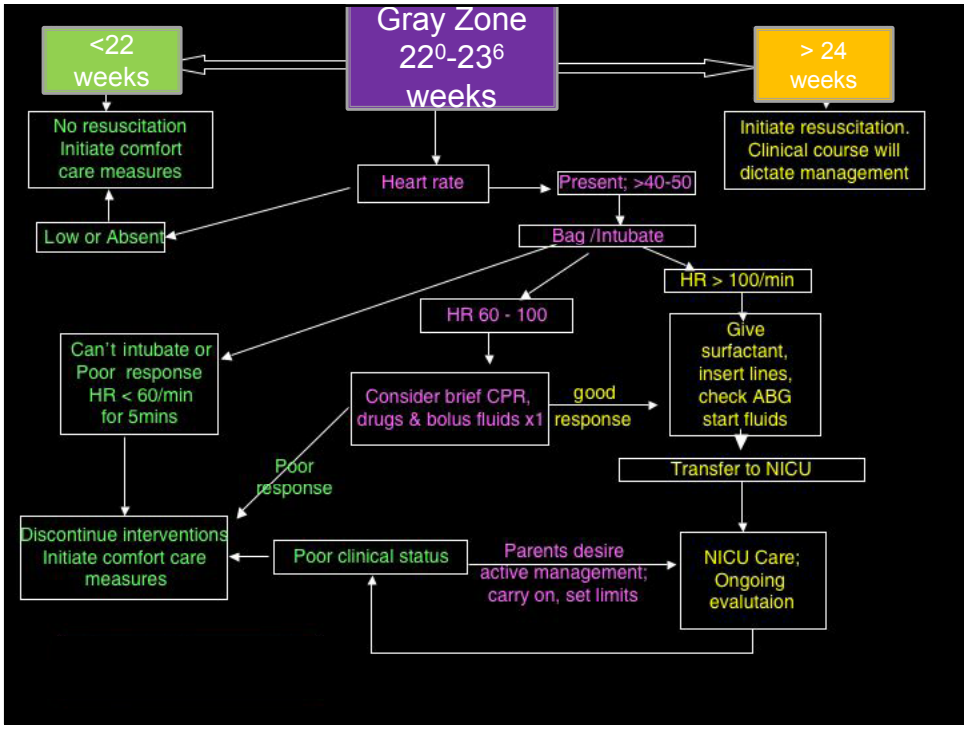
Uncertainty :
Comfort Care vs Aggressive Intervention

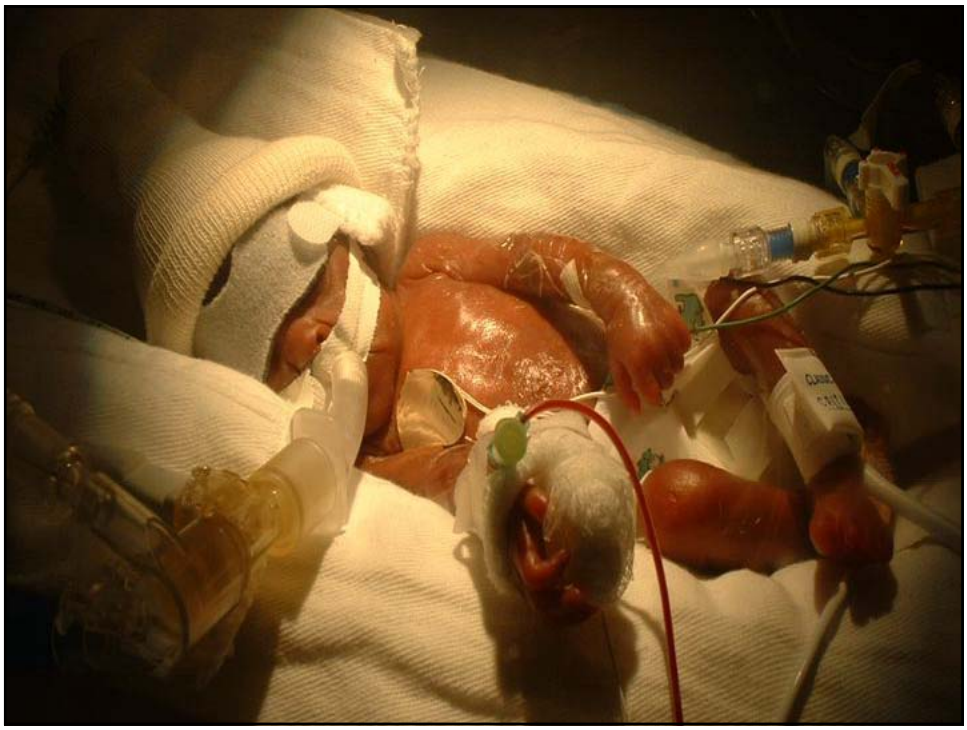


Intact survival of infants <500grams and <23 weeks is very small and burden of care great, but outcome for an individual infant often difficult to determine

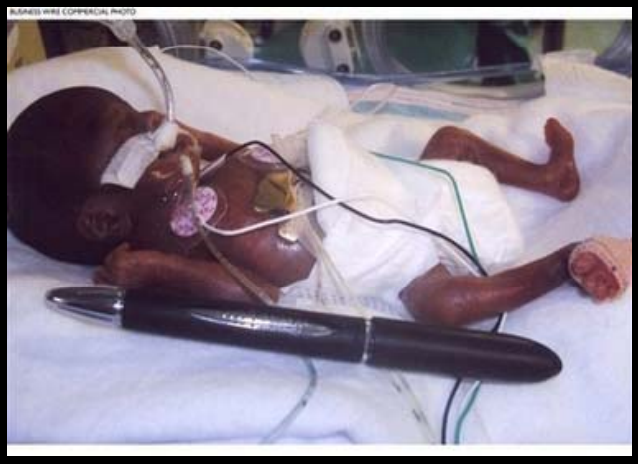

Working Paradigm
Gestational Age
Too Small Too Immature
Gray Zone: Undefined
Too Big Too Mature
Limit of Viability
???
Active Intervention


Potential Algorithm Based on Internal Data
Unreasonable
Mandatory
<22 weeks
22⁰-23⁶ wks
>24 weeks
Counselling
Comfort Care Only
Intensive Care
Parents indicate definite wishes for non-active intervention
Parents desire active intervention or defer to medical judgement
Follow parents wishes, unless evidence parents not working in best interest
Extent of active intervention based on predictors, condition & response


Gray Zone
22^0-23^6 weeks
<22 weeks
> 24 weeks
No resuscitation
Initiate comfort care measures
Initiate resuscitation. Clinical course will dictate management
Heart rate
Present; >40-50
Low or Absent
Bag /Intubate
HR > 100/min
HR 60 - 100
Can't intubate or Poor response HR < 60/min for 5mins
Consider brief CPR, drugs & bolus fluids x1
good response
Give surfactant, insert lines, check ABG start fluids
Poor response
Transfer to NICU
Discontinue interventions Initiate comfort care measures
Poor clinical status
Parents desire active management; carry on, set limits
NICU Care; Ongoing evalutaion



21 weeks

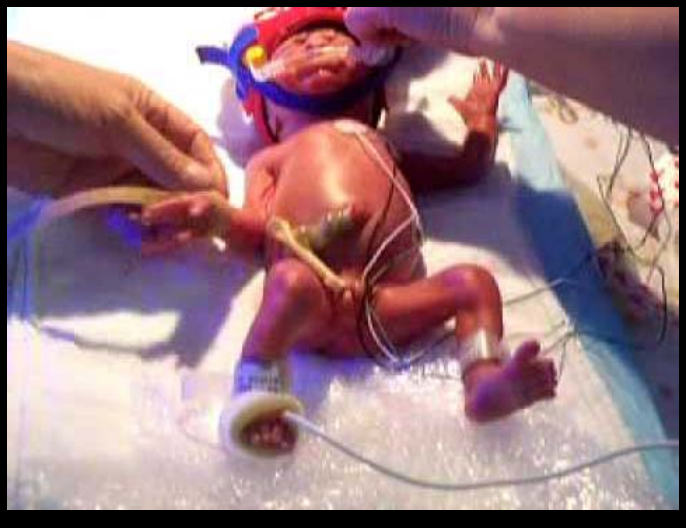


22 weeks

23 weeks

24 weeks

28 weeks




COLLECTOR'S EDITION
LIFE
BORN TOO SOON
The high-tech, high-risk drama of keeping the tiniest babies alive
Jason Waldmann weighed pounds
MAY 2000/$3.99

AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

MONDAY, OCTOBER 25, 2010

Moderator – Edwin Spitzmiller, DO, FACOP
Co-Moderator (BOT Member) – James E. Foy, DO, FACOP

7:00 am – 4:30 pm	**AOA Registration**
8:00 am – 9:30 am	**AOA Opening Session/Keynote Address**
9:30 am – 10:30 am	**Vision Screening Update and to Refer or Treat?** Kenneth P. Adams, DO, JD
10:30 am – 11:30 am	**Sexual Exploitation – What It Is and What It Isn't** Marty Klein, PhD
11:30 am – 1:00 pm	**Alumni Lunches**
1:00 pm – 2:00 pm	**What is a Meaningful Use of Electronic Information as Directed by the American Recovery and Investment Act?** Michael G. Hunt, DO, FACOP, FAAP
2:00 pm – 2:45 pm	**State of the College** Margaret Orcutt Tuddenham, DO, FACEP, FACOP
2:45 pm – 3:00 pm	Break
3:00 pm – 4:00 pm	**Discharge Planning for NICU Patients** Ronald S. Cohen, MD
4:00 pm – 5:00 pm	**Medical Information: Is it Really Portable?** Michael G. Hunt, DO, FACOP, FAAP
5:00 pm – 7:00 pm	**CME Committee, Pediatric Program Director and Vaccine Committee Meetings**

MONDAY, OCTOBER 25, 2009

Moderator – Edwin Spitzmiller, DO, FACOP
Co-Moderator (BOT Member) – James E. Foy, DO, FACOP

9:30 am – 10:30 am

Vision Screening Update and to Refer or Treat?

Kenneth P. Adams, DO, JD

Objective: Upon completion of this lecture, the participant will understand why vision screening, what screening is recommended, how to screen, and eye exam and ophthalmology pearls.

AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

MONDAY, OCTOBER 25, 2009

Moderator – Edwin Spitzmiller, DO, FACOP
Co-Moderator (BOT Member) – James E. Foy, DO, FACOP

10:30 am – 11:30 am

Sexual Exploitation – What It Is and What It Isn't

Marty Klein, PhD

Objective: Upon completion of this lecture, the participant will be able to learn diagnostic criteria for pursuing possible sexual exploitation, learn key characteristics of healthy childhood sexual expression, and learn how adults can support the development of healthy childhood sexual expression.

MONDAY, OCTOBER 25, 2009

Moderator – Edwin Spitzmiller, DO, FACOP
Co-Moderator (BOT Member) – James E. Foy, DO, FACOP

1:00 pm – 2:00 pm

What is a Meaningful Use of Electronic Information as Directed by the American Recovery and Investment Act?

Michael G. Hunt, DO, FACOP, FAAP

Objective: Upon completion of this lecture, the participant will have a familiarity with the pros and cons of electronic information, know the terminology and resources for transmitting information, define discrete data, guage difficulties of the use of electronic information, and define/describe what is needed to implement the EMR to meet the incentive requirements.

AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

MONDAY, OCTOBER 25, 2009

Moderator – Edwin Spitzmiller, DO, FACOP
Co-Moderator (BOT Member) – James E. Foy, DO, FACOP

2:00 pm – 2:45 pm

State of the College

Margaret Orcutt Tuddenham, DO, FACEP, FACOP

Objective: Upon completion of this lecture, the participant will become aware of and invited to participate in the short term, medium term and long term goals of the college.

MONDAY, OCTOBER 25, 2009

Moderator – Edwin Spitzmiller, DO, FACOP
Co-Moderator (BOT Member) – James E. Foy, DO, FACOP

3:00 pm – 4:00 pm

Discharge Planning for NICU Patients

Ronald S. Cohen, MD

Objective: Upon completion of this lecture, the participant will have a better understanding of the problems facing the NICU graduate affecting their transition from hospital to home care, have a greater knowledge of the possible issues facing NICU graduates and their caregivers once they come home, and provide an up-date on the outcome of NICU graduates.

DISCHARGING PREMATURE INFANTS

RONALD S. COHEN, MD

DIRECTOR – INTERMEDIATE & SPECIAL CARE NURSERIES
LUCILE S. PACKARD CHILDREN'S HOSPITAL

CLINICAL PROFESSOR OF PEDIATRICS
STANFORD UNIVERSITY SCHOOL OF MEDICINE

MCCPOP – January 2010

Discharging Premature Infants

- Disclaimer: no commercial conflict of interest!
- Abbreviations used:
  - EGA = Estimated Gestational Age (weeks + days).
  - PMA = Post-Menstrual Age (weeks + days).
  - ABD = Apnea, Bradycardia, Desaturation.
  - LOS = Length of Stay (days).
  - ROP = Retinopathy of Prematurity.
  - ELBW = Extremely Low Birth Weight (< 1000 gm).
  - SpO_2 = Oxygen Saturation by Pulse Oximetry.

3 "When will my baby go home"?

- Probably parents most common question.
- No predetermined "magic" number.
- No specific discharge weight.
- No required age.

R. S. Cohen, MD

4 Three Physiologic Competencies

1. Oral feeding sufficient to support appropriate growth;
2. Ability to maintain normal body temperature in a home environment; and
3. Sufficiently mature respiratory control.

"These competencies are achieved by most preterm infants between 36 and 37 weeks' postmenstrual age…"

AAP COFN *Pediatrics* 2008; 122:1119-26.

R. S. Cohen, MD

5 "Your baby will go home when …"

- Able to maintain temperature in open crib.
- Able to maintain oxygenation safely.
- Able to feed & gain weight consistently.
- All acute medical issues resolved, e.g. –
  - Off IV medications.
  - Important tests all completed.
- No further surgical care needed acutely, e.g. –
  - ROP.
  - Ventriculomegaly.

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6 General Guidelines for Parents

- Babies usually go home close to their due date.
  - Surgical problems usually delay discharge.
  - ROP can delay discharge for ELBW babies.
- Most common final delay – FEEDING!
  - Doesn't matter if RN staff can feed the baby!
  - Parents are critical part of feeding care!
- Next source of delay – ABD's
  - Home Monitoring?
  - Parental anxiety?

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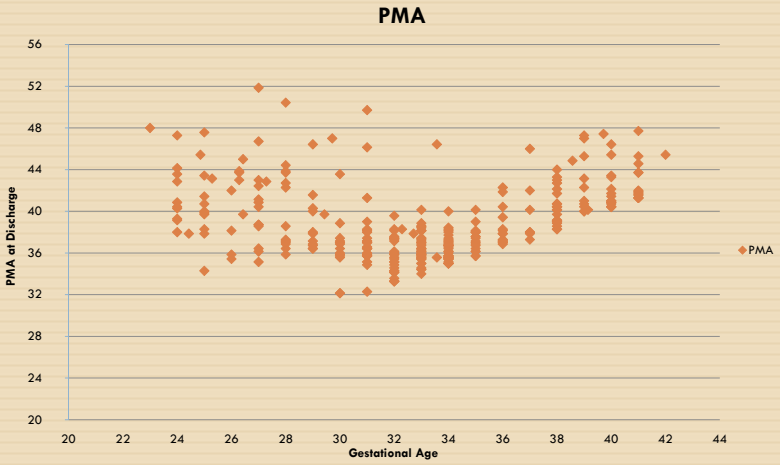

7

PMA at Discharge vs Gestational Age

Mean EGA = 32.9 ± 4.5 wk; Mean Birth Weight = 2073 ± 996 gm.
N = 326.

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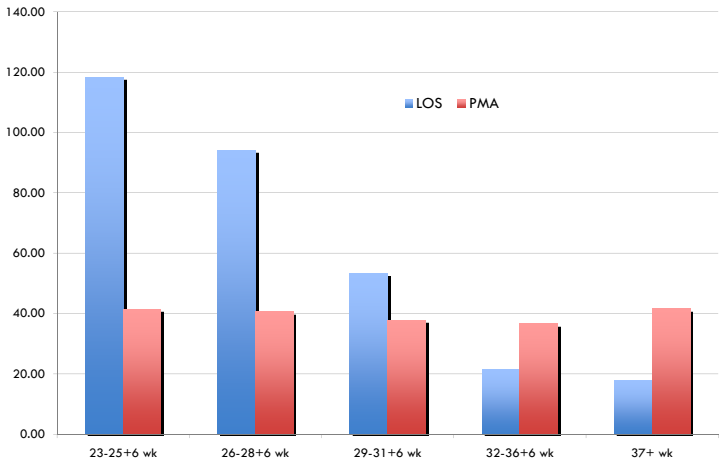

8

Mean LOS & PMA and Gestational Age Group

Mean EGA = 32.9 ± 4.5 wk; Mean Birth Weight = 2073 ± 996 gm.
N = 326.

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9 "Predicting Time to Hospital Discharge for Extremely Preterm Infants"

- "… prediction of exact PMA in days at the time of discharge was poor, even in models that included the complete variable set."
- "… prediction of early or late discharge seems to be feasible."
- Late discharge associated with:
  - Late Sepsis
  - BPD
  - Post-natal Steroids
  - NEC
  - ROP Stage 3
  - Surgery

R. S. Cohen, MD

Hintz SR, et al. *Pediatrics* 2010; 125:e146-e154.
www.pediatrics.org/cgi/doi/10.1542/peds.2009-0810

10 Variation between NICU

- Compared 15 NICU in Massachusetts
  - 30+0 to 34+6 wk EGA.
  - Comparable populations.
  - Wide variability in PMA at discharge.
- Late discharge PMA associated with:
  - Later PMA when stopped ABD's.
  - Later PMA when stopped Gavage feeds.
  - Longer duration of Pulse Oximetry.

Eichenwald EC, et al. *Pediatrics* 2001;108:928-33.

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11 Birth EGA vs Discharge PMA

TABLE 3. Hospital Site Admission GA and Discharge PMA

Site	GA at Birth (weeks)	PMA at Discharge
1	33.5 ± 0.9	35.2 ± 0.5
2	32.9 ± 1.1	35.3 ± 0.7
3	33.7 ± 0.9	35.4 ± 0.6
4	32.8 ± 1.6*	35.5 ± 0.6
5	32.9 ± 1.2	35.5 ± 0.8
6	33.2 ± 1.4	35.6 ± 0.9*
7	32.4 ± 1.2*	35.6 ± 1.0*
8	33.0 ± 1.2	35.8 ± 0.7*
9	33.7 ± 1.0	35.8 ± 1.0*
10	33.5 ± 1.2	35.9 ± 0.7*
11	33.3 ± 1.1	36.0 ± 0.9*
12	33.3 ± 0.9	36.1 ± 1.2*
13	33.3 ± 1.1	36.1 ± 1.2*
14	32.9 ± 1.4	36.5 ± 1.1*
15	33.2 ± 1.0	36.5 ± 1.2*

* $P < .05$ compared with site 1.

Eichenwald EC, et al. *Pediatrics* 2001; 108:928-33.

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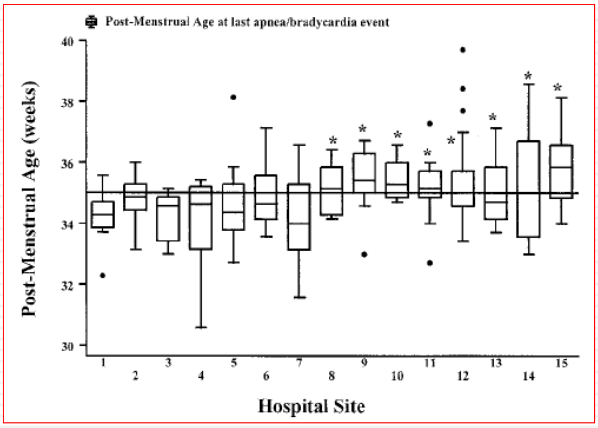
12 PMA & Last ABD



Eichenwald EC, et al. *Pediatrics* 2001; 108:928-33.

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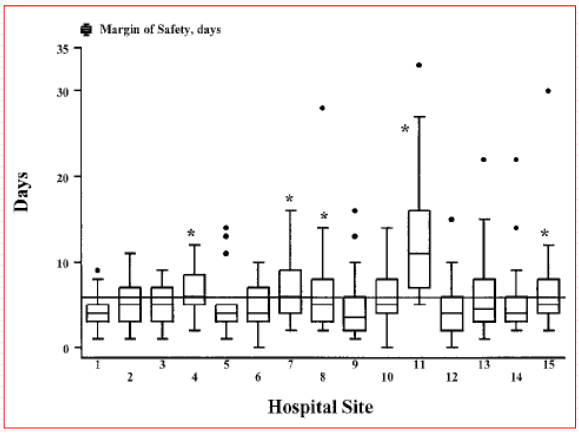
13 Margin of Safety & Discharge



Eichenwald EC, et al. *Pediatrics* 2001; 108:928-33.

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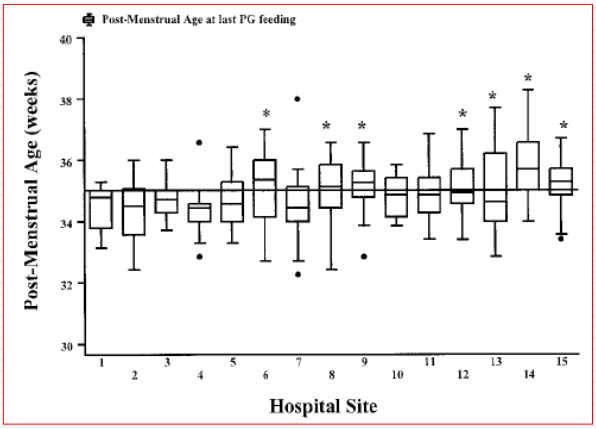
14 PMA & Last Gavage Feeding



Eichenwald EC, et al. *Pediatrics* 2001; 108:928-33.

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15

Eichenwald et al Conclusions: 1

"A description of monitoring techniques and definitions of clinically significant apnea or bradycardia events are essential if national guidelines for the safe discharge of the convalescent premature infant are to effectively reduce length of hospital stay and costs."

Eichenwald EC, et al. *Pediatrics* 2001; 108:928-33.

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16

Eichenwald et al Conclusions: 2

"We speculate that in the absence of a biological explanation, individual NICUs or practitioners with a more conservative approach to feeding, apnea management, or incubator use may prolong hospital stays even in an otherwise healthy population of premature infants."

Eichenwald EC, et al. *Pediatrics* 2001; 108:928-33.

R. S. Cohen, MD

Early Weaning From Incubator and Early Discharge of Preterm Infants: Randomized Clinical Trial

AUTHORS: Enrico Zecca, MD, Mirta Corsello, MD, Francesca Priolo, MD, Eloisa Tiberi, MD, Giovanni Barone, MD, and Costantino Romagnoli, MD

Division of Neonatology, Department of Pediatrics, University Hospital "A. Gemelli," Catholic University of the Sacred Heart, Rome, Italy

KEY WORDS
preterm infants, incubator, open crib, discharge, length of stay

ABBREVIATIONS
LOS—length of stay
GV—growth velocity
ET—early transition
ST—standard transition
GA—gestational age

WHAT'S KNOWN ON THIS SUBJECT: Reduction of LOS is an important goal to be achieved for preterm infants. There currently is little evidence from randomized trials to inform practice regarding the preferred weight for transfer of preterm infants from incubators to open cribs.

WHAT THIS STUDY ADDS: Weaning of moderately preterm infants (GAs of 30–35 weeks at birth) from incubators to open cribs at weights as low as 1600 g significantly reduced LOS without apparent adverse effects.

17

Wean from Incubator at 1600 vs 1800 gm?

Zecca E, at al. *Pediatrics* 2010; 2010;126;e651-6.

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Early Incubator Wean

TABLE 1 Baseline Characteristics of Studied Newborns

	ET Group	ST Group	*P*
GA, mean ± SD (range), wk	32.2 ± 1.7 (27–35)	32.0 ± 1.7 (27–35)	.53
Birth weight, mean ± SD (range), g	1378 ± 208 (840–1590)	1360 ± 188 (1010–1595)	.66
Male, *n* (%)	17 (36)	22 (47)	.26
Small for GA, *n* (%)	15 (32)	13 (28)	.82

TABLE 2 Comparison of Relevant Data From Incubator Weaning to Discharge Home

	ET Group	ST Group	*P*
Weight at transition to open crib, mean ± SD (range), g	1638 ± 25 (1600–1680)	1851 ± 29 (1800–1890)	<.0001
Time spent in open crib, mean ± SD (range), d	6 ± 3 (2–17)	6 ± 2 (2–15)	.51
LOS, median (interquartile range), d	23.5 (19–30.5)	33.0 (27–44.5)	.0002
Weight at discharge, mean ± SD (range), g	1842 ± 126 (1680–2315)	2067 ± 134 (1855–2410)	<.0001
Postmenstrual age at discharge, mean ± SD (range), wk	35.6 ± 1.5 (33–41)	37.0 ± 1.1 (34–40)	.0006
GV, mean ± SD (range), g/kg per d	19 ± 5 (12–39)	22 ± 16 (3–55)	.15
Individual amount of breastfeeding at discharge, mean ± SD, %	43 ± 31	46 ± 29	.60

Zecca E, at al. *Pediatrics* 2010; 2010;126;e651-6.

