Children's National™

NICU PROTOCOL BOOK

Written and Edited by Members of
THE DEPARTMENT OF NEONATOLOGY
& MEMBERS OF THE NICU CARE TEAM

Revised 2016

Starting NICU TPNs

Preterm

	Initiate	Advance	Goal
Dextrose	4-6 mg/kg/min (or 1-2 mg/kg/min above current GIR)	1-2 mg/kg/min	11-12 mg/kg/min (or to meet kcal goals)
Lipid	0.5-1 g/kg	0.5-1 g/kg	3 g/kg
Protein	3-4 g/kg	1 g/kg	3.5-4 g/kg

*Note: lipids are run over 24 hours, with few exceptions (usually only if IR is consulting).

Term

	Initiate	Advance	Goal
Dextrose	6-8 mg/kg/min (or 1-2 mg/kg/min above current GIR)	1-2 mg/kg/min	10 mg/kg/min (or to meet kcal goals)
Lipid	1-2 g/kg	1 g/kg	3 g/kg
Protein	2.5-3 g/kg	--	2.5-3 g/kg

Preterm infants should start PN ASAP. **Term** infants can be NPO x 3 days.

Max GIR for infants: 15-17 mg/kg/min.

Electrolytes

	Initiate	Adjust	Needs
Sodium	0-3 mEq/kg	1-2 mEq/kg	1-6 mEq/kg
Potassium	0-2 mEq/kg	0.5-1 mEq/kg	1-6 mEq/kg
Magnesium	0-0.3* mEq/kg	0.05-0.1 mEq/kg	0.2-0.3 mEq/kg

*Magnesium: If lab ≤1.7, start at 0.2-0.3 mEq/kg. Otherwise, put no Mg in PN.

Sample TPN for preterm infant.

Src	Substance	Value	Numer	Denom
U	Volume	267	ml	/day
T	Duration	24	hour	/-
T	Period	24	hour	/-
T	Overfill	100	ml	/day
U	Dextrose 70%	10	gm%	/-
U	Intralipid 20%	1	gram	/PatKg
U	Premasol10%	3	gram	/PatKg
U	Sodium	5	mEq	/PatKg
U	Potassium	3	mEq	/PatKg
T	Acetate	2.82	mEq	/PatKg
U	Phosphate	1	mM	/PatKg
U	Calcium	40	mg	/PatKg
U	Magnesium	0	mEq	/PatKg
T	Chloride	6.53	mEq	/PatKg
T	MVI-Pediatric	2	ml	/PatKg
T	Heparin	1	Unit	/mlAV
U	Zinc Chloride 1	350	mcg	/PatKg
U	L-CARNITINE	20	mg	/PatKg
U	Multitrace 5	0.05	ml	/PatKg
U	Selenium	1	mcg	/PatKg

← TPN volume in **ml/day**.
TPN volume = (Total fluid goal x weight) - (lipids + continuous infusions + 24 hour feeding volume)

} Per charts above

} Na and K per team. Infants on day of life 0-2 may not require any Na or K.

} Usually start Ca at 40 mg/kg and Phos at 0.8-1 mmol/kg (may be less during Na/K Phos shortage)

← Check lab. See note above for details.