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19 Effect of Incubator Weaning

- Weaned at about 200 gm lower weight.
- LOS shortened by about 10 Days.
- PMA at discharge decreased by about 1 ½ weeks.
- No difference in growth velocity.
- Patients with lung disease or ABD excluded.

Zecca E, at al. *Pediatrics* 2010; 2010;126;e651-6.

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20 ABD after Discharge?

- Swedish longitudinal study
  - N = 33; EGA 23 – 28 wk
  - Studies until ~ 45 wk PMA
  - Mean discharge PMA = 38.3 ± 0.5 wk
- Results of studies at > 36 wk PMA
  - Apnea/hypoventilation – 67%
  - Bradycardia – 17%
  - Prolonged Apnea resulted in Bradycardia

Hofstetter AO, et al. *ActaPædiatrica 2007; 97:285–92.*

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21 Periodic Breathing after Discharge?

Table 1 Patient Characteristics

Patient characteristics ($N = 28$)	Median (range)
Gender (M/F)	15:13
Birth weight (g)	1660 (1062–2612)
Weight at recording (g)	2042 (1717–2495)
Gestational age (weeks)	32 (27–34)
Corrected gestational age at recording (weeks)	35 (33–37)

Table 2 PB Parameters

PB parameters	Median (range)
Percent PB	13 (6.7–54.4)
Episodes per 100 min quiet time	10.6 (4.6–28.3)
Mean duration of episodes (min)	1.2 (0.76–2.52)
Duration of longest episode (min)	4.2 (1.5–20.7)

Razi NM, et al. *J Perinatol*2002; 22:442-4.

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22 Desaturation& Feedings?

- N = 22; EGA 28±2 wk
- Studied at PMA 36.5±1.6 wk

Table 2
Description of feedings and desaturation events

	Mean	S.D.	Range
Feeding variables			
Length of feeding (min)	21	11.3	6–43.5
Time with $SpO_2 < 90\%$ (s)	302	378.9	1–1202
Percentage of feeding $SpO_2 < 90\%$	20.13%	17.98%	0–70.19%
Desaturation events (n = 238)			
Number of desaturation events per infant[a]	10.8	8.9	1–28
Length of desaturation events (s)	29.5	57.4	1–416

[a] $SpO_2 < 90\%$ for 1 or more seconds with 10 or more seconds of higher SpO_2 separating events.

Thoyre SM, Carlson J. *Early Hum Dev* 2003; 72:25-36.

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23 Transfusion for ABD?

- Mean 25 wk, 740 gm at Birth
- Mean 5.5 wk, 1058 gm at Study
- Hgb 7.8 gm%

"We conclude that blood transfusions significantly reduced heart and respiratory rates in these anemic infants, but had little effect on apnea of prematurity."

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24 Apnea Management per COFN

- "…maturation of respiratory control to a point that allows safe discharge may take longer, occasionally up to 44 weeks' postmenstrual age."
- "Use of a home monitor does not preclude the need for demonstrated maturity of respiratory control before discharge and should not be used to justify discharge of infants who are still at risk of apnea."
- "Formal laboratory analyses of breathing patterns (ie, "pneumograms") are of no value in predicting SIDS and are not helpful in identifying patients who should be discharged with home monitors."

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AAP COFN *Pediatrics* 2008; 122:1119-26.

25 ABD &the "5 Day Rule"

TABLE 3. Characteristics of Apnea in the Study Population

	Mean ± SEM	Median	25th Percentile	75th Percentile
PMA off xanthines (wks)	35.3 ± 0.3	34.6	33.6	36.8
PMA on last apnea day (wks)	37.7 ± 0.3	37.1	35.4	39.4
LAD* to discharge (days)	14.8 ± 1.1	11.0	9.0	17.5
LAD-1† to LAD (days)	4.0 ± 0.4	3.0	1.0	5.0
LAD-2‡ to LAD-1 (days)	3.3 ± 0.5	2.0	1.0	4.0
Maximum interval (between 1 and LAD or between 2 and 1)	5.3 ± 0.5	4.0	2.0	7.0

* LAD, day on which last apnea occurred.
† LAD-1, apnea day previous to day on which last apnea occurred.
‡ LAD-2, apnea day previous to LAD-1 (see Fig 1).

Darnall RA, et al. *Pediatrics* 1997;100:795– 801.

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26 Margin of Safety for Apnea

Conclusions. **We conclude that otherwise healthy preterm infants continue to have apneas separated by as many as 8 days before the last apnea before discharge. Conversely, infants with longer apnea intervals often have identifiable risk factors other than apnea of prematurity.**

Darnall RA, et al. *Pediatrics* 1997;100:795–801.

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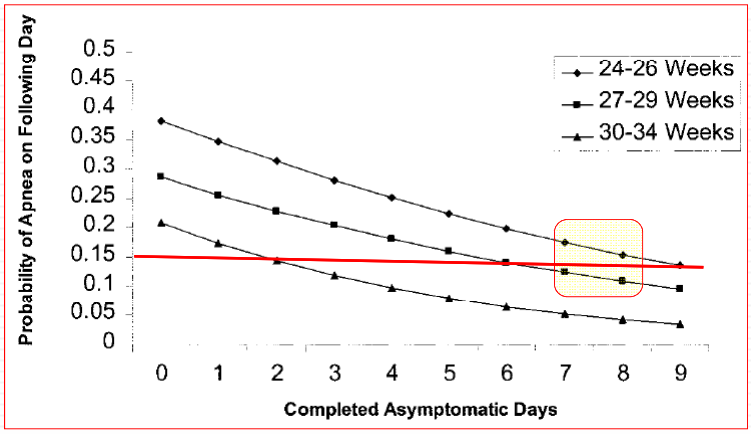
27 Probability of Recurrent ABD



Zupancic JAF, et al. *Pediatrics* 2003;111:146-52.

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28 Cost-effectiveness Analysis

"Compared with the typical strategy of monitoring all infants for 5 days, a policy of monitoring infants of 30 to 34 weeks' gestation for 4 days and those below 30 weeks' gestation cohorts for 7 days would consume 453 fewer bed days, cost $621,000 less, and generate 21 more QALYs."

Zupancic JAF, et al. *Pediatrics* 2003;111:146-52.

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29

SIDS and ABD?

Extreme and Conventional Cardiorespiratory Events and Epidemiologic Risk Factors for SIDS

Toke Hoppenbrouwers, PhD, Joan E. Hodgman, MD, Anusha Ramanathan, MD, and Fred Dorey, PhD

Objective To test the hypotheses that there is a lack of correlation between extreme events and epidemiologic risk factors for sudden infant death syndrome (SIDS), and if conventional events are normal, their numbers should increase once a circadian decrease in breathing rate is established. In addition, the number of events should decrease with maternal smoking.
Study design Three outcome variables were derived from the Collaborative Home Infant Monitoring Evaluation (CHIME) of 1082 infants: (1) at least 1 extreme event lasting ≥30 seconds, (2) at least 1 conventional event lasting ≥20 seconds, and (3) being part of the 50% of infants with the most events.
Results Multivariate logistic regression analyses found that extreme events were not statistically associated with any known SIDS risk factors and occurred less often during the early morning. Healthy term infants had significantly fewer of these events compared with preterm infants, subsequent siblings of infants with SIDS, and infants with an apparent life-threatening event, a finding that was not evident after 43 weeks (3 weeks postterm). Conventional events increased during the night, whereas maternal smoking was associated with a decrease in conventional events. Apneic episodes persisting for ≥40 seconds occurred in 1.8% of the infants.
Conclusions Extreme events are associated with immaturity and do not seem to be immediate precursors of or causally related to SIDS. *(J Pediatr 2008;152:636-41)*

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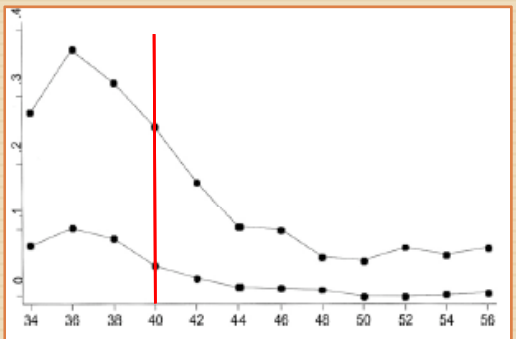

Figure 1. Percentage of infants (ordinate) with conventional events (top line) and extreme events (bottom line) as a function of postmenstrual age (PMA, abscissa). The graphs were adjusted for number of hours monitored.

30

Extreme and Conventional Cardiorespiratory Events and Epidemiologic Risk Factors for SIDS

Hoppenbrouwers T, et al. *J Pediatr* 2008; 152:634-41.

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31 Extreme and Conventional Cardiorespiratory Events and Epidemiologic Risk Factors for SIDS

"Therefore, conventional and extreme events are probably normal, part of a continuum and not fundamentally different in mechanism. The duration of any event that marks entry into a danger zone that will inevitably be followed by an infant's death remains to be determined."

Hoppenbrouwers T, et al. *J Pediatr* 2008; 152:634-41.

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32 What About Insurance?

- Clinically significant event:
  - Apnea > 20-sec.
  - Apnea with Bradycardia < 80 bpm.
  - Apnea with Desaturation< 85%.
- Stop caffeine:
  - At > 32 wk PMA, or
  - 3-7 days without significant event.
- Feeding-related events:
  - "…do not warrant … apnea countdown."
  - "…significance … should be assessed…"
- Discharge after 8 days event free if < 34-wk EGA

Paradigm Health "Neonatal Clinical Management Guidelines, 5th ed".

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33 Uniform Definition for ABD?

- Apnea > 20 seconds or
- Apnea 10-20 seconds with
  - Bradycardia < 80 beats/minute or
  - Desaturation to SpO_2< 80%

Finer NN, et al. *Pediatrics* 2006; 117:S47-S51

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34 SpO_2 and ROP

Table 1 Outcome at 1 year in all babies of 23–27 weeks gestation born during 1990–1994 and its relationship to minimum and maximum pulse oximeter alarm settings[31]

Oximeter alarm settings (%)	Number of babies admitted	Number of survivors (%)	1 year survivors: Median number of days ventilated, n	1 year survivors: Cerebral palsy, n (%)	1 year survivors: Threshold retinopathy, n (%)
88–98*	123	65 (52.8)	21	11 (16.9)	18 (27.7)
85–95	235	128 (54.5)	16	20 (15.6)	20 (15.6)
84–94	84	37 (44.0)	15	6 (16.2)	5 (13.5)
70–90	126	64 (50.8)	7	10 (15.6)	4 (6.3)

*Nellcor pulse oximeter measurements (functional saturation). Other measurements are fractional saturation measurements.
Target saturation was in the upper half of the accepted range.

Tin W, Gupta S. *ADC FNE* 2007;92:F143–F147.

R. S. Cohen, MD

35 Growing Preemie Monitor Orders

- Heart Rate Alarms: 80-200 beats/minute.
- Apnea Alarm: 20 second delay.
- SpO_2 Alarms: 80-100% in Room Air.
- Apnea: no ventilation unless HR or SpO_2 alarms.
- Brady: no ventilation unless Apnea or SpO_2 alarms.
- If need to Ventilate –
  - Start with Room Air,
  - Increase FiO_2 slowly.

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36 ABD Response Matrix

Episode	*Response*
Apnea	Stimulate after 20 seconds, then room air breaths
Bradycardia	Stimulate only if other alarm or Heart Rate < 60
Desaturation	Stimulate first, then room air breaths, then slow O_2 increase

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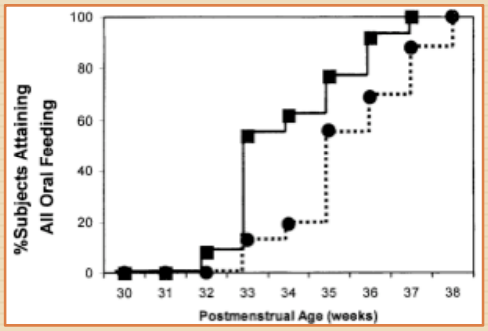


37 Early Introduction of Oral Feeding in Preterm Infants

Simpson C, et al. *Pediatrics* 2002; 110:517-22.

TABLE 2. Oral Feeding Milestones

	Experimental	Control	*P* Value
Full tubefeeding			
Postnatal age (d)	19.5 ± 4.7	20.4 ± 7.6	.72
PMA (wk)	30.6 ± 1.2	30.5 ± 1.7	.77
Transition from tube to all oral feeding (d)	26.8 ± 12.3	38.4 ± 14.0	<.05
Introduction to oral feeding			
Postnatal age (d)	22.9 ± 5.0	42.8 ± 11.2	<.001
PMA (wk)	31.1 ± 1.3	33.7 ± 0.9	<.001
First successful oral feeding			
Postnatal age (d)	32.1 ± 9.9	46.9 ± 10.9	<.001
PMA (wk)	32.4 ± 1.0	34.3 ± 0.9	<.001
4 Successful oral feedings			
Postnatal age (d)	43.6 ± 13.7	54.4 ± 12.6	<.05
PMA (wk)	34.1 ± 1.7	35.3 ± 1.4	<.05
All oral feeding			
Postnatal age (d)	46.4 ± 13.9	58.7 ± 14.5	<.05
PMA (wk)	34.5 ± 1.6	36.0 ± 1.5	<.05
Introduction of oral feeding to first successful oral feeding (d)	9.3 ± 7.7	3.7 ± 3.5	<.05
First successful oral feeding to all oral feeding (d)	13.8 ± 8.8	11.9 ± 6.4	.51
Hospital discharge			
Postnatal age (d)	57.0 ± 17.7	67.0 ± 16.6	.13
PMA (wk)	36.0 ± 2.1	37.1 ± 1.8	.13

Mean ± standard deviation.

38 Early Introduction of Oral Feeding in Preterm Infants

Simpson C, et al. *Pediatrics* 2002; 110:517-22.

39 Predictors of nutritive sucking in preterm infants

Journal of Perinatology (2006) 26, 695–699

ORIGINAL ARTICLE

Predictors of nutritive sucking in preterm infants

RH Pickler[1], AM Best[1], BA Reyna[2], G Gutcher[1] and PA Wetzel[1]

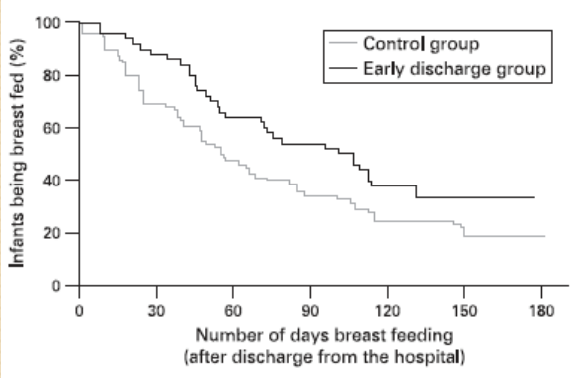
[1]School of Nursing, Virginia Commonwealth University, Richmond, VA, USA and [2]Virginia Commonwealth University Health System, Richmond, VA, USA

Study design: A longitudinal, non-experimental study was conducted in a Level 3 neonatal intensive care unit using a convenience sample of 88 preterm infants. Statistical analyses were performed using a repeated-measures mixed-model in SAS.

Conclusion: Experience at feeding may result in more rapid maturation of sucking characteristics.

Pickler RH, et al. *J Perinatol*2006: 26:693-9.

R. S. Cohen, MD



40 Early discharge with tube feeding at home for preterm infants is associated with longer duration of breast feeding

Meerlo-Habing ZE, et al. *ADC-FNE* 2009; 94:F294-7.

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41

VLBW Discharge "Check List"

- Newborn Screen Status
- Hearing Screen Status
- Car Seat Test
- Vaccination Status (RSV prophylaxis in Season)
- ROP Status and follow-up
- General vision follow-up at ± 4 months
- High-Risk Infant Follow-up at ± 4 months

R. S. Cohen, MD

THE END

MONDAY, OCTOBER 25, 2009

Moderator – Edwin Spitzmiller, DO, FACOP
Co-Moderator (BOT Member) – James E. Foy, DO, FACOP

4:00 pm – 5:00 pm

Medical Information: Is it Really Portable?

Michael G. Hunt, DO, FACOP, FAAP

Objective: Upon completion of this lecture, the participant will have a familiarity with the pros and cons of electronic information, know the terminology and resources for transmitting information, define discrete data, guage difficulties of the use of electronic information, and define/describe what is needed to implement the EMR to meet the incentive requirements.

American College of Osteopathic Pediatricians

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

8:00 am – 9:00 am	**Pediatric Office Dermatology** Melinda F. Greenfield, DO
8:00 am - 10:00 am	**AOA Town Hall Meeting**
9:00 am – 9:45 am	**Prep for Court/Depositions** Mary Angel Meyer, JD
9:45 am – 10:15 am	**Break**
10:15 am – 11:00 am	**Special Needs Advocation** Barbara L. Baldwin, DO, FACOP
11:00 am – 12:00 n	**Gastric Banding as Treatment for Adolescent Obesity** Alison A. Clarey, DO
12:00 n – 1:00 pm	**Lunch On Own/Posters and Exhibits**
1:00 pm – 2.00 pm	**A Case-Based Review of Influenza** James H. Brien, DO, FAAP
2:00 pm – 3:00 pm	**A Case-Based Review of MRSA** James H. Brien, DO, FAAP
3:00 pm – 4:00 pm	**Optimizing Revenue in Your Pediatric Practice** Mary Jean Sage, CMA-AC
4:00 pm – 5:30 pm	**CME Committee, Pediatric Education Leadership Committee, *eJournal***
7:00 pm – 10:00 pm	**AOA/AAOA President's Reception**

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

8:00 am – 9:45 am

Pediatric Office Dermatology

Melinda F. Greenfield, DO

Objective: Upon completion of this lecture, the participant will understand the didactics and case studies which will be used so the participant will be able to recognize and treat or refer for, as well as updates on: Pediatric acne, hemangiomas, impetigo and some 'unusual' cases.

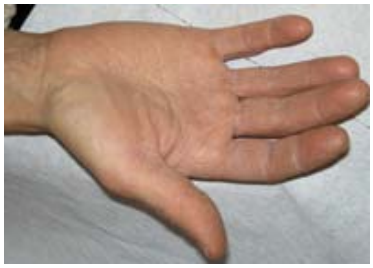
DERMATOLOGY FOR THE PEDIATRIC OFFICE

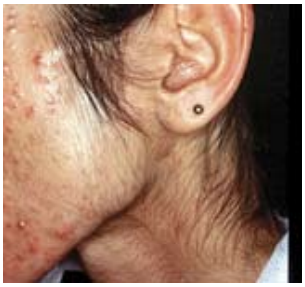
MELINDA F. GREENFIELD, DO
ALBANY DERMATOLOGY CLINIC
ALBANY, GEORGIA

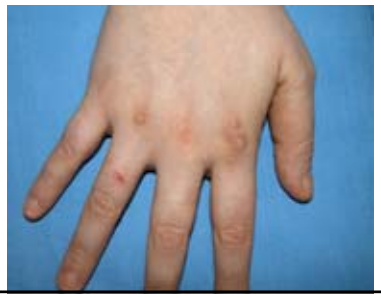
Objectives

- Upon completion of this lecture, the participant will become familiar with the didactics and case studies presented in the lecture

15 year old female



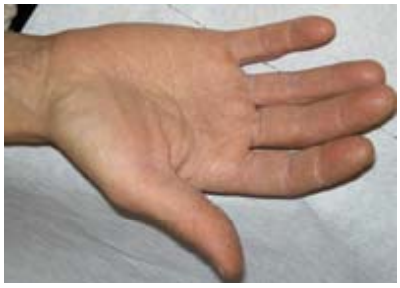




15 year old female

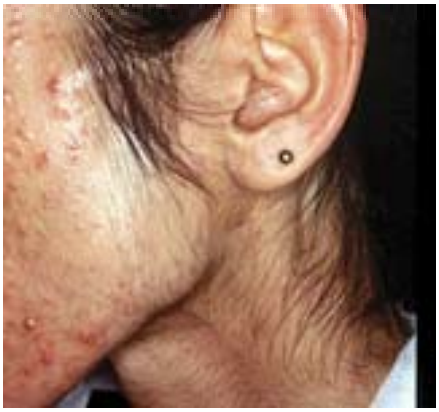
- Mom brings her in because she is worried about some ‘changes’ in her daughter
- Daughter is moody, withdrawn, sleeps a lot, spends excessive time in the bathroom
- Mom has noticed some of these skin changes and wants to know what is going on
- Mom has also noticed that her daughter has terrible breath

Hands are very ‘dry’ and yellow-orange



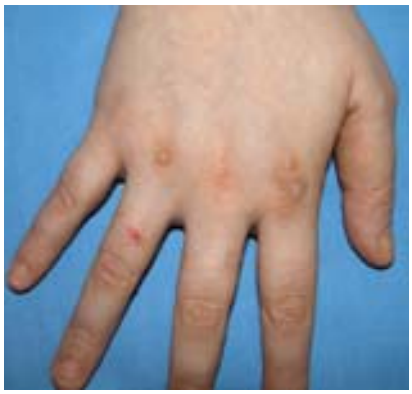
- Carotenoderma- due to increased serum carotenoids
- This patient’s diet consisted of carrots, plums, pumpkin, millet and soy beans
- Asteatotic skin afflicts 70% of these patients

Terrible acne and facial hair



- Lanugo-like hairs develop on face, back, abdomen, forearms
- Excessive amounts of acne in areas that previously had none

New calluses on the back of the hands



- Calluses on the hands, known as Russel's sign, are often seen

Anorexia nervosa

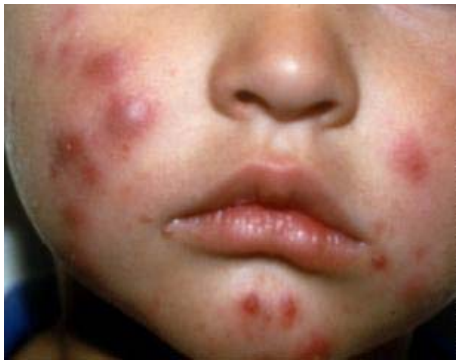
- Worldwide prevalence of 0.3%
- 1% adolescent girls in the USA
- One study of female ballet students found anorexia in 4.1%
- Skin signs in anorexia occur due to starvation, malnutrition, self-induced vomiting, use of diuretics and enemas along with psychiatric illness
- These signs usually develop when the BMI reaches 16 or less

Anorexia Nervosa-skin signs

- Dry skin, follicular hyperkeratosis, carotenoderma, hyperpigmentation, acne, pruritus, lanugo-like hair, Russell's sign, dental enamel erosions….
- Prutitus increases in severity along with the decrease in BMI and will improve with proper nutrition
- All of the skin signs are reversible

Pediatric Acne

- Acne is a multifactoral disorder
- Microcomedo is the origin of all acne lesions
- >50% of children with acne report impairment in body image



Acne-are milk and sugar to blame?

- Recent studies have linked the consumption of milk and high glycemic diets to exacerbation of acne
- Milk-may influence comedogenesis due to hormones and bovine growth hormones
- Carbohydrates-exacerbate acne via insulin production

Pediatric Acne

- Compliance is biggest issue:< 50% in children and teenagers
- Finding combo treatments, like *Epiduo, Ziana, Benzaclin, Duac* can improve compliance
- Newer, novel therapies such as those with a pump, pad or foam may improve compliance
- Patients need to be told that it takes at least 3 months to see improvement

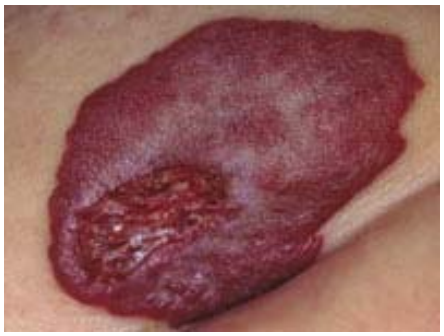
Pediatric Acne

- Antibiotic resistance remains a concern, never give an open RX for antibiotics
- Try to limit to 3 months, or use sub-microbial dosing
- I also try to limit topical erythro or clinda due to resistance concerns
- My new favorite topical is Epiduo
- Isotretinoin is used for patients who are at high risk for severe scarring or those not responding to conventional therapies
- There are limited studies looking at the use of isotretinoin in severe, recalcitrant cases in children

Pediatric Acne

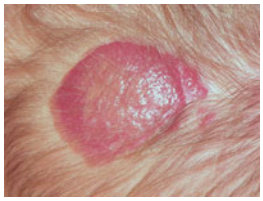
- Sever or persistent childhood acne may be linked to premature adrenarche, Cushing's syndrome, CAH, gonadal/adrenal tumors, and true precocious puberty
- Work-up should include: tanner staging, total/free testosterone, DHEA-S, androstenedione, LH, FSH, prolactin, 17-OH progesterone levels

Cutaneous Hemangioma

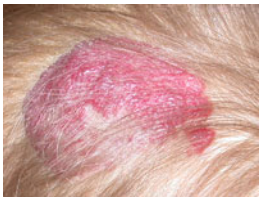


- Common, benign tumors of childhood
- Present in 1-2.6% of neonates and 10-12% of infants by 12 months
- In most cases growth is complete by 5 months
- Involute by 5-10 yrs of age
- Usually no treatment is necessary

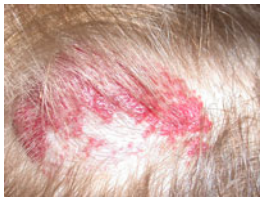
Typical involution



2 months

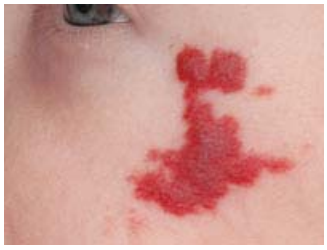


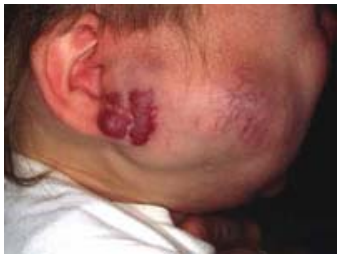
1 year



2 years

Hemangioma



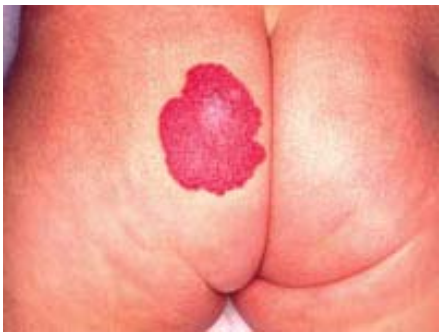


- 80% are solitary
- Size ranges from 1mm to 5 cm
- Can be seen on all body locations, but 60% are located in the head and neck region
- Most are asymptomatic but some can lead to severe problem

Sites associated with complications

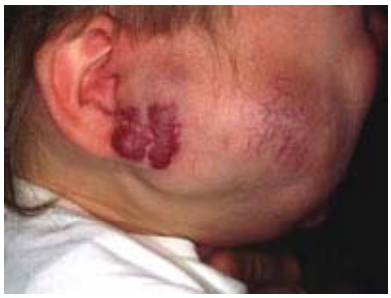
- Airways
- Eyes
- Lumbosacral
- Mandibular and neck (beard area)
- Periocular
- Any ulcerated or bleeding lesion
- Any lesion that obstructs a bodily function

Lumbosacral



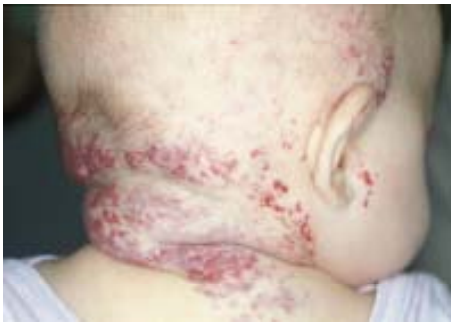
- Spinal dysraphism
- Tethered cord
- Genitourinary anomalies
- "PELVIS"-perineal hemangioma, external genitalia malformations, lipo myelomeningocele, vesico-renal abnormalities, imperforate anus, and skin tags
- MRI for imaging

PHACE Syndrome

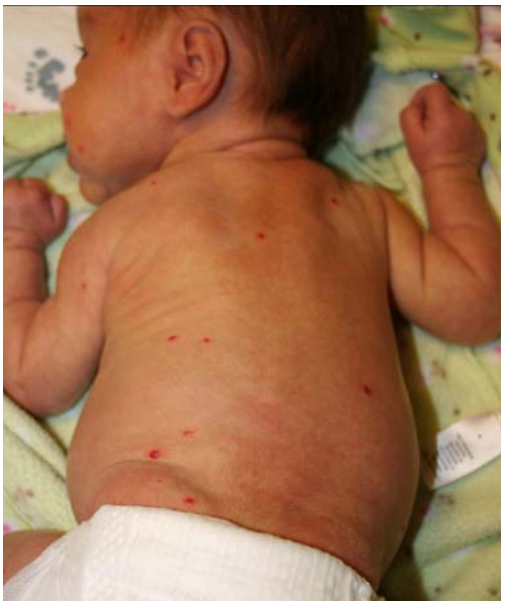


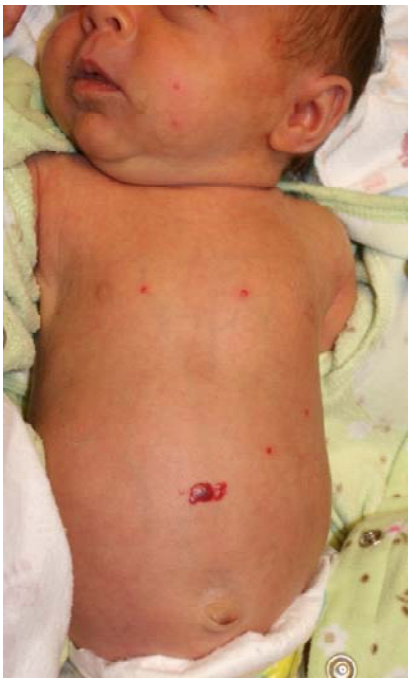
- Posterior fossa malformation
- Hemangioma
- Arterial anomalies
- Coarctation of the aorta and cardiac defects
- Eye abnormalities
- MRI, MRA, ECHO, optho eval, thyroid studies

PHACES



- Segmental infantile hemangioma in an infant with PHACES syndrome
- Involving the posterior neck and right forehead
- Associated with an absent right vertebral artery and a laryngeal hemangioma





Eruptive Neonatal hemangiomatosis

- This healthy 4 week old had over 50 hemangiomas scattered over the body
- She also had a rapidly enlarging hepatic hemangioma which was discovered on ultrasound
- Propanolol was used to shrink the hepatic lesion
- Any infant with multiple lesions needs to have ultrasound of the liver

Liver Hemangiomas

- Liver is the most common extracuaneous site
- Infants with >5 hemangiomas should be evaluated with a hepatic US
- Even if present, most hepatic hemangiomas are asymptomatic
- Some can be life-threatening
- Most common problem is high-output congestive heart failure

Management and treatment

- Prevention of life- or function-threatening complications, or permanent disfigurement
- First-line: topical, IL and systemic steroids
- Second-line: interferon alfa-2a, 2b, laser, surgical
- Third-line: cytotoxins, embolization, angiogenesis inhibitors
- Others: compression, cryo, radiotherapy, sclerotherapy, electrocautery, imiquimod

Hemangioma- Research

- Extensive study>1000 infants
- Discovered a unique immunohistochemical staining profile, stain with GLUT-1, a glucose transporter not seen in other vascular tumors or blood vessels
- Profile is shared with placental blood vessels, so we now know that the neoplasm is not from normal cutaneous vessels

Use of Propanolol

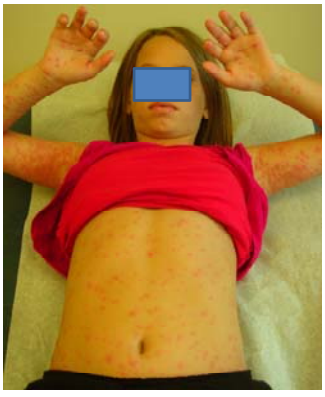
- Few studies have shown that propanolol (1-2mg/kg/day, in 3 divided doses) can inhibit the growth of hemangiomas
- A good second line therapy when corticosteroids are not effective
- Thought to work via vasoconstriction, decreased expression of vascular endothelial growth factors (*VEGF*) and the triggering of apoptosis of capillary endothelial cells

Propanolol

- No consensus on how to monitor these infants
- Side effects- hypoglycemia, bradycardia, hypotension, hypothermia, exacerbation of asthma
- Large clinical trial in US and Europe is underway (www.clinicaltrials.gov)
- Use of propanolol in these cases is completely off-label

2 months of propanolol

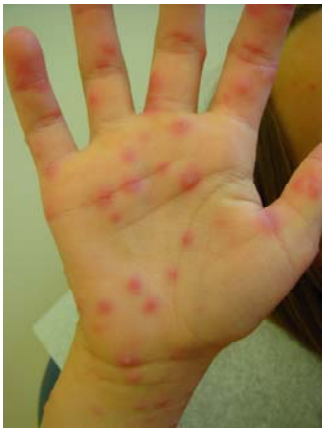
13 year old with pruritic rash



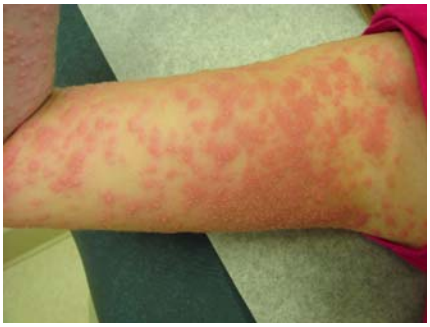
- 5 day history of a spreading severely pruritic eruption
- No constitutional symptoms
- No new contacts
- No new meds

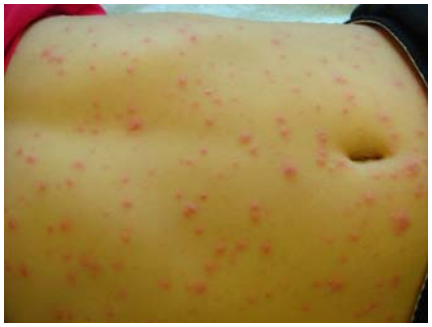
Pruritic rash

- Multiple discrete erythematous papules and vesicles noted on trunk and extremities
- Some areas forming confluents plaques, especially around axillae
- No fever or constitutional symptoms



Pruritic rash

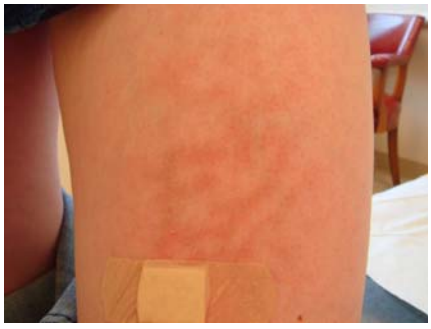




Varicella

- Patient had one vaccine dose at 1 year of age
- 79% of children develop immunity after one dose of vaccine
- Approx. 99% are immune after the 2nd dose
- Vaccine was introduced to the US in 1995
- Despite this, outbreaks still occur so be on the lookout

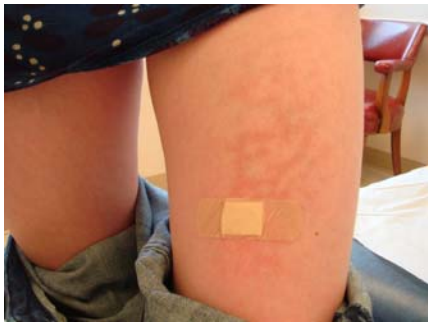
17 year old with rash on leg



- 5 month history of progressive nonpruritic eruption of bilateral thighs
- Lesions were non-palpable, reticular and completely asymptomatic

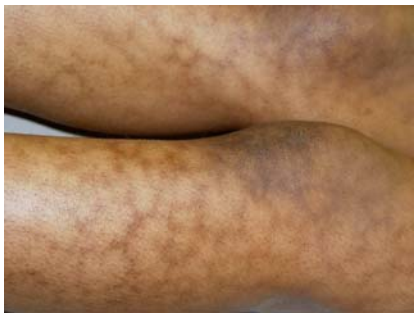
Erythema ab igne

- Aka: Toasted skin syndrome, fire stains
- Due to repeated exposure to heat at a lower level than that which causes a thermal burn (43-47 C)
- Lesions start out as erythematous but later change to purple or brown

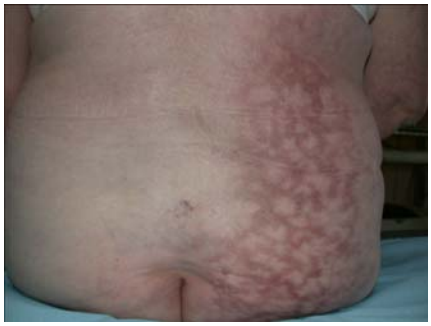


Erythema ab igne

- Historically seen on the inner thighs and legs of women who sat in front of a stove or open fire
- More commonly seen today from use of heating pads especially in the lumbosacral region

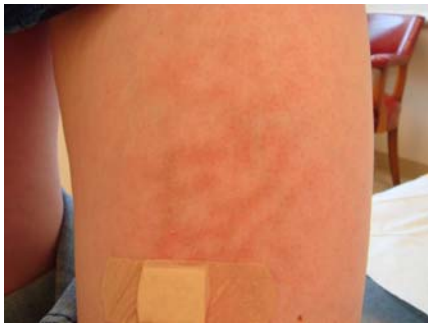


Erythema ab igne



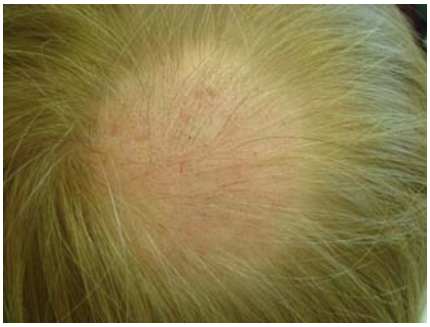
- Carcinoma can develop from dysplastic keratinocytes, in the same way that ultraviolent radiation can result in squamous cell carcinoma

‘Computer ab igne’



The cure for computer ab igne?

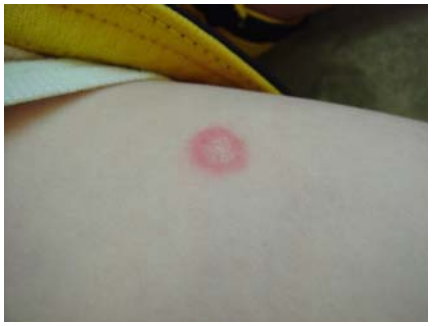
6 year old with hair loss



- 2 week history of slight rash and hair loss
- Lesion is mildly pruritic, slightly tender
- Black dots are noted on close inspection of the scalp

Rash and hair loss

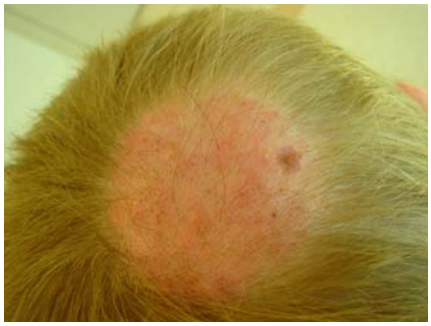
- There are also a few discrete lesions noted on neck and leg
- Fungal cultures were obtained from scalp and neck lesions
- Pt started on topical antifungal cream and shampoo (ciclopirox)



Rash and hair loss

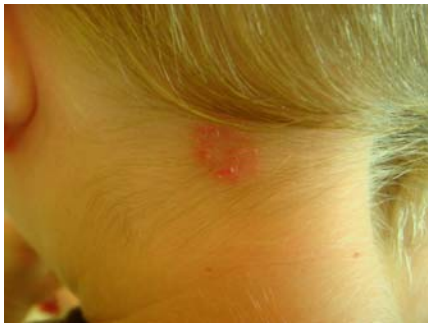
- We received 3 phone calls following the initial visit and the patient's parents insisted that he be seen 3 more times the following week
- Fungal cultures were negative
- First follow up with one PA: started on oral Lamisil and a topical antibiotic after parents noted draining pustules
- Next day returns again, seen by another PA: started on oral antibiotic

Rash and hair loss and VERY angry parents



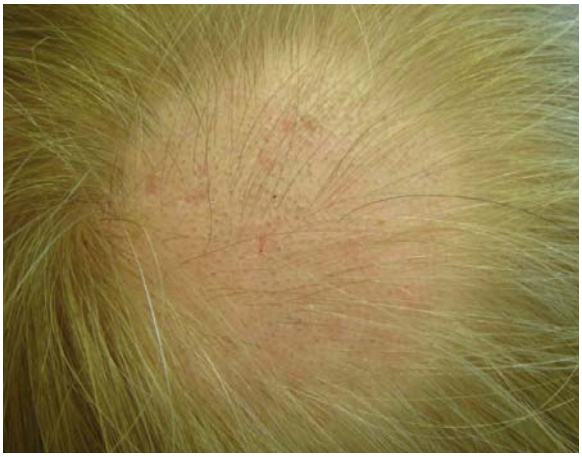
- I see him the next day, mom insists on biopsy
- She decided to stop the shampoo and cream on her own, because it 'wasn't working'
- Demanding to know what in the world is going on with her son
- Child is not bothered by any of the lesions

Hair loss and angry parents

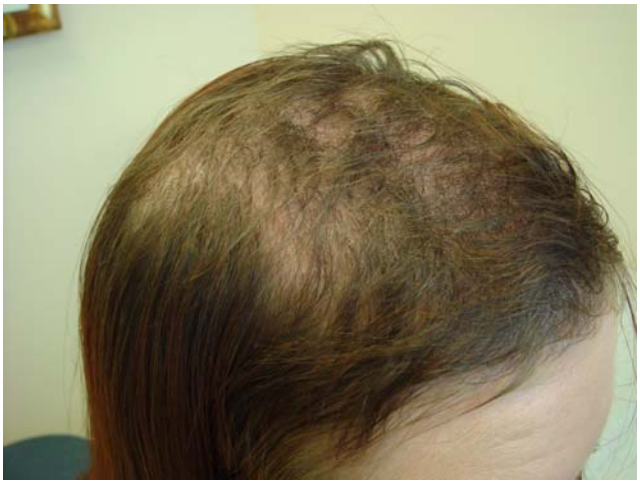


- Skin lesions had cleared with use of the shampoo and cream but returned after stopping it
- Biopsy shows tinea capitis with fungal folliculitis

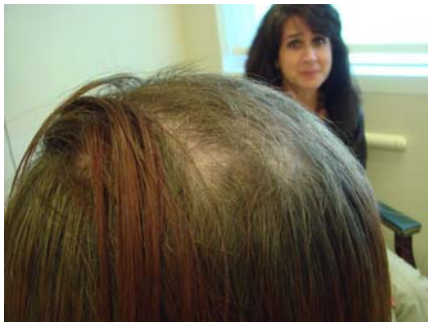
Look for the black dots



Hair loss, again….

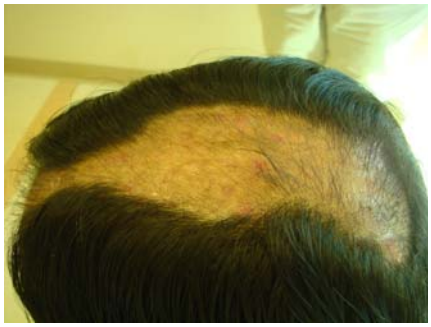


Hair loss, Mom is worried



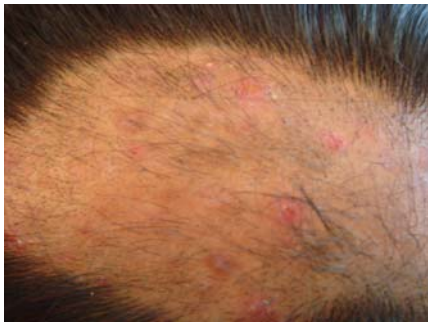
- 16 year old female
- Hair loss x 6 months
- Dad thinks it's from overuse of flat-iron
- Patient 'combs-over' hair to hide huge patch of hair loss

One more hair loss, and a very worried family…..



- 12 year old Indian female
- Treated by pediatrician with griseofulvin, ketoconazole shampoo for 3 weeks
- Scalp itches

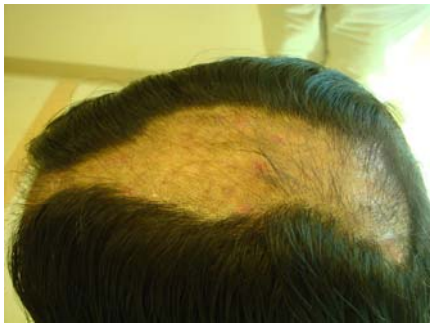
Hair loss

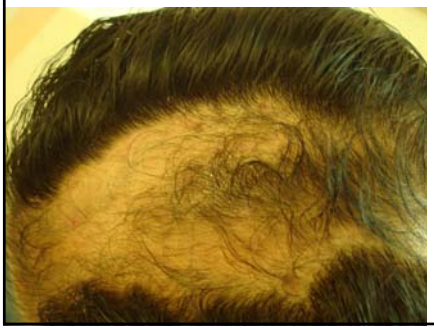


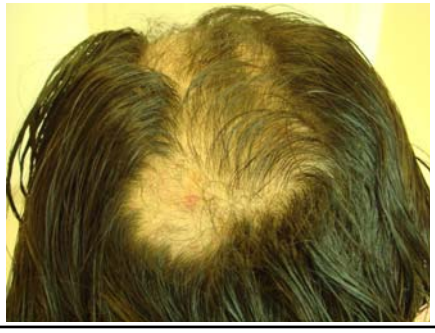
- Physical exam: excoriated papules on scalp, with significant hair loss. Hairs are broken off at different lengths. Pattern of loss is bizarre.
- Fungal culture taken
- Griseofulvin dose is increased to 25mg/kg

3 weeks later…
Fungal culture is negative
Hair loss is progressing..

What is going on here?????