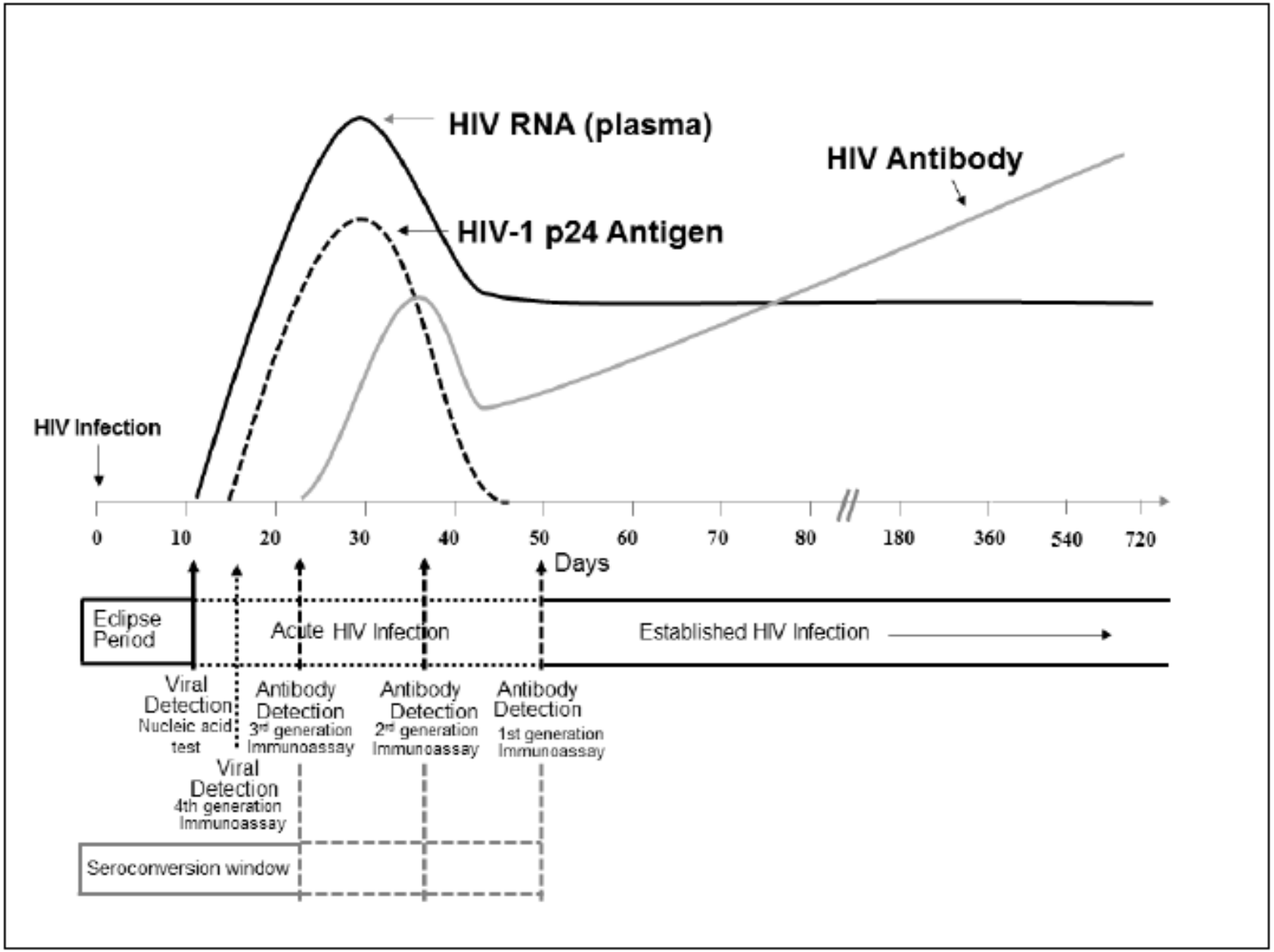
← Max Cl unless indicated otherwise by labs or team. See TPN Survival Guide for more information.

} OK to leave Multitrace 5 and Se out on first few days of PN. Zn starts at 200; if leaving out Multitrace 5 and Se, increase Zn to 400 for <2.5 kg and 250 for >2.5 kg.