Trichotillomania

- Hair loss from a patient's repetitive self-pulling of hair
- Repeated urge to pull out scalp hair, eyelashes, facial hair, nose hair, pubic hair, eyebrows, or any/all body hair
- Classified in DSM-IV as an impulse control disorder
- Jury is out on whether this is more like a habit, or a tic, an addiction or obsessive-compulsive disorder

Trichotillomania

- Has been seen in infants, but peak onset is 9-13 years of age
- Hair pulling may occur during a 'trance-like' state, therefore children may not remember the act of pulling out the hair
- Scalp is most common area involved especially in children
- Classically, hair is seen at different lengths, with broken hairs with blunt ends

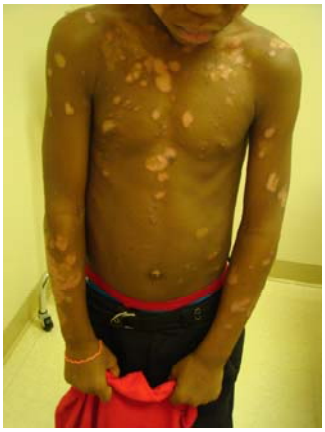
Trichotillomania

- Classic presentation is the “Friar Tuck” form of vertex and crown alopecia
- Some children engage in trichophagia, where they consume the hair that is pulled, extreme cases can lead to trichobezoar
- Treatments include therapy, medications
- 2009 study in Archives of General Psychiatry reported on the use of N-acetylcysteine in the treatment of trichotillomania

Trichotillomania

- 12 week, double-blind, placebo-controlled trial looked at 50 patients (45 women, 5 men avg age 34.3 years)
- Dosing range 1200-2400 mg/d
- Results showed that those assigned to receive NAC had a significantly greater reduction in hair-pulling symptoms when compared to placebo (56% vs 16%)

Childhood Psoriasis

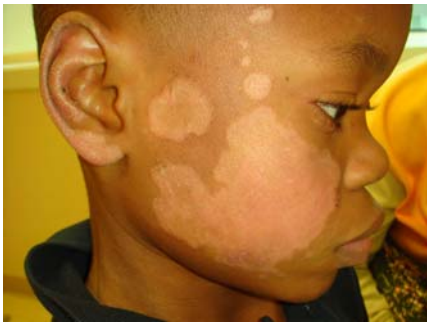


- Study *J Am Acad Dermatol*, June 2010, looked at 887 patients dx with psoriasis under 18
- Mean age of dx 10.6
- 1/3 of patients with psoriasis will develop it during childhood
- 74% will have plaque type
- 2% of overall population will develop psoriasis in lifetime

Treatment of Psoriasis

- Literature review of the studies looking at treating psoriasis in children was done by *de Jager, et al* in the June 2010 edition of the *J Am Acad Dermatol*
- 64 studies reviewed describing 646 children
- Treatment of choice is calcipotriene, and if necessary, combined with mild topical steroid
- Other modalities studied in children have only a low level of evidence

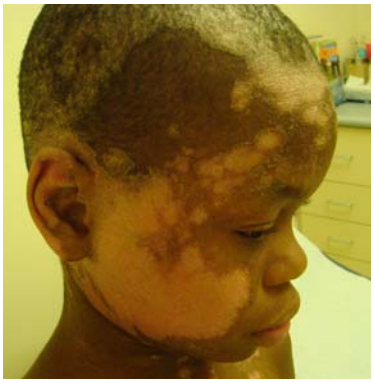
NB-UVB

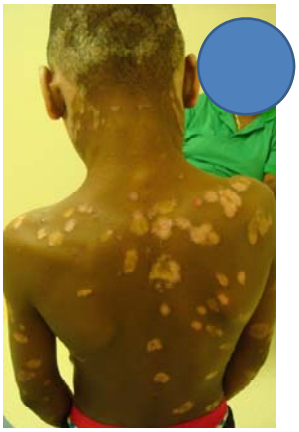



UVB Phototherapy in Pediatric Patients

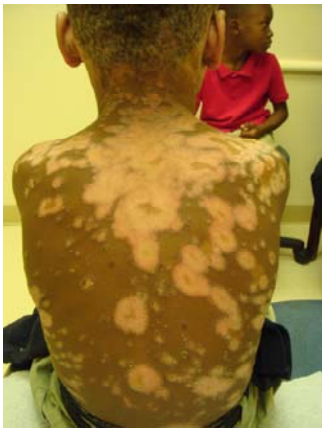
- A retrospective study of patients from 1994-2000 showed no evidence of an increased risk of skin cancer associated with NBUVB or BBUVB
- Another study looked at 4600 patients treated with NBUVB between 1985 and 2002, which also showed no increase in skin cancer

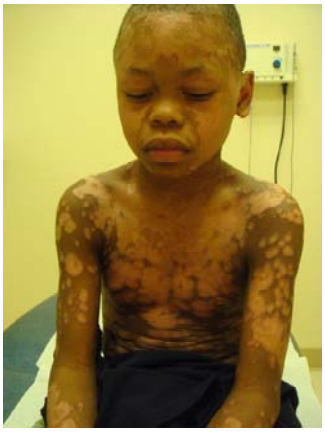
Childhood Psoriasis





Psoriasis





Psoriasis-Methotrexate

- MTX is a folic acid analog that reversibly inhibits dihidrofolate reductase, disrupting DNA synthesis, repair and replication of Tand B lymphocytes
- Approved for use in children for juvenile idiopathic arthritis, aka. JRA
- Used off-label in children for many other rheumatologic and dermatologic conditions

Methotrexate

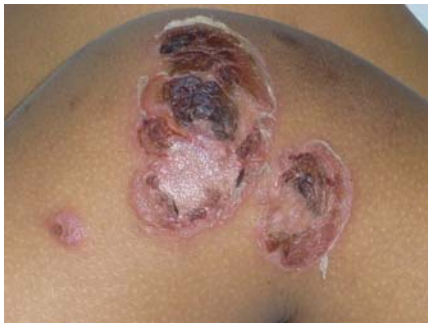
- Studies are limited in children
- Reserved for only severe or recalcitrant cases
- Most common side effects: nausea and vomiting which are relieved by folic acid supplementation
- Dose range is 0.2-0.7 mg/kg/wk (dosed weekly)
- Blood work is monitored
- Bone marrow suppression is most severe side effect and generally occurs within the first 2 months of treatment

Impetigo Update

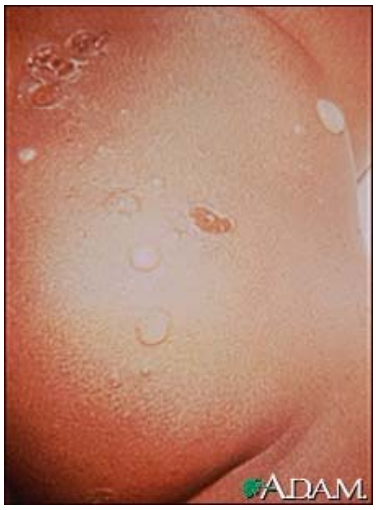
- Bacterial infection of the superficial epidermis commonly seen in infants and children
- Crusted erosions or ulcers
- Bullous and nonbullous forms
- Staph aureus is most common cause
- Strep pyogenes also commonly seen, especially in warm and humid climates
- CA-MRSA is becoming more of a problem

Bullous impetigo

- Commonly affects neonates
- Rapidly enlarging vesicles that evolve to flaccid bullae
- Fluid progresses from clear yellow to turbid/dk yellow
- 24-48 hrs pustules rupture leaving collarette of scale and thin crust



Bullous impetigo



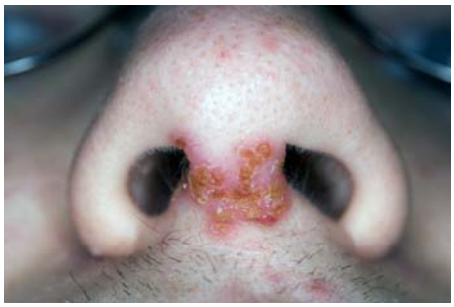
- Less contagious than nonbullous
- Sporadic in presentation
- Typically seen on trunk, extremities and intertriginous areas

Bullous impetigo D/D

- Bullous erythema multiforme
- Bullous pemphigoid
- Bullous scabies
- Contact dermatitis
- Dermatitis herpetiformis
- Pemphigus vulgaris
- Thermal burn

Nonbullous impetigo- aka. impetigo contagiosa

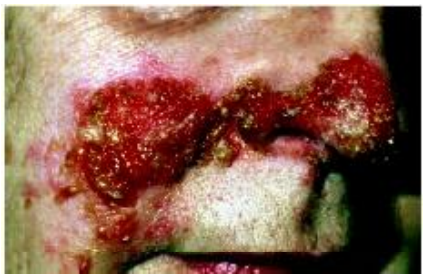
- Preschool-aged children
- Epidemics
- Commonly seen in exposed skin areas: face, extremities
- May begin as small vesicle or pustule that rupture and form yellow crusts



Nonbullous impetigo D/D

- Atopic dermatitis
- Contact dermatitis
- Dermatophytosis
- Discoid lupus
- Herpes simplex
- Herpes zoster
- Varicella
- Pediculosis/scabies

Common impetigo



- Secondary impetiginization of conditions that disrupt the skin
- Seen commonly in eczema, bites, abrasions, HSV

Complications

- Rate of invasive infections and SSSS have declined with use of antibiotics
- Acute poststreptococcal glomerulonephritis (PSGN) occurs in 5%, using antibiotics does not affect the incidence
- Streptococcal skin infections are not thought to be associated with rheumatic fever

MRSA

- First discovered in 1961, only two years after the introduction of methicillin
- Incidence has dramatically increased
- Despite concerns and enhanced virulence of MRSA, most cases can be managed with good hygiene, removal of crusts and topical antibiotics

MRSA

- Community and hospital type are genetically distinct
- *Community–type strains:* only resistant to methicillin, usually present at folliculitis, abscess. Can cause pneumonia in young children
- *Hospital-type strains:* resistant to multiple antibiotics, usually vancomycin sensitive. Commonly seen in leg ulcers

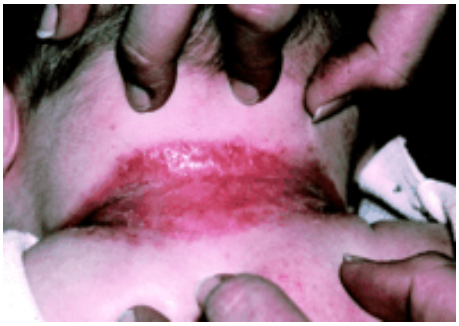
MRSA-treatment

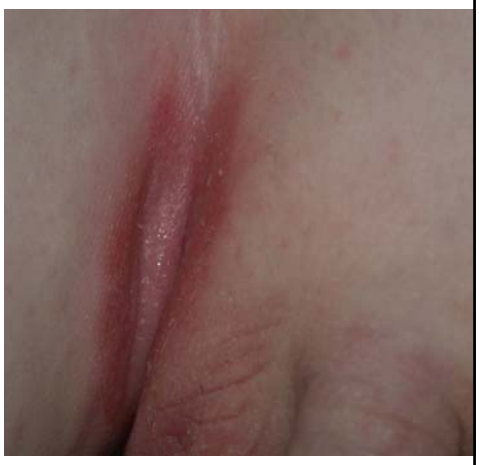
- Drainage- uncomplicated abscess<5cm
- If larger/or complicated-oral antibiotics
- Address: nares, groin, axillae, skin folds…
- Mupirocin/Retapamulin (Altabax) for nares
- Bleach baths for body/ tea tree oil
- No sharing of towels, soap

Treatment

- Usually self-limiting
- Treatment is usually started to avoid complications, prevent recurrence and spread
- Recurrences are common despite treatment

Rash in body folds





Rash in body folds

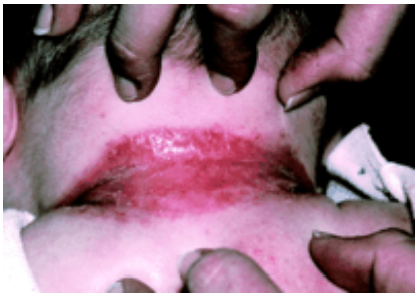
- 5 month old with 8 week history of persistent foul smelling intertriginous eruption on neck, groin, flexural creases of arms and legs
- Unresponsive to topical and oral nystatin
- Lesions are beefy red

D/D Rash in body folds

- Candidiasis
- Inverse psoriasis
- Seborrheic dermatitis
- Atopic dermatitis
- Langerhans cell histiocytosis
- Bacterial intertrigo

Rash in body folds

- Culture yielded heavy growth of Group A beta-hemolytic strep
- Bacterial and fungal cultures should be done for intertrigo in babies, esp in the neck folds
- Topical mupirocin alone may be sufficient for some

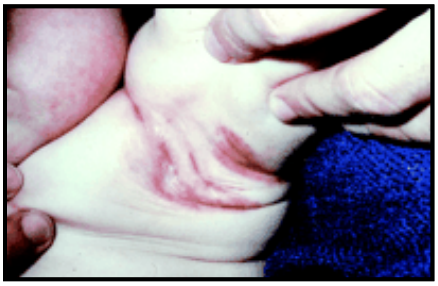


GABHS

- Produces a number of skin infections:
- ✓ Cellulitis
- ✓ Ecthyma
- ✓ Erysipelas
- ✓ Perianal cellulitis
- ✓ Intertrigo (very under-recognized)

GABHS-Intertrigo

- Foul odor
- No satellites
- Not responding to anti-yeast preparations
- Patients may have low grade fevers, fussiness



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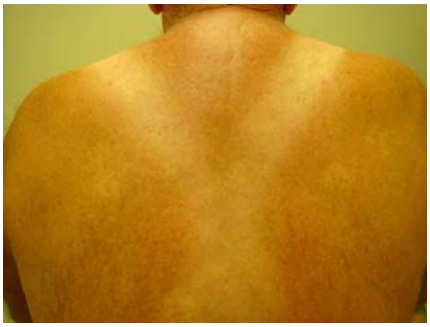
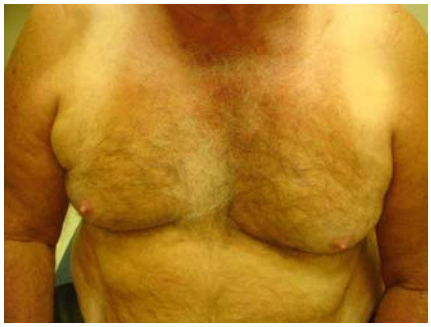
You know you are in the South when…….





AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

9:00 am – 9:45 am

Prep for Court/Depositions

Mary Angel Meyer, JD

Objective: Upon completion of this lecture, the participant will be able to identify the types of testimony physicians may be called upon to provide in legal proceedings, utilize preparation techniques that will improve confidence and responsiveness in testimony, and provide good, truthful testimony when called upon to do so.

PREPARING FOR SWORN TESTIMONY- MAKE IT YOUR BEST

AOA/ACOP PEDIATRIC TRACK
SAN FRANCISCO, CA.
OCTOBER 26, 2010

Mary Angela Meyer, J.D.
Texas Medical Liability Trust

The information contained in this presentation does not in anyway constitute legal or professional advice. If you have a situation requiring legal or professional advice, you should consult with a lawyer or professional of your own choosing.

The information and opinions in this course and the supplemental materials should not be used or referred to as primary legal sources nor construed as establishing medical standards of care for the purposes of litigation, including expert testimony. The standard of care is dependent upon the particular facts and circumstances of each individual case and no generalization can be made that would apply to all cases. The information presented should be used as a resource, selected and adapted with the advice of your attorney. It is distributed with the understanding that neither Ms. Meyer nor Texas Medical Liability Trustis engaged in rendering legal services.

Objectives

- Upon completion of this course, the participant should be able to:
  - 1) Identify the types of testimony physicians may be called upon to provide in legal proceedings
  - 2) Utilize preparation techniques that will improve confidence and responsiveness in testimony; and
  - 3) Provide good, truthful testimony when called upon to do so.

Types of Testimony

- Sworn Statement
- Pre-suit Deposition
- Deposition
- Trial testimony

Providing Information About Patient Care

- Medical Record Subpoena Affidavits
- Interviews
  - Plaintiff counsel
  - Defense counsel
  - Pre-suit investigation
- Sworn Testimony
  - Pre-suit depositions
  - Deposition as a defendant
  - Fact Witness/Expert Witness
  - Trial Testimony as a defendant

Responding to the Pre-suit Letter or Call

- Provide records within the allowed time period.
- Do not call or write the plaintiff lawyer.
- Contact your insurance company.
- Start a separate file for lawsuit related documents to be shared only with your lawyer.

Sworn Statement

Affidavits

- Read affidavits thoroughly.
- Make sure records are complete before signing the medical records affidavit.
- Do not sign an affidavit unless everything is true.

The Deposition

Getting Ready for Your Deposition

- Records
- Memory
- Regular Practice

PREPARATION IS KEY

- You cannot spend too much time getting ready.

Know your Records

- Be able to read your own handwriting.
- Review your records meticulously.
- You must be intimately familiar with all records pertaining to the care of the patient.
- Your chart is a summary of the care given.
- Do not fall prey to the "if it was not charted it was not done" argument.

Know the Literature

- Review all literature that has been produced in the case prior to your deposition.
- Do not validate an article unless you have read the entire article and agree with the whole thing.
- You are entitled to review literature if a lawyer asks you to agree to a statement in the document.
- Guidelines vs. the Standards of Care.

Review Prior Sworn Testimony

- Prior depositions
- Interrogatory answers
- Affidavits
- Requests for Admissions

Review Documents Produced in the Litigation

- Expert reports
- Pleadings
- Policies and Procedures

Deposition Testimony

- Tell the Truth.
- Wait for lawyer objections.
- If you do not understand a question, ask for clarification.
- Do not speculate.
- Answer only the question asked.
- Do not interrupt the question, but stand your ground if you have not finished your answer to the previous question.

- Is that all you can remember?
- Do not educate the lawyer unless it is responsive to a question.
- Do not allow the lawyer to force you to answer a simple "Yes" or "No" if that is not a complete answer.
- Think about the question before you answer.
- Do not stray from the question.

- Do not guess or speculate.
- Do not volunteer information.
- Stay within your field of expertise.
- If you are asked about the records, look at the records in question.
- Do not lose your temper.
- Be wary of summary questions at the end of the deposition.

Address Difficult Information with Your Lawyer Before the Deposition

- Peer review information
- Divorce
- Arrests
- State Board Investigations
- National Practitioners Data Bank Information
- Previous lawsuits
- EEOC investigations/ employee lawsuits

Appearances Matter

- Your Deposition will most likely be videotaped.
- The jury will see the video.
- Things to think about:
  - Clothing
  - Jewelry
  - Movement
  - Eye Contact
  - Body language

Do not Allow the Plaintiff Lawyer to Misstate your Testimony

- Your words may be twisted – do not agree to a misstatement of your testimony.
- Correct misstatements before answering.
- Do not allow the opposing lawyer to bully you into changing your answers.
  - Just because the opposing lawyer says you are "nonresponsive" it does not mean that your answer was nonresponsive.

What Are The Standards of Care?

- Know how the standards of care are defined in your jurisdiction.
- Read the Jury Charge.
- There is usually no singular standard of care for a particular treatment.
- What role does literature play in Standards of Care?
- Be wary of the lawyer asking what "should" be done.

After the Deposition

- If your jurisdiction allows you to make changes, read your transcript carefully and make timely changes.
- Stay involved in your defense.
- Attend plaintiff, co-defendant and expert depositions, if allowed in your jurisdiction.

Trial Testimony

Trial Testimony

- Your testimony starts before you take the stand.
- Make time to prepare.
- Tell the truth.
- Listen.
- Be respectful.
- Know your deposition and discovery answers.

The Jury

- Know your jury.
- You are best person to explain the case to the jury.
- After the Plaintiff's lawyer's opening statement, you may need to overcome a presumption by some jurors that you are not telling the truth.

- Prepare for trial as you would for a deposition, but spend even more time on it.
- Call your lawyer whenever you need her.
- Believe in your case.
- Get all the support you need:
  - Lawyer
  - Therapist
  - Counselor

Questions

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

10:15 am – 11:00 am

Special Needs Advocation

Barbara L. Baldwin, DO, FACOP

Objective: TBA

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

11:00 am – 12:00 n

Gastric Banding as Treatment for Adolescent Obesity

Alison A. Clarey, DO

Objective: Upon completion of this lecture, the participant will be able to discuss indications and contraindications for SWL in the adolescent, know the criteria for weight loss surgery and the benefits for the adolescent's health, discuss surgical approaches in SWL for the adolescent, discuss risks and complications associated with laparoscopic adjustable band, gastric bypass, and gastric sleeve, and discuss the current literature for SWL in the adolescent.

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

2:00 pm – 3:00 pm

A Case-Based Review of Influenza

James H. Brien, DO, FAAP

Objective: Upon completion of this lecture, the participant will be able to recognize the clinical findings of a child with Influenza, discuss the differential diagnosis of influenza, and prescribe the appropriate treatment therapy for influenza at all ages and it's complications.

Influenza Review

- History
- The virus
- Clinical features
- Treatment
- Prevention
- A word about the Pandemic

James H. Brien, DO - May 4, 2009

Influenza in History

- Described by Hippocrates ~400 BC
- Pandemic of 1580, which was the first accurate description, swept through Russia, Europe and Africa, killing > 8000 in Rome alone & nearly wiping out small towns in Spain.

Pandemics in History

- On average three pandemics per century have been documented since the 16th century, occurring at intervals of 10 to 50 years.
- During the 20th century, influenza pandemics have caused millions of deaths, social disruption and profound economic losses worldwide.

Pandemics in History

- 1918-20: Spanish Flu
- 1957-58: Asian Flu
- 1968-69: Hong Kong Flu

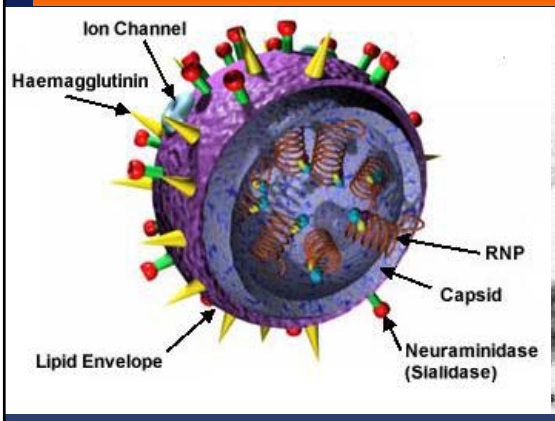
Pandemics in History

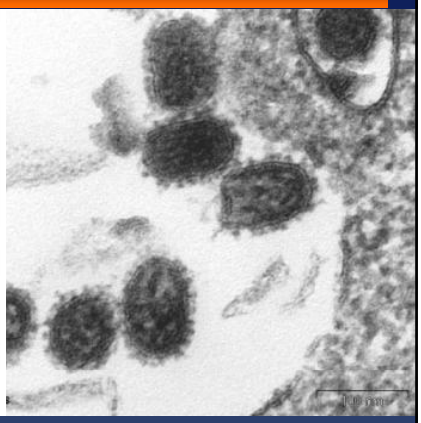
Occurrence	HA/NA Subtype	Years Since Last	(Excess) US Deaths
1918-20	H1N1	27	500,000
1957-58	H2N2	37	70,000
1968-69	H3N2	10	40,000

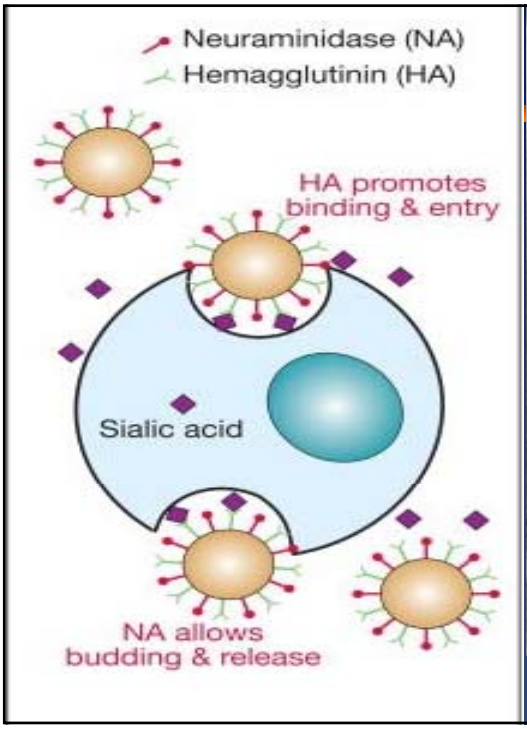
Pandemics in History

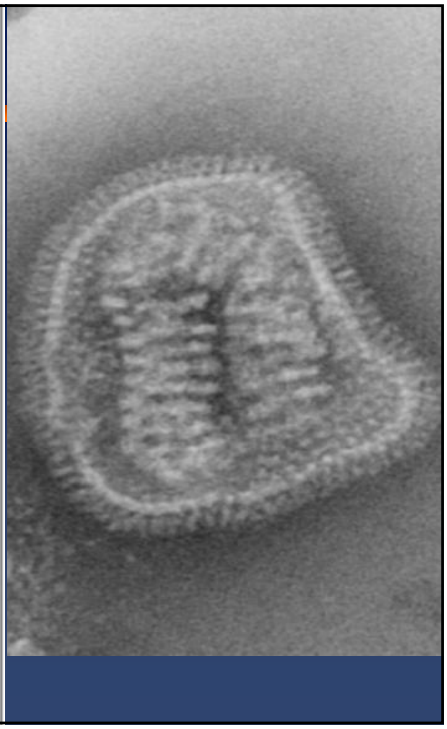
- Many experts thought that the next pandemic would involve sustained transmission of highly pathogenic avian influenza (H5N1) – Bird Flu.
- So much for predictions based on the SWAG method.

An RNA Virus


Ion Channel
Haemagglutinin
RNP
Capsid
Neuraminidase
(Sialidase)
Lipid Envelope




Neuraminidase (NA)
Hemagglutinin (HA)
HA promotes
binding & entry
Sialic acid
NA allows
budding & release



Clinical Features of Influenza

- **Sudden onset of symptoms after 1 to 4 days of incubation**
  - an infectious period may begin the day before symptoms manifest and continue for 5 days; longer in children
- **Symptoms persist for 1 to 2 weeks**
  - Some have chronic cough for much longer
- **Varying symptomatology**

CDC. *MMWR Morb Mortal Wkly Rep.* 2001;50(RR-4):1-44.

Presentation of Clinical Influenza Differs by Age Group

Sign/Symptom	Children	Adults	Elderly
Cough (nonproductive)	++	++++	+++
Fever	+++	+++	+
Myalgia	+	+	+
Headache	++	++	+
Malaise	+	+	+++
Sore throat	+	++	+
Rhinitis/nasal congestion	++	++	+
Abdominal pain/diarrhea	+	–	+
Nausea/vomiting	++	–	+

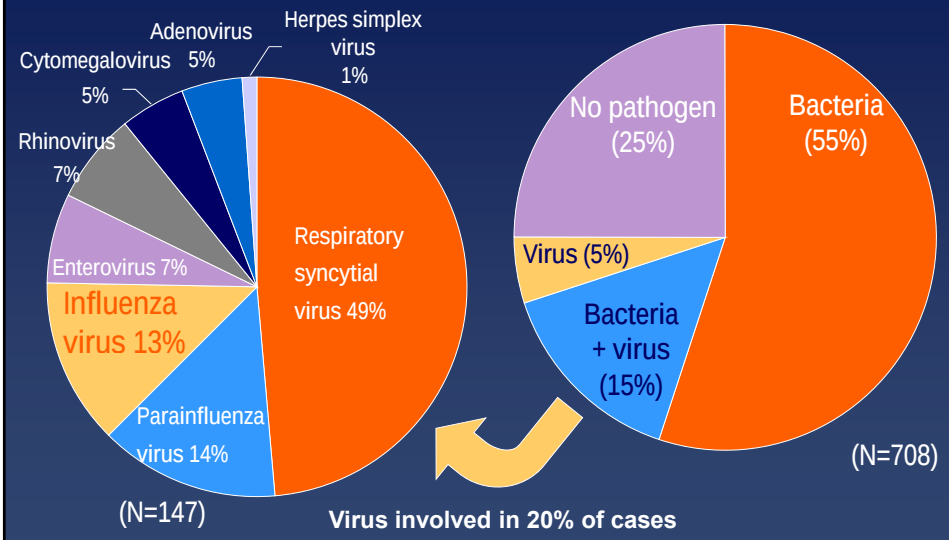
Monto AS et al. *Arch Intern Med*. 2000;160:3243-3247;
Cox NJ, Subbarao K. *Lancet*. 1999;354:1277-1282.

++++ Most frequent sign/symptom; + Least frequent; – Not found

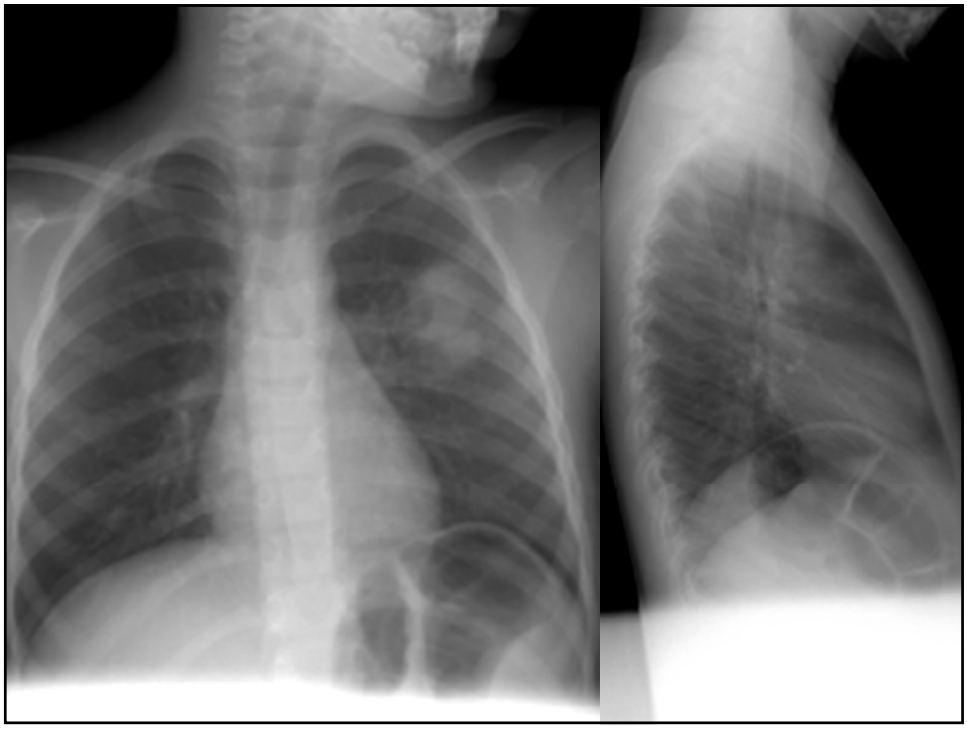
Influenza Virus Infections Cause a Spectrum of Illnesses and Complications

- **Influenza syndrome ("typical influenza")**
  - upper respiratory illness
  - croup/laryngitis
  - tracheobronchitis
  - bronchiolitis/asthma exacerbation
  - gastrointestinal symptoms (children)
- **Common complications**
  - acute otitis media (children)
  - sinusitis
  - pneumonia
  - bacterial superinfection
  - exacerbation of underlying diseases
  - dehydration (infants)
- **Rare complications**
  - encephalopathy
  - Reye's syndrome (associated with aspirin)
  - myositis, myocarditis

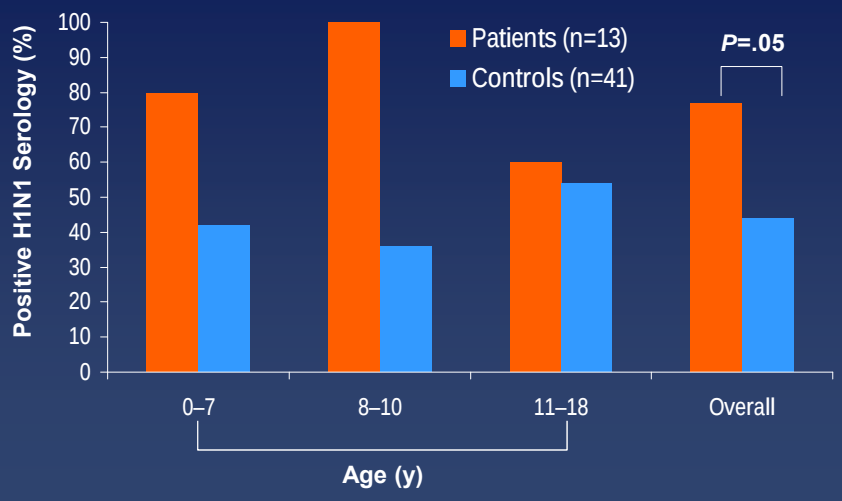
Microbiology of AOM



Chonmaitree T. *Pediatr Infect Dis J*. 2000;19:S24-S30.

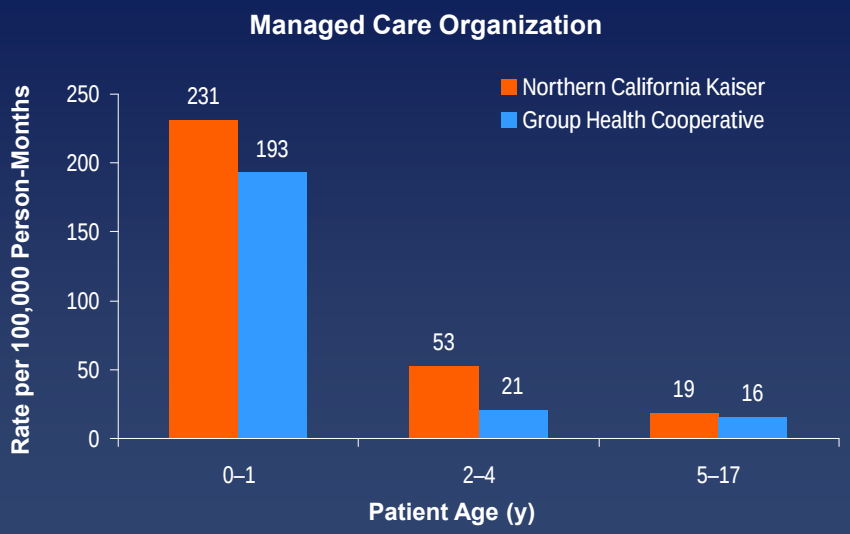


Influenza as a Precursor to Pneumonia



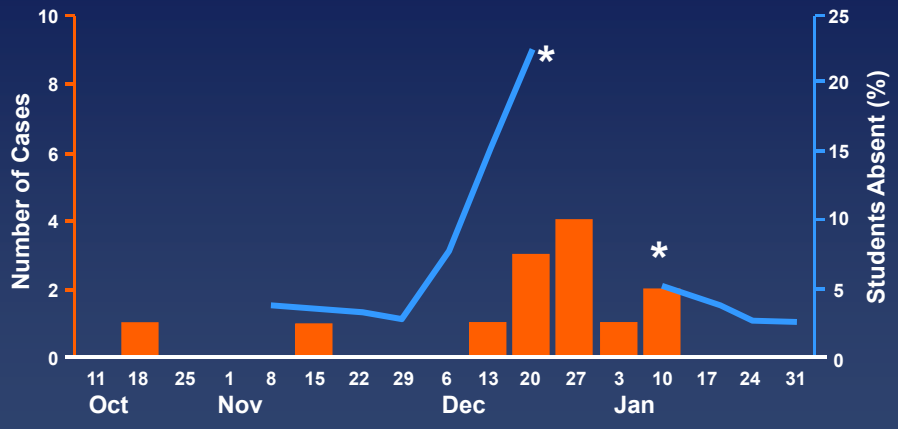
O'Brien KL et al. *Clin Infect Dis*. 2000;30:784-789.

Hospitalization Among Children Without High-Risk Conditions



Izurieta HS et al. *N Engl J Med.* 2000;342:232-239.

Pediatric Hospital Admissions for Pneumococcal Pneumonia preceded by Influenza-Like Illness



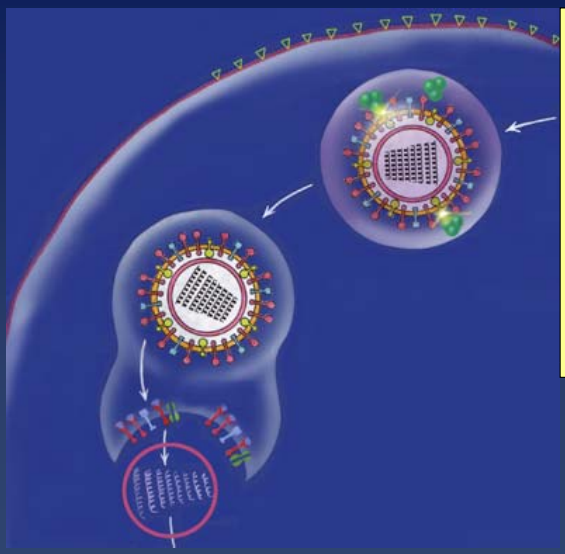
*Beginning and end of winter school break.

Adapted with permission from O'Brien KL et al. *Clin Infect Dis.* 2000;30:784-789.

Treatment and Prevention Modalities

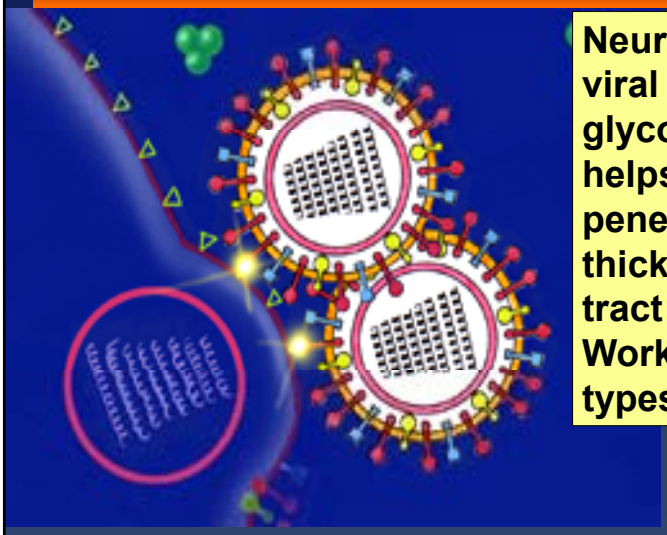
- **Anti-viral agents**
  - **What & How**

Amantadine and Rimantadine: Mechanism of Action



Works by blocking the M2 channel, preventing the ribonucleoprotein complexes from entering the cell. Only works on Influenza A.

Neuraminidase Inhibitor Drugs: Mechanism of Action



Neuraminidase is a viral envelope glycoprotein that helps with the penetration through thick respiratory tract mucous. Works against both types A & B.

Antiviral Drugs for Influenza Prophylaxis and Treatment

Drug	Approval	Age
M2 Inhibitors (A only)		
Amantadine	Prophylaxis	≥1 y
(Symmetrel)	Treatment	≥1 y
Rimantadine	Treatment	Adults
(Flumadine)	Prophylaxis	Children, adults
Neuraminidase Inhibitors (A and B)		
Zanamivir	Treatment	≥7 y
(Relenza)		
Oseltamivir	Treatment	≥1 y
(Tamiflu)	Prophylaxis	≥13 y

CDC. *MMWR Morb Mortal Wkly Rep*. 2002;51(RR-3):1-34.

Results of Treatment Studies of Influenza With Antiviral Drugs

- All four antivirals are equally effective if used ≤48 hours of onset & the virus is not resistant.
- Antivirals reduce:
  - influenza symptoms by 1–2 d (all)[1]
  - duration of fever by 1–2 d (oseltamivir)[2,3]
  - antibiotic use by ~30% (zanamivir)[4]
  - acute otitis media by 44% (oseltamivir)[2]
  - secondary disease transmission in families (all)[5,6,7]

1. Couch RB. *N Engl J Med*. 2000;343:1778-1787.
2. Whitley RJ et al. *Pediatr Infect Dis*. 2001;20:127-133.
3. Treanor JJ et al. *JAMA*. 2000;283:1016-1024.
4. Kaiser L et al. *Arch Intern Med*. 2000;160:3234-3240.
5. Couch RB et al. *J Infect Dis*. 1986;153:431-440.
6. Welliver R et al. *JAMA*. 2001;285:748-754.
7. Hayden FG et al. *N Engl J Med*. 2000;343:1282-1289.

Influenza Prophylaxis: Indications

- Adjunct to vaccination of high-risk persons
- Unvaccinated persons caring for high-risk persons
- Immunodeficient persons (poor response to vaccine expected)
- Persons with contraindications to influenza vaccine (eg, severe egg allergy)
- Others if desired to prevent disease

CDC. *MMWR Morb Mortal Wkly Rep*. 2003;52(RR-8).

Antiviral Drugs for Influenza Prophylaxis and Treatment

- Recommendation will depend on the sensitivity of the strain of Influenza circulating.

Agent, group	Treatment	Chemoprophylaxis
Oseltamivir 75 mg caps 60 mg / 5ml suspension		
Adults	**75mg capsule twice per day for 5 days**	**75mg capsule once / day**
Children **(age ≥1 YR, weight)**		
15 kg or less	**60 mg per day divided BID**	**30 mg once per day**
15–23 kg	**90 mg per day divided BID**	**45 mg once per day**
24–40 kg	**120 mg per day divided BID**	**60 mg once per day**
>40 kg	**150 mg per day divided BID**	**75 mg once per day**

Agent, group	Treatment	Chemoprophylaxis
Zanamivir 5mg per inhalation (Diskhaler)		
Adults and Children ≥ 7yrs	2 inhalations (10mg) BID for 5 days.	2 inhalations (10mg) once daily for 10 days
Children ≥ 5 yrs		2 inhalations (10mg) once daily for 10 days.

Agent, group	Treatment	Chemoprophylaxis
Amantadine 100mg tabs 50mg/5ml suspension		
Adults	**Two 100mg tabs BID** or as single dose for 48 hrs past disappearance of symptoms.	**Same as treatment.**
Children	1 – 9 yrs – 5 – 8 mg/kg per day single or divided – not to exceed 150mg/day. 9 – 12 yrs – same as adults.	**Same as treatment.**

Agent, group	Treatment	Chemoprophylaxis
Rimantadine 100mg tab 50 mg/5ml suspension		
Adults	200 mg/day as single or BID dosing	Same as treatment.
Children	Not FDA-approved.	1 – 9 yrs – 5 mg/kg/day as single dose, not to exceed 150 mg. ≥ 10 yrs – as adult.

Off-Label Use of Tamiflu for Infants

Age	Recommended treatment dose for 5 days
<3 months	12 mg twice daily
3-5 months	20 mg twice daily
6-11 months	25 mg twice daily

FDA-approved for emergency treatment during 2009 - 2010 H1N1 Pandemic - No Longer Recommended

Off-Label Use of Tamiflu for Infants

Age	Recommended prophylaxis dose for 10 days
<3 months	Not recommended unless situation judged critical due to limited data on use in this age group
3-5 months	20 mg once daily
6-11 months	25 mg once daily

FDA-approved for emergency treatment during 2009 - 2010 H1N1 Pandemic - No Longeer Recommended

Off-Label Use of Tamiflu for Infants

- **As of June 23, 2010, the emergency use authorization recommendation ended and is no longer in effect.**

Treatment and Prevention Modalities

- **Vaccine**
  - **What & How**

Two Influenza Vaccines Are Available

- **Trivalent inactivated vaccine (TIV), delivered by intramuscular injection**
- **Trivalent live attenuated cold-adapted vaccine (CAIV-T), delivered by intranasal administration**

CDC. *MMWR Morb Mortal Wkly Rep.* 2003;52(RR-8):1-36.

Both TIV and CAIV-T Contain 2 Influenza A and 1 Influenza B Viruses

- **Strains chosen annually based on surveillance data from the World Health Organization**
  - **both vaccines contain two influenza A viruses**
  - **both vaccines contain one influenza B virus[1]**
- **Both vaccines contain hemagglutinin and neuraminidase, resulting in:**
  - **antibodies to hemagglutinin, which neutralize virus infectivity**
  - **antibodies to neuraminidase to modify disease severity[2]**

1. Malhotra A, Krilov LR. *Pediatr Clin North Am*. 2000;47:353-372.
2. Cox NJ, Subbarao K. *Lancet*. 1999;354:1277-1282.

Both TIV and CAIV-T Contain 2 Influenza A and 1 Influenza B Viruses

The 2010 vaccine will contain:

- A/California/7/2009 (H1N1)
  (The 2009 – 2010 pandemic strain)
- A/Perth/16/2009 (H3N2)
- B/Brisbane/60/2008

Strain / Geo. Origin / Strain # / Yr of isolation (Subtype)

Trivalent Inactivated Influenza Vaccine (TIV): Production and Activity

- TIV production
  - 50 years of clinical use[1]
  - produced in embryonated chicken eggs[1]
  - subvirion (disrupted virus) or subunit (purified hemagglutinin and neuraminidase antigens)[1,2]
- TIV contains
  - ≥15 μg hemagglutinin antigen per 0.5 mL dose
  - variable amounts of other components
- TIV activity
  - humoral antihemagglutinin immune response[2]
  - antineuraminidase immune response possible[2]

1. Malhotra A, Krilov LR. *Pediatr Clin North Am.* 2000;47:353-372.
2. Cox NJ, Subbarao K. *Lancet.* 1999;354:1277-1282.

TIV Prevents Complications of Influenza

- Elderly living in the community, prevented:
  - hospitalization for pneumonia and influenza: 30%–70%
- Healthy adult population, prevented:
  - influenza-like illness–related work loss, 32%–45%
  - physician office visits, 34%–44%
  - antibiotic use, 25%[1]
- Pediatric household contacts of influenza vaccinees, reduced:
  - respiratory illnesses, 50%
  - febrile respiratory illnesses, 80%
  - missed school days, 72%[2]

1. CDC. *MMWR Morb Mortal Wkly Rep.* 2001;50(RR-4):1-44.
2. Hurwitz ES et al. *JAMA*. 2000;284:1677-1682.

CAIV-T: Production and Activity

- The parent influenza virus grows best at low temperature (cold adapted) in nasopharynx, not in lower respiratory tract[1]
- Vaccine made from genetic reassortant that retains cold adaptation but represents latest variety of influenza[2]
- Vaccine contains equal amounts of each of three recommended strains[2]
- Vaccine induces serum and mucosal antibodies when administered intranasally[1,2]

1. CDC. *MMWR Morb Mortal Wkly Rep.* 2001;50(RR-4):1-44.
2. Boyce TG, et al. *Vaccine.* 2000;18:1682-1682.

Comparing TIV and CAIV-T

Category	TIV	CAIV-T
Administration	Intramuscular Serum antibodies	Intranasal Mucosal immunity
Formulation	Inactivated	Live attenuated
Efficacy young children Efficacy adults <65 y	~50%–90% 70%–90%	70%–90% 70%–90%
Safety	Sore arm	Runny nose
Growth medium	Chick embryos	Chick cells
Indication	Any person ≥6 mo	Anyone 2-49 yr

Comparing TIV and CAIV-T Summary

TIV	CAIV-T
Very efficacious	More efficacious in children
Painful to receive	Painless nasal spray
Less acceptable	More acceptable
Approved 6mo – up	Approved 2-49 yrs
Cheap	More Expensive

Improve Vaccine Acceptance

- **Currently, children receive up to 20 sticks by their 2nd birthday.**
- **Receiving an additional annual stick at any age may exacerbate the needle phobia that develops in many.**
- **The topical, nasal spray influenza vaccine (CAIV-T) makes compliance with these recommendations much more likely.**

CAIV-T Indications

- CAIV-T is approved for healthy persons
  - Children aged 2-8 years receiving vaccination with any influenza vaccine for the first time need two doses, 6-10 weeks apart; children aged 2-8 previously vaccinated need one annual dose
  - Persons 9-49 years need one annual dose
- Not approved for persons with underlying chronic disease, including children with asthma

Influenza Vaccine 2-dose Rule

- Those younger than 9-years who are receiving it for the first time.
- Separated by at least 4 weeks.
- Were vaccinated last season, but only received one dose.

Influenza Vaccine 2-dose Rule For 2010 Season

- **Children aged 6 months--8 years who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine, who have never received a seasonal influenza vaccine before, or who were vaccinated for the first time with the seasonal 2009--10 seasonal vaccine but who received only 1 dose should receive 2 doses of the 2010--11 influenza vaccine formula, spaced 4 or more weeks apart.**

Persons at Highest Risk for Influenza Complications

- ≥65 y
- Residents of chronic care facilities
- People with chronic conditions
  - chronic pulmonary, metabolic, or CV disorders
  - renal dysfunction
  - hemoglobinopathies
  - immunosuppression, including HIV infection
- Pregnant women in second or third trimester during the influenza season
- Children 6 mo–18 y receiving long-term aspirin therapy

CDC. *MMWR Morb Mortal Wkly Rep.* 2003;52(RR-8):1-34.

ACIP Recommendations

- Advisory Committee on Immunization Practices (ACIP) sets priorities for vaccinating each population group
- Vaccinate in October and earlier
  - People <50 y (including children 6–23 mo) at high risk for influenza complications
  - People ≥50 y
  - Healthcare workers
  - All children ≥6 mo – 19 years of age
  - Household contacts of high-risk persons
  - Vaccinate household contacts and caretakers of children <6 months of age
- Vaccinate everyone else beginning in November
  - Do not defer these people if they request vaccination before November

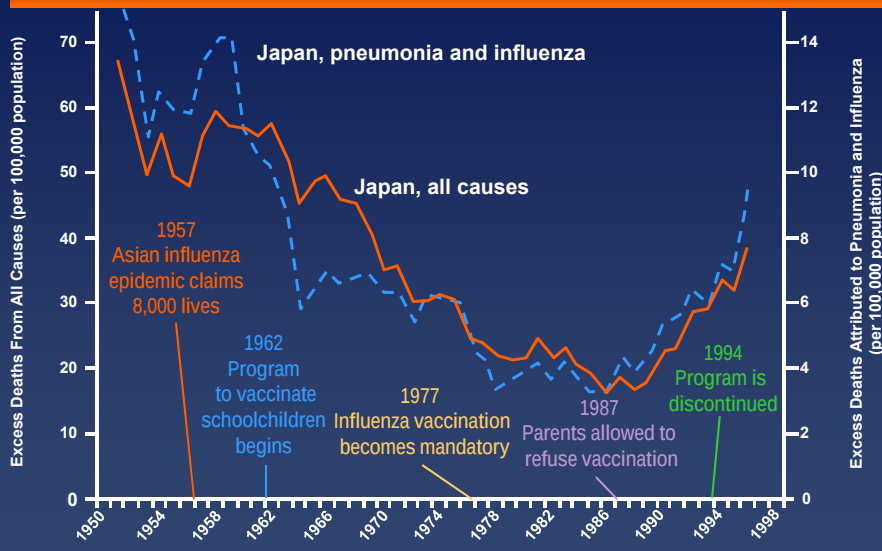
CDC. *MMWR Morb Mortal Wkly Rep.* 2003;52(RR-8):1-34.

The Benefits of Herd Immunity (Indirect Effect)

- **Higher vaccination rates in a population protect both vaccinated and unvaccinated individuals**
- **A high proportion of vaccinees reduces:**
  - **risk for becoming infected**
  - **severity of symptoms if infected**
  - **infectivity after becoming infected**
  - **risk of exposure for unvaccinated individuals**

De Jong MCM, Bouma A. *Vaccine*. 2001;19:2722-2728.

A Mass Vaccination Program of Schoolchildren in Japan showing Herd Immunity



Adapted with permission from Reichert TA et al. *N Engl J Med*. 2001;344:889-896.

Strategies for Community Protection

Propose strategies for reducing community outbreaks:

a) **Primary providers must be on board**

b) **Public education regarding:**

- **Myths about disease & vaccine**
- **Identifying & vaccinate high-risk patients**
- **Published recommendations**

c) **Increase immunization rate of healthy people (Herd Immunity).**

Global Pandemic Control Phases

- WHO Pandemic Phases
  - Inter-pandemic Period
  - Pandemic Alert
  - Pandemic
  - Post-Pandemic

Pandemic Planning

- Global level: WHO
- National level: CDC
- State level: Department of Health
- Local level: Health authorities develop strategies for implementing pandemic phase objectives within their jurisdictions.

State Pandemic Influenza Planning

- Non-medical measures will be the principal control measures until adequate supplies of vaccine are available:
  - Shelter in place
  - Hygiene
  - Supportive Rx
- Anti-viral therapy

Items of Note

- Decisions made in an atmosphere of scientific uncertainty.
- Risk communication to public, policy makers and health care staff must be well orchestrated.
- Legal authority and procedures for introducing unusual public health measures must be established and understood by key personnel.
- Better prepared now than in years past – good exercise for the system.

All recommendations can be found on line

www.cdc.gov

Additional information can be found at

www.aap.org

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

2:00 pm – 3:00 pm

A Case-Based Review of MRSA

James H. Brien, DO, FAAP

Objective: Upon completion of this lecture, the participant will be able to interpret the sensitivities of Staph Aureus cultures in order to select the best therapy, recognize the key features that distinguish Staph Aureus infections from other bacteria, and describe the complications of MRSA bacteremia.

Staphylococcus aureus
From Job's Boils to MRSA

ACOP
October 26, 2010

James H. Brien, D.O.

1

Staph aureus History

- **Alexander Ogston – Scottish surgeon – 1881, described and named the organism from a stained drop of pus from a patient with a carbuncle.**
- **Pustules, boils, carbuncles, furuncles – all abscesses of varying size.**
- **Abscess – common denominator, and typical of *Staph aureus*.**
- **A golden bunch of grapes.**

2

Historical Facts & Figures

- Pre-antibiotic staph Mortality 90%
- 1941 Pen G - by 1944 β-lactamase, 1945 = 12-22% Resistance
- 1959 Methicillin - resists β-lactamase
- 1960, >90% resistant to pen, as it is now.
- 1961 noticed resistance (MRSA) – mostly confined to hospitals
- CA-MRSA is the challenge today

3

Staphylococcus aureus

- Very resilient – can withstand:
  - heat to 50° C
  - drying, remaining viable in soil for years and can survive on fomites (stethoscopes) for prolonged periods.
  - high salt content (salt pork, etc.)

4

Staphylococcus aureus

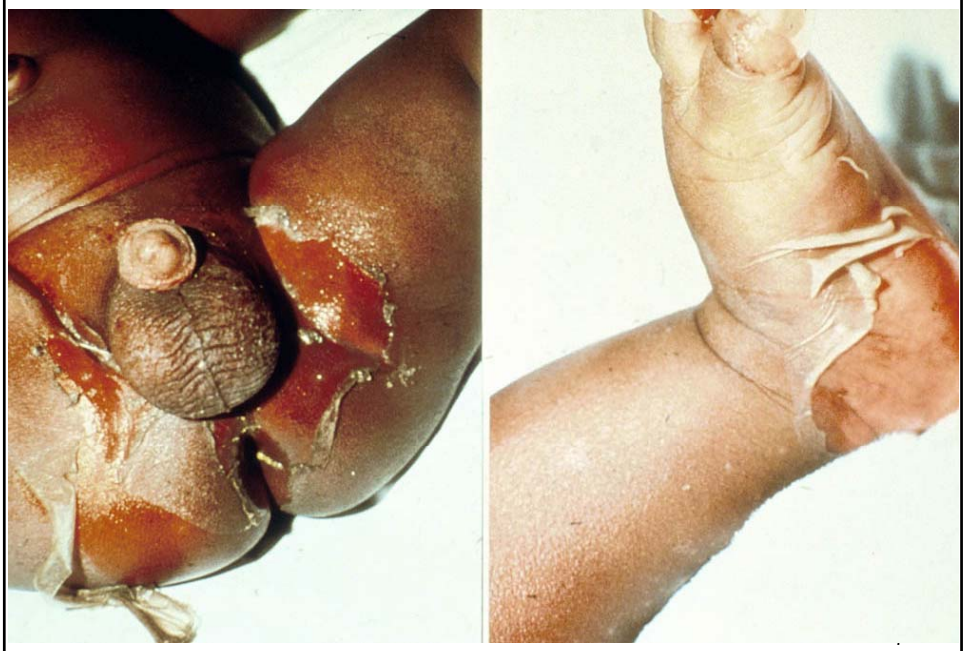
- **Identification by testing for a virulence factor – <u>coagulase production</u>:**
  - ***Staph aureus* secretes free coagulase into the broth – reacts with coagulase-reacting factor in plasma with the conversion of fibrinogen to fibrin and clot formation.**
  - **Coagulase + on the report is almost always a problem.**

5

Staphylococcus aureus

- **Virulence factors – proteins that exist to turn you into breakfast, lunch and dinner:**
  - **Hemolysins – damage cell membranes**
  - **Enzymes – hyaluronidase, nuclease, proteases, lipase, catalase, coagulase, lysozyme, & lactate dehydrogenase.**
  - **Epidermolytic toxins – causes SSSS.**
  - **Toxic Shock Syndrome Toxins**
    - Multi-organ effects.

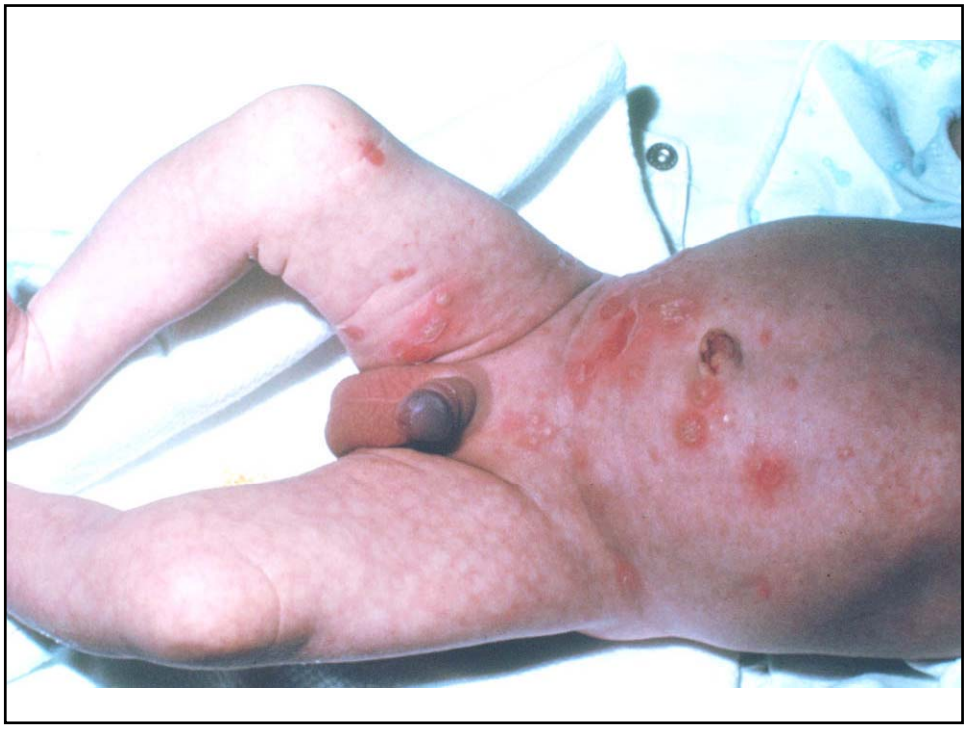
6



Bullous Pyoderma

- A blistering bacterial skin infection.
- Essentially the same as bullous impetigo, but usually reserved for the more severe cases.
- Usually responds well to oral antib.

8



Toxic Shock Toxins

Staphylococcus aureus

- **More Virulence factors:**
  - **Enterotoxins A – E – food poisoning.**
  - **Leukocidin – (Panton-Valentine, PVL) attacks the leukocyte exclusively, damaging the membrane, causing death of the cell, contributing to tissue necrosis, esp. in pneumonia & associated with sepsis.**
  - **Most severe cases are PVL-positive.**
  - **Most PVL-positive are CA-MRSA.**

11

Methicillin-Resistant *Staph aureus* - MRSA

- **MRSA first isolated in 1961, 2 years after methicillin was marketed.**
- **Initially confined to hospitals.**
- **Community-acquired MRSA (CA-MRSA) began to be increasingly seen in mid-90's.**
- **Now called Community-associated MRSA.**
- **CA-MRSA linked to most severe infections**

12

CA-MRSA Sepsis Syndrome

- Infants and young children
- Hypotension and shock
- Necrotizing pneumonia (esp after influenza)
- Coagulopathy: Waterhouse - Friderichsen.
- Thrombocytopenia
- High mortality
- PVL-positive MRSA, & maybe MSSA also
- Similar to meningococcemia

13

Brief Review of the Basic Mechanisms of Resistance

- Enzyme production – β-lactamases
- Altered antibiotic target – penicillin-binding proteins (PBP)
- Prevention of antibiotic uptake - active efflux of antibiotic

14

Genetics of MRSA Resistance

- *MecA* is the gene in all MRSA & CA-MRSA.
- 5 types of *MecA* gene: I, II, III, IV, & V.
- All code for PBP (2a) target, therefore the B-lactam antibiotic cannot bind.
- CA-MRSA contain types IV & V, but no other resistant genes & usually remains susceptible to other antib.
- MRSA (hospital) may contain other resistance genes with multiple resistance.

15

MRSA Resistance

- Hospital MRSA typically resistant to all but Vancomycin, Gentamicin, Rifampin.
- CA-MRSA usually susceptible to Clindamycin, TMP/SMX, Rifampin & Tetracyclines as well as Vancomycin. However, beware of inducible resistance to Clindamycin.

16

Community-Associated MRSA

- **Outbreaks in community of serious skin/soft tissue infections or necrotizing pneumonia.**
- **MRSA isolates--multiply susceptible, share types IV & V *MecA* gene & the PVL locus.**
- **Are resistant to PCN, Oxacillin, +/- E-mycin.**
- **PVL MRSA strains:**
  - **Are widely distributed in some communities**
  - **Have been transmitted in hospitals**
  - **Associated with severe infections**

17

Community-Associated MRSA

Diseases and Clinical Management.

18

MRSA (Community-Acquired)

- Increasingly common - - - > 50% of our inpatients with staph infections.
- Most community-acquired strains are sensitive to clindamycin. Must beware of erythromycin resistant strains. If so, there could be inducible-resistance to clindamycin.
- A simple "D" test should be done to rule-out this problem (*The Pediatric Infectious Disease Journal* 2002; 21:530-534)

19

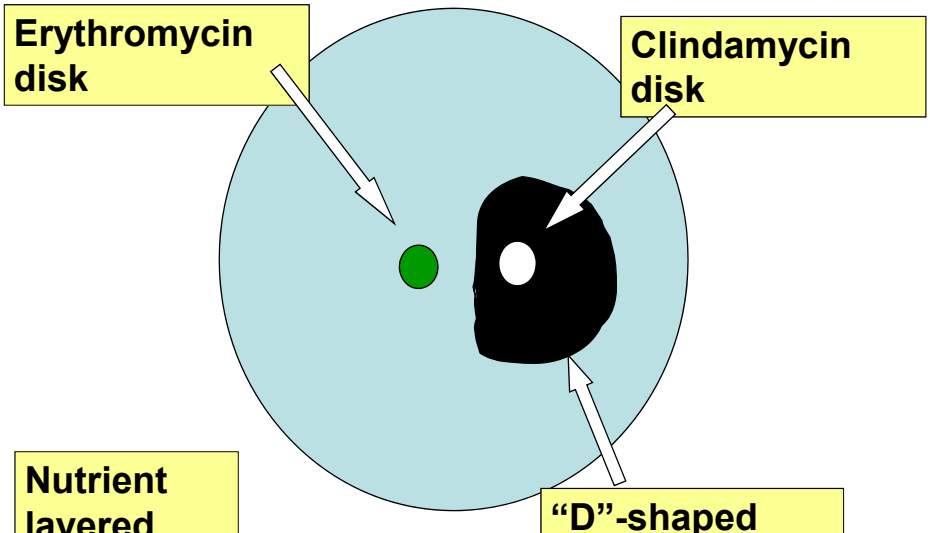
MRSA (Community-Associated)

- Increasingly common - - - > 50% of our inpatients with staph infections.
- Most community-associated strains are sensitive to clindamycin. Must beware of erythromycin resistant strains. If so, there could be inducible-resistance to clindamycin.
- A simple "D" test should be done to rule-out this problem (*The Pediatric Infectious Disease Journal* 2002; 21:530-534)

20

ORGANISM	S. aureus	
ANTIBIOTIC	MIC-ug/ml	INT
Amox/Clav	>4/2	R
Amp/Sul	8/4	R
Ampicillin	>8	R
Cefazolin	8	R
Clindamycin	<=0.25	S
Erythromycin	>4	R
Gentamicin	<=1	S
Oxacillin	>2	R
Penicillin	>8	R
Rifampin	<=1	S
Tetracycline	<=1	S
Trimeth/Sulfa	<=2/38	S
Vancomycin	<=2	S

21



22

MRSA

- If inducible resistance is detected, consider using oral TMP/SMX (consider adding Rifampin) or Vancomycin if IV therapy is needed.
- Minocycline may work for older patients.
- If suppurative, surgical drainage remains of paramount importance.
- Remember contact isolation if hospitalized.

23

Worried About MRSA? What if there's no culture to guide therapy?

Consider a nasal culture for MRSA, it's better than nothing.

"A trick of the trade"

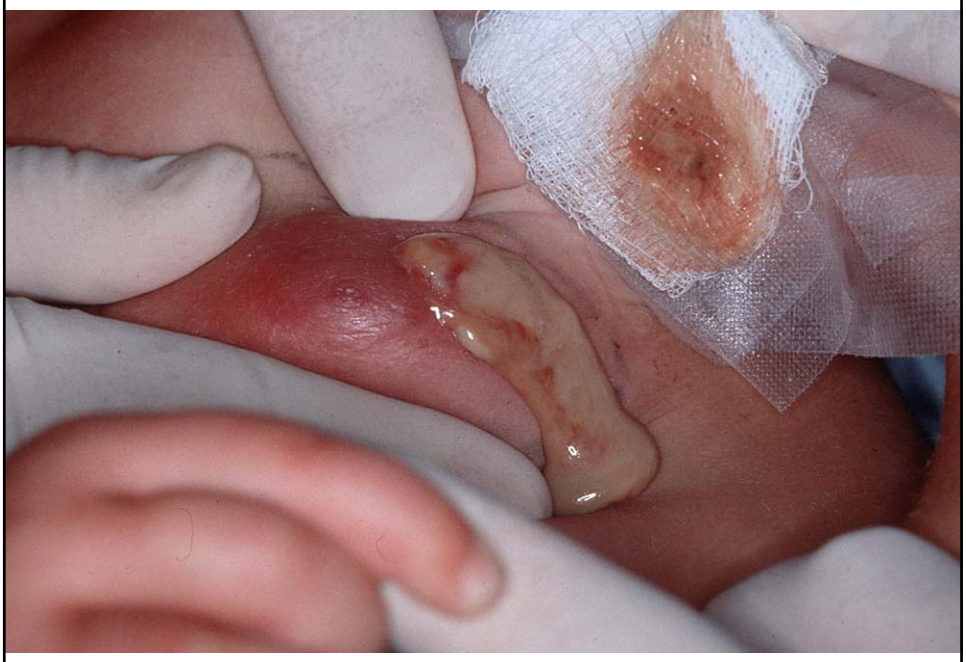
James W. Bass, COL, MC, USA - 1982

24

Staph aureus Infections
MRSA & MSSA

Soft Tissue Infections

25



Staph Abscess

Drainage Alone
Is
Often Curative

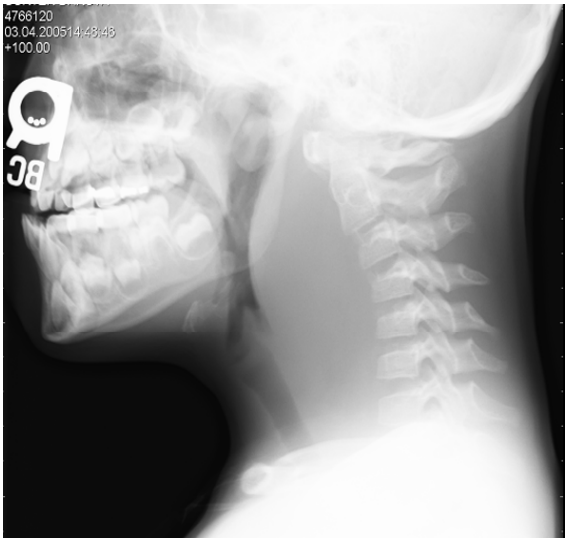
27

Case #2

An Unusual Soft Tissue Infection

28

Retropharyngeal Abscess - MRSA



29

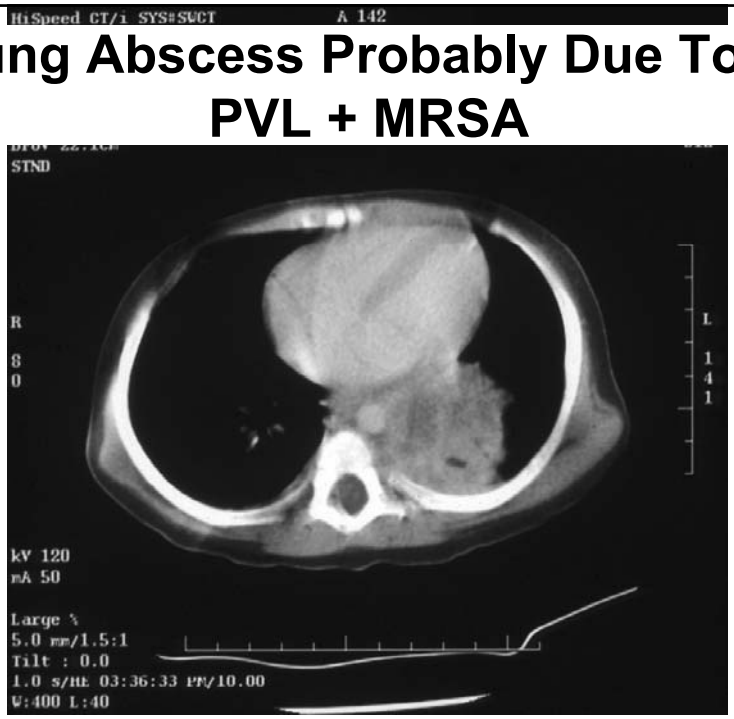
Cases 3

Unusual Pneumonias

On The Rise

30

Lung Abscess Probably Due To A PVL + MRSA



31

What Do You Do Now?

1. Continue Vancomycin -- Yes
2. Consult surgery -- Yes
3. Change antibiotic to Clinda. -- No
4. Add Rifampin -- Maybe

32

Case #4

Severe Bone & Joint Infections

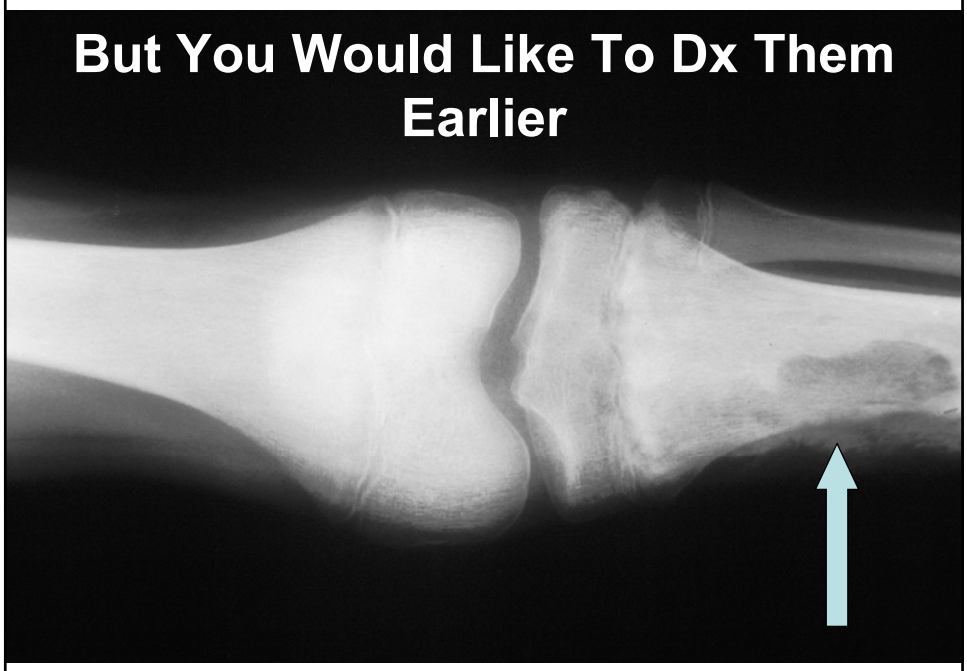
33

12-Year-Old Male

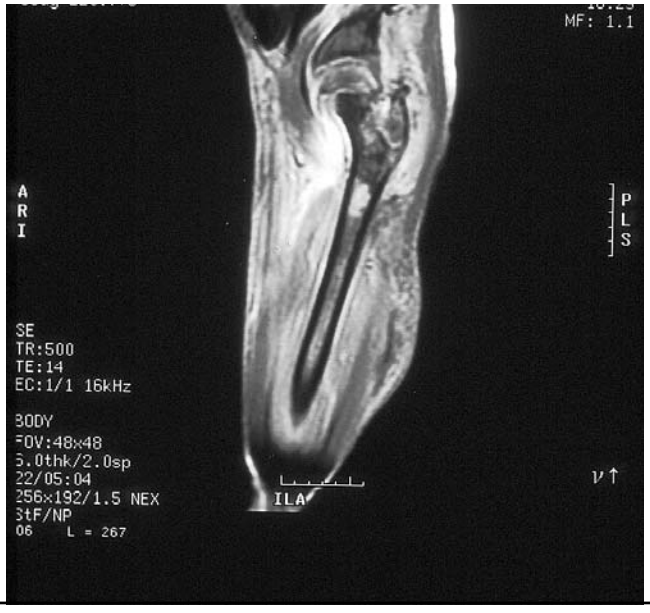
- Sent from comm. hosp. after failing to improve on Rocephin® for fever and leg pain for a week.
- History is that of a typical male this age with lots of rough-housing preceding the onset of fever & pain.
- Exam - marked pain of entire left leg and knee swelling.

34

But You Would Like To Dx Them Earlier



MRI of Acute Osteomyelitis



36

12-year-old Male

- Blood culture + for MRSA.
- Joint fluid sterile, just inflammatory.
- Has multi-focal osteomyelitis.
- Never treat a potential Staph infection with Ceftriaxone!!!!!
- We start with Clindamycin pending culture results.

37

Cases 5 & 6

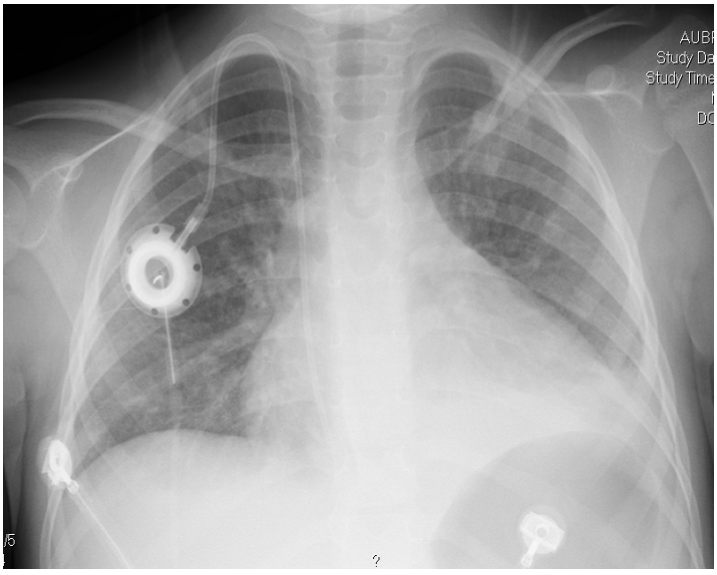
Devise & Line Infections

38

4-Year-Old Female

- **Admitted with fever & emesis.**
- **PMHx + for short gut syndrome and is TPN-dependent via Port-a-Cath®.**
- **Exam – temp of >103° F.**
- **Cultures of catheter and peripheral blood as well as urine are all + for Staph aureus (pan-sensitive).**

39

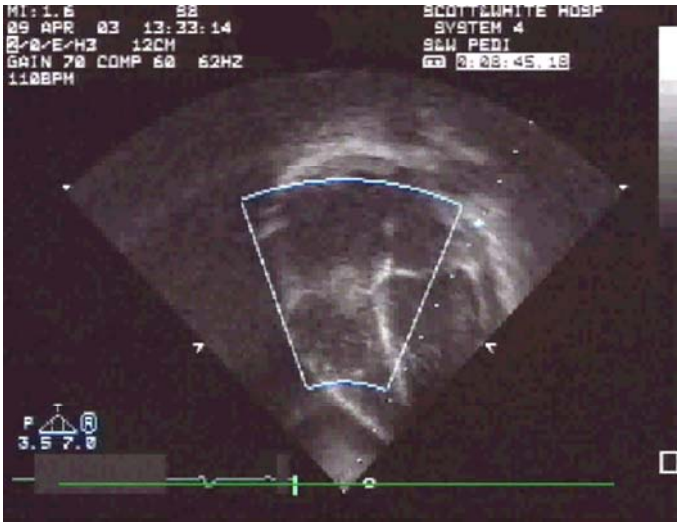


40

4-Year-Old Female

- Was treated with 10 days IV Nafcillin after port was removed.
- Seemed to do well for a couple of weeks, then got sick with fevers.
- Exam revealed a new murmur.
- BC again + for same Staph aureus.
- Cardiac echo revealed:

41



42

What Is Your Therapy?

1. High-dose penicillin for 6 weeks
2. High-dose nafcillin for 6 weeks
3. Standard-dose nafcillin for 6 weeks
4. High-dose nafcillin for 4 weeks

43

What Is Your Therapy?

1. High-dose penicillin for 6 weeks

For penicillin-sensitive *Staph aureus* endocarditis.

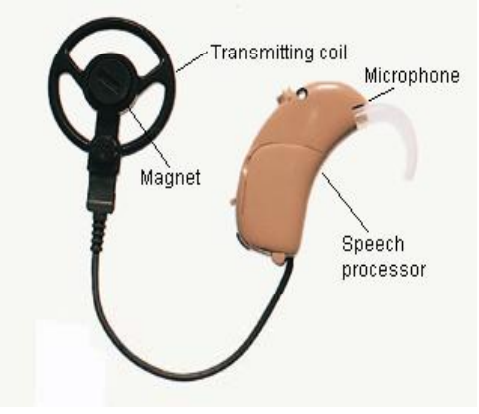
Duration of therapy is likely to be at least 6 weeks depending on response & follow-up echo.

44

30-Month-Old Female

- Hx of congenital deafness.
- Got cochlear implant.
- Hearing much improved.

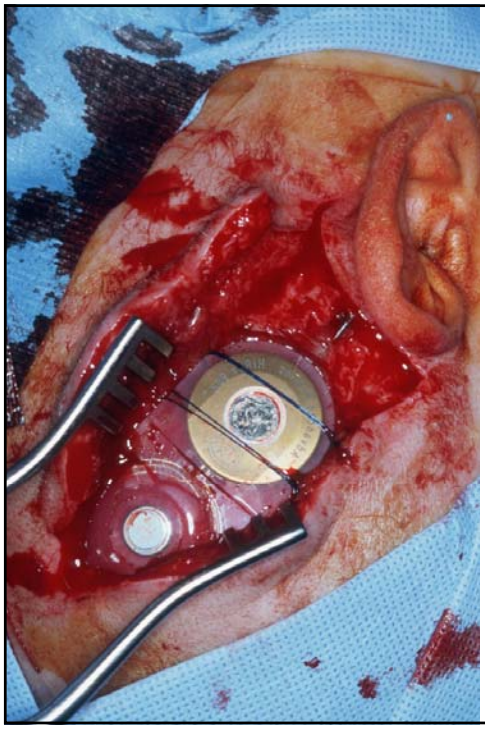
45



30-Month-Old Female

- 7-weeks later, she began having erythema, swelling, drainage and pain near the implant site a few days after the area was struck with a toy thrown by her sibling.
- 5-days later, she was admitted with an MRSA infection of the site and had the implant surgically removed.

47



48

What Is The Recommended Antibiotic?

1. **Vancomycin – 60mg/kg/day**
2. **Clindamycin – never for CNS-related inf.**
3. **Ceftriaxone (Rocephin®) – don't ever trust for any staph infection**
4. **Rifampin – may use to augment other anti-staph drug, but never alone.**

49

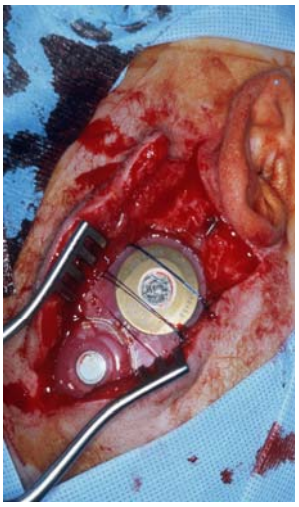
What Other Serious Complication is Associated with Cochlear Implants?

3. **Meningitis – occurs more in children with implants than controls & most are caused by *Streptococcus pneumoniae*.**

50

Cochlear Implant Meningitis

- ⅔ are children <7 years of age.
- 3/1000 incidence.
- Inner ear malform.
- Temporal bone.
- Vaccines (our job).



51

Cochlear Implant Meningitis

Excellent review with specific recommendations by

Charles Bluestone, M.D.

In

The Pediatric Infectious Disease Journal

22(5) May 2003 pp 477-478

52

Case #7

A 12-Year-Old with Severe CP & G-button problem

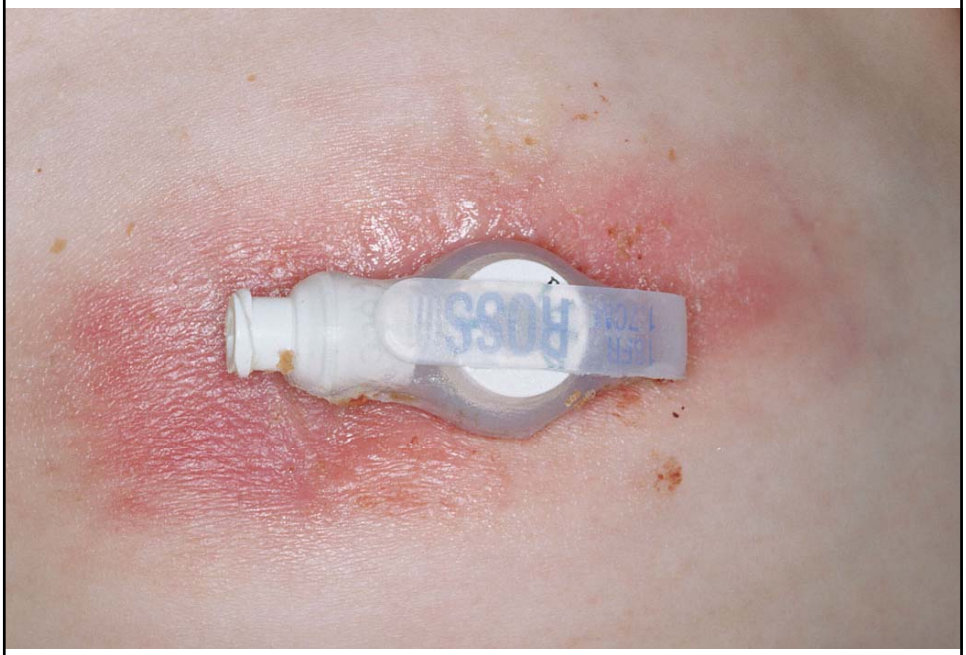
CP – Rapidly Increasing Population

53

12-year-old with CP

- Admitted for evaluation & treatment of fever after recent surgery.
- Has the usual problems of seizures, reflux, aspiration, etc., etc. and on multiple medications.
- Exam revealed a G-button with some spreading erythema and drainage.

54



12-year-old with CP

- **Culture of the site grew methicillin-resistant Staph aureus (MRSA) and vancomycin-resistant enterococcus (VRE), specifically, *Enterococcus faecalis.***

56

Which of the following should be considered for therapy?

1. **Vancomycin – no, already resistant.**
2. **Linezolid (Zyvox®) – Can treat both.**
3. **Quinupristin/dalfopristin (Synercid®) – not for *E. faecalis*.**
4. **Gentamicin – not appropriate.**

57

New products for MRSA and ?VRSA

- **Quinupristin/Dalfopristin (Synercid)**
  - A streptogramin
  - For MRSA & VRE - NOT for E. faecalis
- **Linezolid (Zyvox)**
  - Oxyzolidinone antibiotic
  - For MRSA & VRE
- **Daptomycin (Cubicin)**

58

The Future

- **When will you see vancomycin-resistant *Staphylococcus aureus* (VRSA)?**
- **Look to the Enterococcus:**
  - **Vancomycin resistance is common**
    - Alteration of antibiotic target.
    - Plasmid mediated & can be transferred to Staph aureus.

59

The Future Is Now

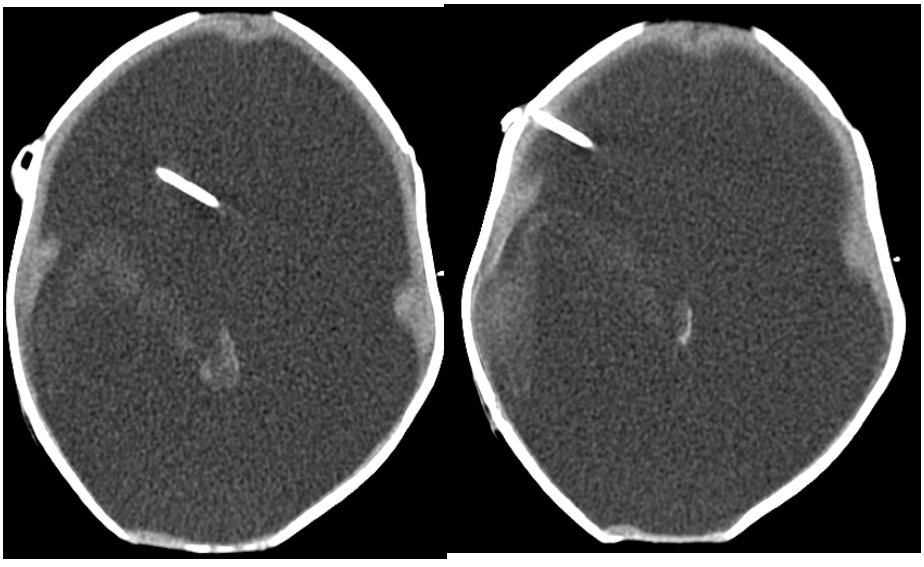
- **VRSA first seen in this country in July 2002 in Michigan diabetic with infected foot ulcer.**
- **2nd case seen in Pennsylvania.**
- **3rd case in a NY nursing home.**
- **So far they are susceptible to other antibiotics, but for how long???**

60

Case #8
8-Month-Old Male with VPS

- Shunted with holoprosencephaly & multiple other problems.
- Admitted because of bulging AF.
- Also has had some emesis without diarrhea or fever.
- Shunt series & head CT is shown:

61



62

8-Month-Old Male with VPS

- Shunt series was normal, but the valve was questionable per NS.
- Soon, began having some fevers.
- Shunt was tapped - CSF revealed 0 RBCs, 9900 WBCs w/ 78% segs, Glu = 1, Protein = 3149mg, Gram stain = Gram + cocci.

63

VP Shunt Infections

Usual recommendation is a combination of:

Vancomycin (60 mg/kg/day)

+

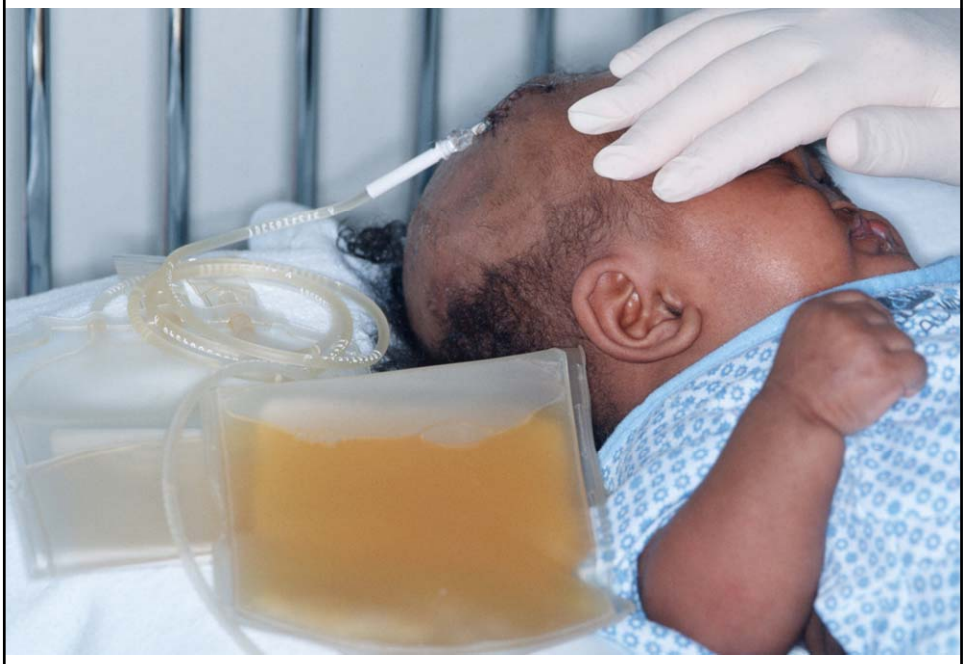
Aminoglycoside OR 3rd-generation Cephalosporin

64

In Addition to IV Antibiotics, Which of the Following Would You Do Next?

1. Remove the shunt and replace with a vetriculostomy drain.
2. Externalize the old shunt.
3. Leave the old shunt in place.
4. Give antibiotics through the old, externalized shunt.

65



VP Shunt Infections

- Case demonstrates the difficulty in clinical assessment of a young child with severe brain damage.
- Excellent review by Rob Wittler and colleagues in *PIDJ:27(7)July 2002 pp632-636* on the treatment of these shunt-related infections, and confirms Ram Yogev's earlier opinion published In PIDJ in 1985.

67

What To Do With Chronic Recurrent Staph Infections (carriers)?

- Goes away with time, but most parents want it gone last week.
- Protocols for eradication from the patient's environment are very difficult to follow & are only about 60% effective; better than nothing.
- For example patient protocol handout:

jhbrien@aol.com

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Hospital Screening for MRSA

1. Universal screening for all admits?
2. Selective screening for high-risk?
3. Screen no one? Can we afford it?

Need to have an enforceable isolation policy before testing patients, otherwise wasting time and money.

69

Summary

- CA-MRSA isolates are increasingly common.
- Panton-Valentine Leukocidin is a major virulence determinant but not universal.
- Many (?most) CA-MRSA isolates are MSSA isolates with MecA IV (Or V) in them.
- CA-MRSA can be treated with Clindamycin, TMP/SMX, Doxy / minocycline, or Vancomycin.
- Clinda can be used only if sensitivity confirmed.
- Rifampin may be added – never alone.

70

Future

- Several *Staph aureus* vaccines in phase III trials.
- If one or more are approved, will likely be recommended only for certain patients at increased risk.

71

Staphylococcus aureus Parting Shot

- For moderately to severely ill patients, we can no longer presume that Nafcillin will work.
- Empiric therapy should begin with vancomycin, clindamycin or TMP/SMX (depending on severity), and consider adding rifampin or gentamicin, pending sensitivity results.

72

Staphylococcus aureus
Parting Shot

REMEMBER

- **If the organism is penicillin sensitive, THAT IS THE DRUG-OF-CHOICE.**
- **If it is pen-resistant but methicillin-sensitive, NAFCILLIN OR SIMILAR ANTIBIOTIC IS THE D.O.C., not vancomycin.**

73

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Parting Shot

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74

Staphylococcus aureus
Parting Shot

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not vancomycin.

75

Staphylococcus aureus
Lastly

- **For our surgical colleagues, surgical prophylaxis is changing.**
- **Vancomycin now recommended for certain procedures**

The Medical Letter. Antimicrobial prophylaxis for surgery. 2009;7(82):1-6

AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

TUESDAY, OCTOBER 26, 2010

Moderator - Judith Thierry, DO

3:00 pm – 4:00 pm

Optimizing Revenue in Your Pediatric Practice

Mary Jean Sage, CMA-AC

Objective: Upon completion of this lecture, the participant will be able to understand the relationship between documentation, coding and billing, determine how to ensure everything done in the practice is being billed, gauge how the billing department (agency/service) is performing, set benchmark goals for billing, and begin to prepare the ICD-10; the new way of reporting your diagnosis.

OPTIMIZING REVENUE

In Your Pediatric Practice

A Seminar for:

American College of Osteopathic Pediatricians

October 2010

San Francisco, CA

2

About This Manual

The material in this manual was written by practice management consultants. Any advice or information contained in this manual should not be construed as legal advice. When a legal question arises, consult your attorney for appropriate advice.

The information presented in this manual is extracted from official government and industry publications. We make every attempt to assure that information is accurate; however, no warranty or guarantee is given that this information is error-free and we accept no responsibility or liability should an error occur.

CPT codes used in this manual are excerpts from the current edition of the CPT (Current Procedural Terminology) book, are not intended to be used to code from and are for instructional purposes only. It is strongly advised that all providers purchase and maintain up to date copies of CPT. CPT is copyrighted property of the American Medical Association.

3

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4

Disclosure

I have no relevant relationships/affiliations to any proprietary entity producing healthcare goods or services.

5

Today's Objectives

- Understand and appreciate the relationship of documentation, coding and billing
  - Everyone on the office has a role
- Determine how to ensure everything done in the practice is billed
- Gauge how the billing department (or agency / service) is performing
- Set benchmark goals for billing

6

REIMBURSEMENT MANAGEMENT

From Appointment Scheduling

↓
↓
↓

To Account Closure

7

The Reimbursement Team

Scheduler
↓
Receptionist
↓
Clinical Staff
↓

8

Reimbursement Team:

Physicians (and Extenders)

↓

Cashier

↓

Insurance Biller

↓

Collector

9

Scheduler

- Do we contract with this patient's insurance?
- Is Pre-authorization required?
- Is the patient eligible for coverage?
- Have you provided financial responsibility information?
- Will you mail a new patient information package?

10

Receptionist

- Verify Patient Information
  - As Needed
  - At Least Annually
- Checkpoint for Other Information
- Collect Co-payment

11

Clinical Staff

- Which ancillary services can you provide?
- Where to patients go for those you do not or can not provide?
- Have ancillary services been recorded?

12

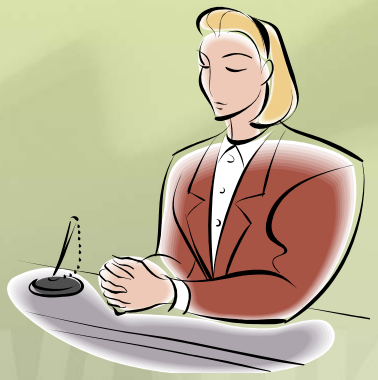
Physician

- Do you code your own services and code correctly?
- Do you know significance of diagnosis and medical necessity?
- Do you know which services might be bundled?

13

Cashier

- Collected the right co-pay or co-insurance?
- Collected for non-covered services?
- Checked the superbill/encounter form for completeness and accuracy?



14

Insurance Biller

- Does this individual know:
  - ALL the plans with which you contract?
  - What is considered a "clean claim"?
  - How to appeal for add'l payment of denied or underpaid claims?

15

Insurance Biller . . . . . .

Do you mail or transmit insurance claims daily or weekly?

How do you handle the day-to-day correspondence from the insurance plans?

16

Collector

17

Collector . . . . . .

- Compliance with the rules and regulations of each contracted plan
  - Know how to read the EOB or RA from each plan
- Expected payment from each contract
- Determine what is billable to patient or another insurance vs. written off

18

Reimbursement Management

- Key Financial Indicators
  - Aging – benchmark percentages in each category – 30, 60, 90, 120 days
  - Days (or months) in accounts receivable
  - Collection ratio - both gross and adjusted

19

Billing Policies & Procedures

- Put them in writing
  - Reduce to paper the steps required to get a claim out the door and paid
  - If you purchase "model" policies, make sure you customize them to YOUR practice
- Annually (more often if needed or there is a change) review and update policies
- Establish Benchmarks for Billing
  - Timely Claim Submission
  - Correspondence Turnaround
  - Account Closure

20

Speed Up Your Payments

21

Speedy Payments Depend On:

- Correct Patient Demographics
  - Name (as on ID card)
  - Date of Birth
  - Health Insurance ID Number
- CMS 1500 or electronic format submitted correctly
  - By Payer
    - Use Your NPI correctly

22

Speedy Payments . . . . . .

- Prompt Claim Submission
  - 1-2 days for office services
  - 7-14 days for out of office
- Immediate reconciliation of claims rejection reports
- Use of correct claim submission addresses
- Prompt Correspondence Turnaround
  - 1-3 days from receipt

23

Compliant Claim Submission

By Payer

24

Assuring Compliant Claim Submission

- Know the requirements of **EACH** payer
- Adhere to Billing Time Limits
- Fill out claim correctly
  - Field 1a (ID)
  - Fields 9 and 9D – other insurance
  - Field 10d
  - Field 11 – insurance info (a-d)

25

- Fields 12 and 13
  - Medicare no longer requires assignment of benefits signature
  - Other payers require it is updated annually
- Fields 17 and 17a
- Field 23
- Fields 24
- Field 31
- Field 32
- Field 33

26

Optimizing Income

Spot
Claims Trends

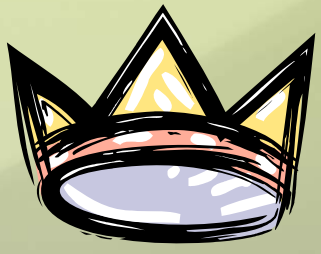
And

Identify Denials

27

Coding Vs. Reimbursement

Who Rules?



28

Reporting Rules

CPT – developed rules for reporting procedures using codes. CPT is written and maintained by the AMA with significant input from medical specialty societies

29

Payment Rules

- Payers
  - Write their own reimbursement rules
  - Determine what codes will be “bundled”
  - Determine what codes are paid separately, if they pay them at all
  - Determine discount rules

30

Payer Rules

- Payers remain autonomous in their payment rules
  - Indemnity
  - Managed Care
  - Government
  - IPA/Medical Groups

You MUST Know Them All ! ! !

31

COLLECTIONS

Do You Have . . . . .

1. Clear Financial Policy
2. Minimum Balance Write-Off
3. Payment Schedule
4. Set Collection Procedure
5. Prompt Follow-Up Policy
6. Effective Outside Collector

33

Do You Have . . . . .

- Procedure for Updating Office Fee Schedule Annually
- Procedure for Updating Office Charge Ticket Annually
- Procedure for Performing Insurance Fee Schedule Analysis

34

Are You Prepared To

- Collect Higher Co-Payments
- Collect Towards Higher Deductibles
- Report Data for Performance

35

ICD-10 is Coming

WILL

YOU

BE

READY

? ? ?

36

Deficiencies of ICD-9-CM

- Insufficient structure for reporting new technology
- Duplicate codes and codes that overlap
- Outdated terminology
- Insufficient specificity and detail
- Lack of codes for certain types of conditions or services

37

Improvements of ICD-10-CM

- Addition of information relevant to ambulatory and managed care encounters
- Creation of combination codes for diagnosis and symptoms, which will reduce the number of diagnosis codes required to describe a specific condition
- Expanded injury codes to include code extensions for injuries and external causes of injury
- Additional pregnancy trimester information

38

ICD-10-CM

- Addition of up to seven characters
- Addition of common four-digit and five-digit subclassifications
- Laterality
- Expanded alcohol and substance abuse codes
- Expanded postoperative complication codes
- Greater specificity in code assignment

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ICD-10-CM Consists of:

- Tabular lists containing cause-of-death titles and codes (Volume 1)
- Inclusion and exclusion terms for cause-of-death titles (Volume 1)
- Ad alphabetical index to disease and nature of injury
- External causes of injury
- Table of drugs and chemicals (Volume 3)
- Description, guidelines, and coding rules (Volume 2)

40

ICD-10-CM Structure (3-7 digits)

- Digit 1 is alpha (A-Z, not case sensitive)
- Digit 2 is numeric
- Digit 3 is alpha (not case sensitive) or numeric
- Digits 4-7 are alpha (not case sensitive) or numeric

41

ICD-9-CM vs. ICD-10-CM

ICD-9	**ICD-10**
17,000 Codes	140,000 Codes

42

GEMS (General Equivalence Mappings)

- The tool used to convert data from ICD-9-CM to ICD-10-CM and vice versa
- Comprehensive translation dictionary
- Practices should use this tool to create crosswalks for their most frequently used diagnosis codes

43

What to you need to do?

- Update or replace practice management system software
- Train clinical and administrative staff
- Review and modify organizational work flow
- Evaluate vendor, clearinghouse and health plan contracts and data requirements
- Develop appropriate processes and budgets to implement these new requirements

44

Additional Resources

- Crosswalk of ICD-9-CM codes to ICD-10-CM codes

  www.cms.hhs.gov

45

? ? YOUR QUESTIONS ? ?

1.

2.

3.

4.

5.

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AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

WEDNESDAY, OCTOBER 27, 2010

Moderator – Margaret Orcutt Tuddenham, DO, FACEP, FACOP

8:00 am – 9:00 am	**Craniosacral Interventions in Pediatrics** Susan Cislo, DO
9:00 am – 10:00 am	**Craniosacral Interventions in Pediatrics - Workshop** Susan Cislo, DO
10:00 am – 10:30 am	Break
10:30 am – 11:30 am	**The Comprehensive Diagnosis and Treatment of Pediatric Migraine** Marc DiSabella, DO
11:30 am – 12:30 pm	**Pediatric Spells: Not All That Moves Is a Seizure** Marc DiSabella, DO
12:30 pm – 2:00 pm	**Lunch**
2:00 pm – 3:00 pm	**Clinical Management of Toxic Substance Exposure in Children** Michael D. Reed, PharmD, FCCP, FCP
3:00 pm – 4:00 pm	**Pediatric Arrhythmia - the Good, the Bad and the Ugly** Alok Bose, MD
4:00 pm - 5:00 pm	**Chest Pain and Syncope - When to Worry** Alok Bose, MD
6:00 pm – 8:00 pm	**AOA Dinner Seminar** *(Must sign in for extra CME)*

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Susan Cislo, DO

Objective: TBA

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The Comprehensive Diagnosis and Treatment of Pediatric Migraine

Marc DiSabella, DO

Objective: Upon completion of this lecture, the participant will be able to differentiate between primary and secondary headaches, discuss the epidemiology of migraine, discuss appropriate work up for patients presenting with headache, present current acute therapies for migraine in the outpatient setting, present current prophylactic therapies for migraine, and discuss alternative therapies for migraine.

The Comprehensive Diagnosis and Treatment of Migraine in Children

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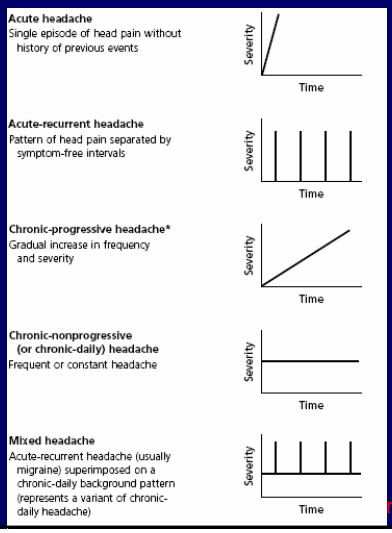
Temporal Profile of Primary and Secondary Headaches

Rothner AD. The evaluation of headaches in children and adolescents. Semin Pediatr Neurol 1995;2:109-118.

1. **Acute Headache**
   - Primary or Secondary
2. **Acute recurrent**
   - Primary
3. **Chronic Progressive**
   - Secondary
4. **Chronic nonprogressive**
   - Primary
5. **Mixed**
   - Primary



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Prevalence of Pediatric Migraine

Pediatric Migraine. Neurol Clin 2009:27;481–501

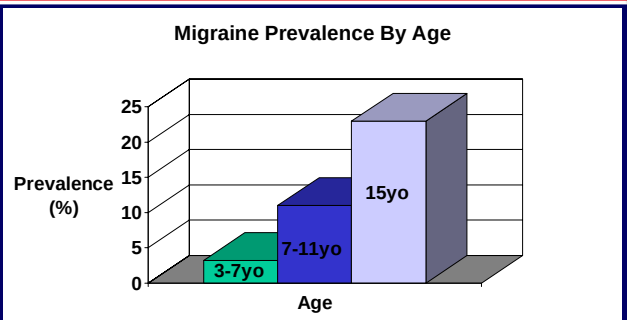

Table 1
Prevalence of migraine headache through childhood

	Age		
	3–7 Years	7–11 Years	15 Years
Prevalence	1.2%–3.2%	4%–11%	8%–23%
Gender ratio	Boys > girls	Boys = girls	Girls > boys

What Type of Headache Do Migraineurs *Think* They Have?

American Migraine Prevalence and Prevention Study. *Headache* 2007;47:355

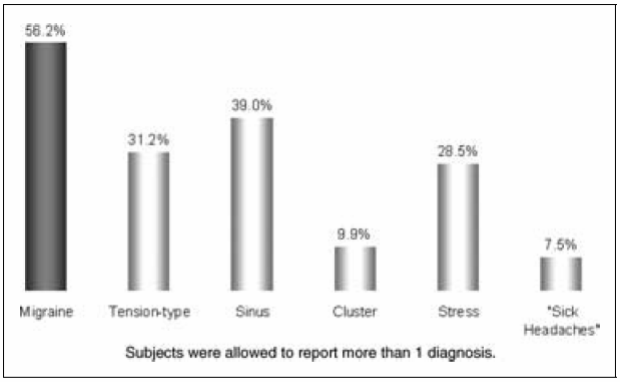

Fig 1.—Proportion of persons with ICHD-2 migraine reporting specific headache diagnosis.

Does the patient require neuroimaging to rule out secondary causes of headache?

Practice parameter: Evaluation of children and adolescents with recurrent headaches
Neurology 2002;59;490-498

- **Recommendations for Neuroimaging by AAN:**
  - 1) Headache of less than 1-month duration
  - 2) Absence of family history of migraine
  - 3) Abnormal neurologic findings on examination
  - 4) Gait abnormalities
  - 5) Occurrence of seizures

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Headache Treatment Plan

My Headache Treatment Plan

Children's National Medical Center

Date: _____

Healthy Habits *(What to do everyday to help resolve headaches?)*

- ☐ Fluids _____ ounces per day, sports drink good, none with caffeine
- ☐ Exercise at least 3 times a week for 30 minutes
- ☐ Sleep _____ hours each night, with no more than 2hrs change
- ☐ Diet 3 meals a day, with riboflavin containing foods

Acute Treatment *(What do I take when I get a headache?)*

- ☐ Ibuprofen _____ mg. Do not take more than 3 days/week.
- ☐ Naproxen sodium _____ mg. Do not take more than 3 days/week.
- ☐ Fluids (sports drink) _____ oz. Take every time you get a headache.
- ☐ _____ _____ mg. Do not take more than 2 days/week.

Do not take any of these medications more than 2 or 3 days per week!

Preventative Treatment *(What do I take every day to prevent my headaches?)*

MEDICATION:

- ☐ Amitriptyline _____ mg at night
- ☐ Topamax _____ mg ____ time(s) a day
- ☐ Cyproheptadine _____ mg in the morning
  _____ mg at night
- ☐ Depakote _____ mg in the morning

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Abortive Treatment In Children

Lewis. Pediatric Migraine. Neurol Clin 2009:27;481–501

Table 2
Evidence summary for treatment of acute attacks of migraine in children and adolescents

Drug	Class	Study Design	n	Age (Years)	Primary End Point	Efficacy	Placebo Response	Clinical Impression of Effect[a]	Adverse Effects	Reference
NSAIDs and nonopiate analgesics										
Ibuprofen	II	DBPC	88	4–16	HA response	68%	37%	+++	Infrequent	45
	II	DBPC	84	6–12	HA response	76%	53%	+++	Infrequent	46
	II	DBPCCO	32	10–17	HA relief	69%	28%	+++		63
Acetaminophen	II	DBPC	88	4–16	HA response	54%	37%	++	Infrequent	45
Triptans (serotonin$_{1B/1D}$ receptor agonists)										
Nasal spray	II	OL	58	4–11	HA relief	78%	—	++	Occasional to	64
Sumatriptan	III	DBPC	14	6–10	HA response	86%	43%	+++	frequent	41
Zolmitriptan	I	DBPC	510	12–17	2-hour HA response	63%–66%	53%	+++		39
	I	SB-DBPC	171	12–17	1-hour HA response	58%	43%	+++		42
Oral triptans										
Naratriptan	I	DBPC	300	12–17	4-hour HA relief	64%–72%	65%	O	Occasional	65
Rizatriptan	I	DBPC	296	12–17	2-hour pain relief	66%	56%	++	Occasional	66
	I	DBPC	96	6–17	2-hour HA relief	74%	36%			43
Sumatriptan	I	DBPC	302	12–17	2-hour pain relief	NA	NA	0	Occasional	68
Sumatriptan	II	DBPCCO	23	8–16	2 hour >50% decrease	34%	21%	0	Occasional	67
Zolmitriptan	IV	OL	38	12–17	HA improvement	88%	—	+	Occasional	69
	II	DBPCCO	32	11–17	2-hour pain relief	62%	28%	++		63
	I	DBPC	850	12–17	2-hour HA response	53%–57%	58%	0		70
Eletriptan	II	DBPC	267	12–17	2-hour HA response	57%	57%	0	Occasional	71
Almotriptan	IV	OL	15	11–17	HA reduction	85%	—	+	Occasional	72
	I	DBPC	866	12–17	2-hour pain relief	67%	55%	++		44
Sumatriptan	IV	OL	17	6–16	HA response	64%	—	+	Occasional	73
Subcutaneous	IV	OL	50	6–18	HA response	78%	—	+	Frequent 80%	74

Abbreviations: DBPC, double blind placebo-controlled; DBPCCO, double blind placebo-controlled crossover; HA, headache; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OL, open-label; SB, single blind.

[a] Clinical impression of effect: O, ineffective: most patients get no improvement; +, somewhat effective: few patients get clinically significant improvement; ++, effective, some patients get clinically significant improvement; +++, very effective: most patients get clinically significant improvement.

Data from Refs. [63–74]

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Prophylaxis in Pediatric Migraine

Lewis. Pediatric Migraine. Neurol Clin 2009:27;481–501

Table 3
Summary of evidence for the preventive therapies for migraine in children and adolescents

Drug	Class	Study Design	n	Age (Years)	Primary End Point	Efficacy	Placebo Response	Clinical Impression of Effect[a]	Adverse Effects	Reference
Antiepileptics										
Divalproex sodium/ sodium valproate	IV	OL	42	7–16	HA/month	81%	—	+	Occasional to frequent	55
	IV	OL	10	9–17	HA/month	83%	—	+		75
	IV	OL	23	7–17	HA/month	65%> 50% reduction	—	+		76
Gabapentin	IV	Retrospect OL	18	6–17	HA freq/month	83% > 50% reduction	—	++	Occasional to frequent	77
Topiramate	II	DBPC	44	9–17	HA/month	75%	38%	++	Occasional to	53
	I	DBPC	51	12–17	HA/month	54%–67%	42%	+++	frequent	52
	I	DBPC	85	12–17	HA/month	76%	45%	+++		54
Levetiracetam	IV	OL	20	6–17	HA/month	90%	—	+	Occasional to	56
	IV	OL	19	Mean 12	HA/month	67%	—	+	frequent	57
Zonisamide	IV	OL	12	Mean 13	HA/month	75%	—	+	Occasional	58
Antidepressants										
Trazodone	II	DBPC	35	7–18	HA freq	45%	40%	O	Occasional to frequent	78
Pizotifen	II	DBPCCO	47	7–14	HA/month	15%	16%	O	Occasional to frequent	91
Tricyclic antidepressants										
Amitriptyline	IV	OL	192	9–15	HA freq/month	84%	—	++	Occasional to	79
	IV	OL	73	3–18	HA freq/month	89%	—	++	frequent	80
Antihistamines										
Cyproheptadine	II	DBPC	68*	17–53	% improve	75%	—	++	Occasional to	81
	IV	Retrospective	30	3–18	HA/month	62%	—	++	frequent	80
Calcium channel blockers										
Flunarezine	II	DBPC	42	7–14	>50% improve	76%	19%	+++	Occasional	82
		DBPCCO	63	5–11	HA/month	67%	33%	+++ +++		83
Nimodipine	II	DBPCCO	37	7–18	HA/month	15%	16%	O	Occasional	92
Antihypertensive agents										
Propranolol	II	DBPC	39	3–12	HA freq	58%	55%	O	Occasional to	84
	II	DBCO	28	7–16	HA freq	71%	10%	++	frequent	85
	II	DBPC	28	6–12	HA freq	NS	NS	O		86
Timolol	II	DBPCCO	19	6–13	HA/month	38%	40%	O	Occasional	87
Clonidine	II	DBPC	43	7–14	HA/6 weeks	NS	NS	O	Occasional to	88
	II	DBPC	54	<15	HA/month	40%	65%	O	frequent	89
NSAIDs										
Naproxen sodium	III	DBPC	10	6–17	HA freq	60%	40%	+	Occasional	90

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WEDNESDAY, OCTOBER 27, 2010

Moderator – Margaret Orcutt Tuddenham, DO, FACEP, FACOP

11:30 am – 12:30 pm

Pediatric Spells: Not All That Moves Is a Seizure

Marc DiSabella, DO

Objective: Upon completion of this lecture, the participant will be able to identify the key clinical features in distinguishing between common spells in pediatric patients including tics, stereotypies, shuddering attacks, various types of seizures, breath holding spells, syncope, and non-epileptic spells, discuss the appropriate diagnostic work up for patients presenting with spells, review.

Current guidelines will be given for treatment of tics, stereotypes, shuddering attacks, seizures, breath holding spells, syncope, and non-epileptic spells, and discuss the prognosis in tics, Tourette Syndrome, stereotypes, shuddering attacks, seizures, breath holding spells, syncope, and non-epileptic spells.

Pediatric Spells: Not All That Moves Is a Seizure

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AAN: Evaluation of First Nonfebrile Seizure

Hirtz et al. 2000;55;616-623 *Neurology*

- Routine EEG *recommended*
- Laboratory tests *should be considered*
  - Vomiting, diarrhea, dehydration, or failure to return to baseline alertness.
  - Toxicology screening if drug exposure or substance abuse.
  - LP if concern about possible meningitis or encephalitis.
- Neuroimaging *should be considered*
  - MRI is the preferred modality

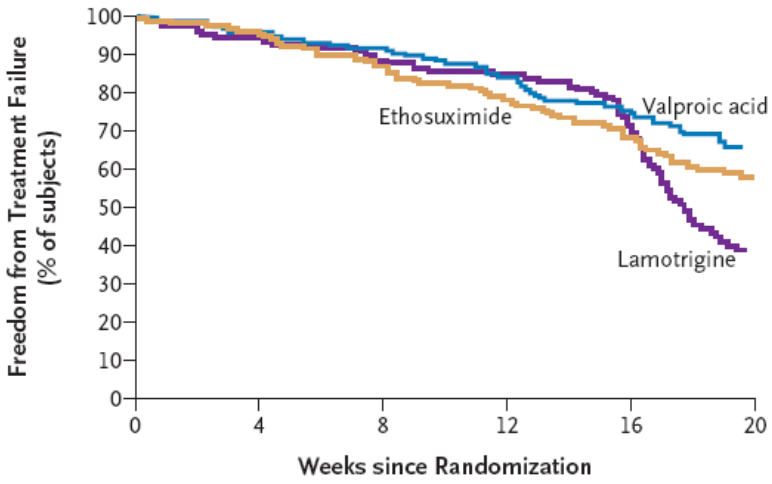
AAN: Treatment of First Nonfebrile Seizure

D. Hirtz et al. *Neurology* 2003;60;166-175

- Treatment with AED *is not indicated* for the prevention of the development of epilepsy
- Treatment with AED *may be considered* in circumstances benefits outweight risks
  - Severe static encephalopathy
  - Swimming or driving “obligation”

Ethosuximide, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy

Glauser et al. N Engl J Med 2010;362:790-9



AAN Practice Parameter
Treatment of Infantile Spasm

M.T. Mackay et al. *Neurology* 2004;62;1668-1681

- Adrenocorticotropic hormone (ACTH) is *probably effective* for the short-term treatment of infantile spasms
- There is insufficient evidence to determine whether oral corticosteroids are effective.
- Vigabatrin is *possibly effective* for the short-term treatment of infantile spasm and is possibly also effective for children with tuberous sclerosis.

Differentiation of Pediatric Spells Based on History

	BEFORE	DURING	AFTER
Tic	Inciting event: Stress, concentration Aura: Sensory or premonitory urge	Event: Simple brief patterned movement or noise Suppressible: Temporarily	Brief relaxation No change in level of consciousness
Stereotypy	Inciting event: Stress, excitement Aura: None	Event: Complex stereotypic movements Suppressible: Rarely as infant/child, more likely as pre-adolescent	No change in level of consciousness
Syncope	Inciting event: Stress, heat, emotion Aura: Diaphoresis, dizzy/vertigo, tachycardia, tunnel vision	Event: Loss of muscle tone and consciousness, eyes closed during event, may have brief stiffening or jerking Suppressible: No	Rapid return to baseline No confusion except event itself
Seizure	Inciting event: rare Aura: Partial onset may have abnormal smell, taste, sensory disturbance, motor twitching	Event: Stereotyped involuntary cortical activity with associated movements/sensory disturbance, eye opening Suppressible: No	Confusion, lethargy, weakness (Todd's), headache None if absence seizure, frontal lobe
Breath Holding	Inciting event: Stress, excitement Aura: crying, tantrum, "silent" scream	Event: Loss of tone, cyanotic or pallor, may have brief stiffening or jerking Suppressible: No	Rapid return to baseline No confusion except event itself Irritability
Shuddering	Inciting event: None Aura: None	Event: Brief trembling of whole body Suppressible: No	No change in level of consciousness

References

- S. Shinnar et al. *Pediatrics* 1996;98;216-225
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WEDNESDAY, OCTOBER 27, 2010

Moderator – Margaret Orcutt Tuddenham, DO, FACEP, FACOP

2:30 pm – 3:00 pm

Clinical Management of Toxic Substance Exposure in Children

Michael D. Reed, PharmD, FCCP, FCP

Objective: Upon completion of this lecture, the participant will understand the epidemiology of poisoning exposures in children, able to describe a rational approach to the diagnosis of a patient who has been exposed to an unknown poison, define the clinical utility and contraindications to the use of oral activated charcoal, understand the clinical utility and limitations of currently available antidotes, and appreciate the initial steps to decontamination in the event of a biologic or chemical event.

WEDNESDAY, OCTOBER 27, 2010

Moderator – Margaret Orcutt Tuddenham, DO, FACEP, FACOP

2:30 pm – 3:00 pm

Pediatric Arrhythmia - the Good, the Bad and the Ugly

Alok Bose, MD

Objective: Upon completion of this lecture, the participant will be able to identify common types of neonatal arrhythmia, describe different types of SVT and their management, and review which types of arrhythmia merit exclusion from sports.

WEDNESDAY, OCTOBER 27, 2010

Moderator – Margaret Orcutt Tuddenham, DO, FACEP, FACOP

2:30 pm – 3:00 pm

Chest Pain and Syncope - When to Worry

Alok Bose, MD

Objective: Upon completion of this lecture, the participant will be able to identify the common causes of chest pain in the pediatric patient, describe syncope as it relates to congenital heart conditions, and review the common presenting features of vasovagal syncope.

AMERICAN COLLEGE OF OSTEOPATHIC PEDIATRICIANS

AOA/ACOP PEDIATRIC TRACK ABSTRACT LISTING

Enzyme Replacement Therapy for Pompe Disease

Authors: Christina Navarro DO (1), Rohit Talwar MD (2), Laura Nimkoff MD (3)
Department of Pediatrics (1) Division of Pediatric Cardiology (2)
Division of Pediatric Critical Care (3)
Good Samaritan Hospital, West Islip NY 11795

Examining BMI Among a Score One Population: From Health Screening to Physician Visit

Author(s): Kaitlin O'Connor, MA; Julie Sahrmann, BA; Annette Campbell, RN; Richard Magie, DO
Kansas City University of Medicine and Biosciences, Kansas City, MO

The Tropics Come to Long Island

Author(s): Wayne Chen, DO; Howard Balbi, MD
Good Samaritan Hospital Medical Center, West Islip
Winthrop University Hospital, Mineola, NY

Title: Enzyme Replacement Therapy for Pompe Disease

Authors: Christina Navarro D.O. (1), Rohit Talwar M.D. (2), Laura Nimkoff M.D. (3)
Department of Pediatrics (1) Division of Pediatric Cardiology (2) Division of Pediatric Critical Care (3**)**

Affiliations: Good Samaritan Hospital, West Islip NY 11795

Abstract Body:

Introduction: Pompe disease is a rare autosomal recessive disorder caused by mutations in the gene encoding lysosomal alpha-1,4-glucosidase. This leads to accumulation of glycogen in lysosomes and cytoplasm which results in tissue destruction. If the patient is not properly treated with enzyme replacement, death usually occurs within the first two years of life from cardiac insufficiency.

Case Description:
Infant was born at Good Samaritan Hospital full term via normal spontaneous vaginal delivery. At six hours of life she was transferred to the Neonatal ICU for respiratory distress and placed on nasal CPAP. Initial x-ray demonstrated prominent cardiac size. An echocardiogram was then performed that revealed biventricular hypertrophy left greater than right. She was eventually weaned off oxygen and discharged. At three months of age during a cardiology follow up exam, the patient was found to be tachycardic and tachypneic. Physical exam also revealed generalized hypotonia, enlarged tongue and palpable liver. Echocardiogram demonstrated dilated and hypertrophic left and right ventricles. The patient was admitted to GSH Pediatric ICU, and started on a Milrinone for management of congestive heart failure. Due to high clinical suspicion for metabolic disorder, a muscle biopsy and genetic testing were performed. She was positive for cross reacting immunologic material (CRIM) Pompe Disease. The patient continues to receive monitored Myozyme IV infusion in the GSH Pediatric ICU every two weeks.

Discussion: Pompe Disease is a metabolic disorder characterized by lysosomal acid maltase deficiency. Symptoms of Pompe disease include cardiomyopathy, hypotonia, tongue enlargement and hepatomegaly. With the development of this new enzyme replacement within the past three years, patients have a significant improvement in prognosis. Thus, Pompe Disease and other inborn errors of metabolism should be in the differential diagnosis for infants with congestive heart failure.

Title: Examining BMI Among a *Score 1* Population: From Health Screening to Physician Visit

Author(s): Kaitlin O'Connor, MA; Julie Sahrmann, BA; Annette Campbell, RN; Richard Magie, DO

Affiliation(s): Kansas City University of Medicine and Biosciences, Kansas City, MO

Background: Childhood obesity is an epidemic in America that is markedly increased in ethnically diverse populations, particularly those in low-income areas. In order to address pediatric obesity and other concerns that plague the urban-core population, and in an effort to integrate public health outreach into medical education, Kansas City University of Medicine and Biosciences and *Score 1 for Health*® began a partnership in 1996. *Score 1* is a non-profit organization that provides health screenings for 13,000 children annually, making referrals to local pediatricians for those who are obese, hypertensive, diabetic, or suffering from other undiagnosed conditions. In addition to addressing the needs of the underserved, *Score 1* allows medical students to practice their physical exam skills and provides a longitudinal database useful for research. This database can be used to perform a retrospective chart review of those children referred to local clinics in order to determine how providers address and treat obesity. Despite its prevalence, we suspect that the recommended treatment protocol for obesity in childhood is seldom followed and that the therapies that are implemented are inconsistent.

Objective: The objective of this study is to determine how well primary care providers identified patients with Body Mass Indices (BMIs) at or above the 95th percentile, as well as which therapies clinicians most often implemented. We also wished to assess which health conditions are typically associated with obesity that may take precedence over BMI counseling during the patient's visit to the clinic, and we hoped to investigate barriers to treatment from the provider's perspective.

Materials/Methods: Using BMI calculations from the *Score 1* database through the years of 2007 to 2010, a study population of children was identified who had BMIs at or above the 95th percentile for at least 2 years. Patient charts from the study population were matched in area primary care clinics and data was collected by retrospective chart review using Microsoft Excel. Captured variables included positive identification of an elevated BMI, specific therapies used in treatment, and comorbid conditions mentioned in the chart. Clinicians also completed a survey and brief interview to address barriers to and attitudes towards treatment.

Results: There were 39,568 BMI measurements done by *Score 1* from 2007-2010. Of those, 1,944 children were identified who fit the study population criteria. At two local clinics, 157 charts were identified. Of those, 57.1% (90) had no mention of elevated BMI or any treatment initiated on any visit. Nutritional counseling was the most commonly implemented strategy for weight management and was provided in some form to 31% (49) of children. Physicians were more likely to document a weight problem on a physical exam (90%) visit rather than a visit for acute illness. Weight problems were more likely to be addressed with repeated visits. Only 18.1% (68) of children who visited the clinic 5 or fewer times received some BMI intervention whereas 60% (25) of children with 15 or more clinic visits received some BMI therapy. Asthma was the most common comorbidity in 11.4% (58) of children.

Conclusions: Obesity in childhood is a complex problem with contributions from the social and economic environments. Though we have come a long way in slowing the growth of this epidemic, many clinicians are not effectively recognizing or treating this problem. There is little consistency among pediatricians as to which therapies are most useful and disagreement as to which barriers to treatment are most prevalent. More research needs to be done on how clinicians can realistically and successfully incorporate effective management of pediatric obesity into the care of each patient.

Title: The Tropics Come to Long Island

Author(s): Wayne Chen, DO; Howard Balbi, MD
Affiliation(s): Good Samaritan Hospital Medical Center, West Islip; Winthrop University Hospital, Mineola, NY

Introduction:
Pyomyositis is a bacterial infection of the skeletal muscles often resulting in abscess formation and severe complications with delayed treatment. Pyomyositis is more common in healthy individuals in tropical regions and typically affects the large muscle groups. In temperate regions it is usually found in patients with comorbidities like diabetes, IV drug abuse, and immunodeficiency disorders.

Case Description:
A 13-year-old male with history of asthma and no recent travel, presented to GSH emergency department complaining of bilateral anterior thigh pain, fever and URI symptoms for several days. Physical exam at admission showed a febrile, male with thighs that were warm, tender to palpation, and painful with movement. A small pustular lesion was noted on his ankle. Lesion and blood cultures were obtained. The patient was then admitted for further evaluation and management. During the patient's stay, labs showed normal CPKs and elevated ESRs. CRPs were elevated initially, but decreased with clinical improvement. Based on the physical, normal CPK, and elevated CPR, pyomyositis was suspected and antibiotics were started. MRI showed extensive myositis and fasciitis on the thigh and pelvis, with bilateral synovitis of the hips. Follow-up MRI showed an abscess on the right obturator internus muscle which was drained by orthopedics. Blood and wound cultures grew *Staphylococcus aureus*. The patient improved clinically. A PICC line was placed to complete six weeks of outpatient antibiotic therapy. After three months, he has since returned to regular activity.

Conclusion:
This case demonstrates a classic case of pyomyositis in a region where it is uncommonly seen in healthy individuals. Such a presentation could easily have been misdiagnosed as viral myositis leading to delayed treatment if pyomyositis was not considered. Physicians must remain aware diseases are not obligated to match its demographic profile and be confident with their diagnosis based on physical findings.

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