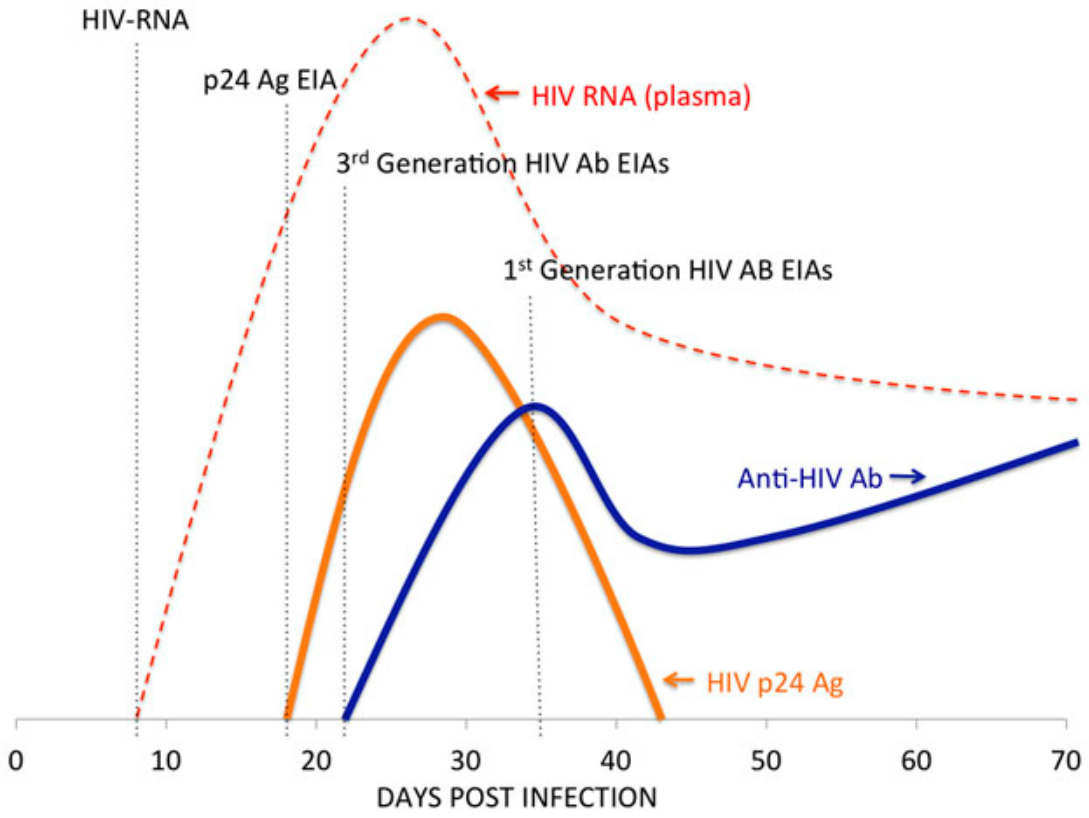
★ Please write in Label Notes:

TFG: ____ ml/kg/day
Feeds: ___ ml
Lipids:___ ml
Drips: ___ ml

Figure 1. Sequence of appearance of laboratory markers for HIV-1 infection



Diagnostic Tests for HIV Infection



Management of Ventriculomegaly

Infants < 32 wks, BW<1500g, ECMO, HIE, seizure, ventriculitis/meningitis/encephalitis
HUS on admission
(or premie or HIE or ECMO protocol)

Ventriculomegaly (VM)?
Ventriculitis?
IVH grade 3 or 4?

No

HUS every 4 weeks, sooner if arrest or major event
Daily HC

No

VM?
Ventriculitis?

Yes

Consult Neurology

HUS every Mon & Thur
Monitor 3rd width, RI, FOR and/or FTHR

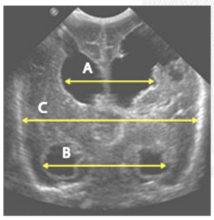
VM on HUS:
3rd ventricle > 2mm or progression
FOR or FTHR > 0.55 or progression*
FOR or FTHR > 0.1 in a week w/wo ↑RI*
(mild ≥ 0.55; moderate ≥ 0.6; severe ≥ 0.7)

HUS every 2-4 weeks, sooner if events or arrest
Daily HC

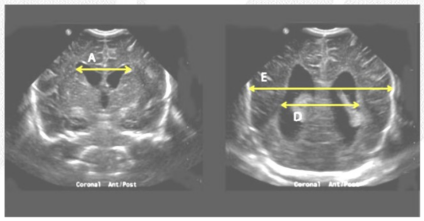
Yes

FOR or FTHR stable x 2 wks?

No



FTHR = (A+B)/2C



FOR = (A+D)/2E

Physical exam:

- Daily HC: ↑HC > 1.5 cm/week for two weeks (confirming rapid progression).
- Anterior fontanel exam: Bulging/tense in sitting position.
- Splayed metopic suture: > 1mm at gabella
- Apnea or Bradycardia: > 3 episodes in 24 hours lasting > 30 seconds, not explained by other medical conditions.

Does HUS demonstrate significant and progressive VM by 3rd or FOR/FTHR?

No

Presence of abnormal exam (at least one criterion) or progression x 2 weeks?

No

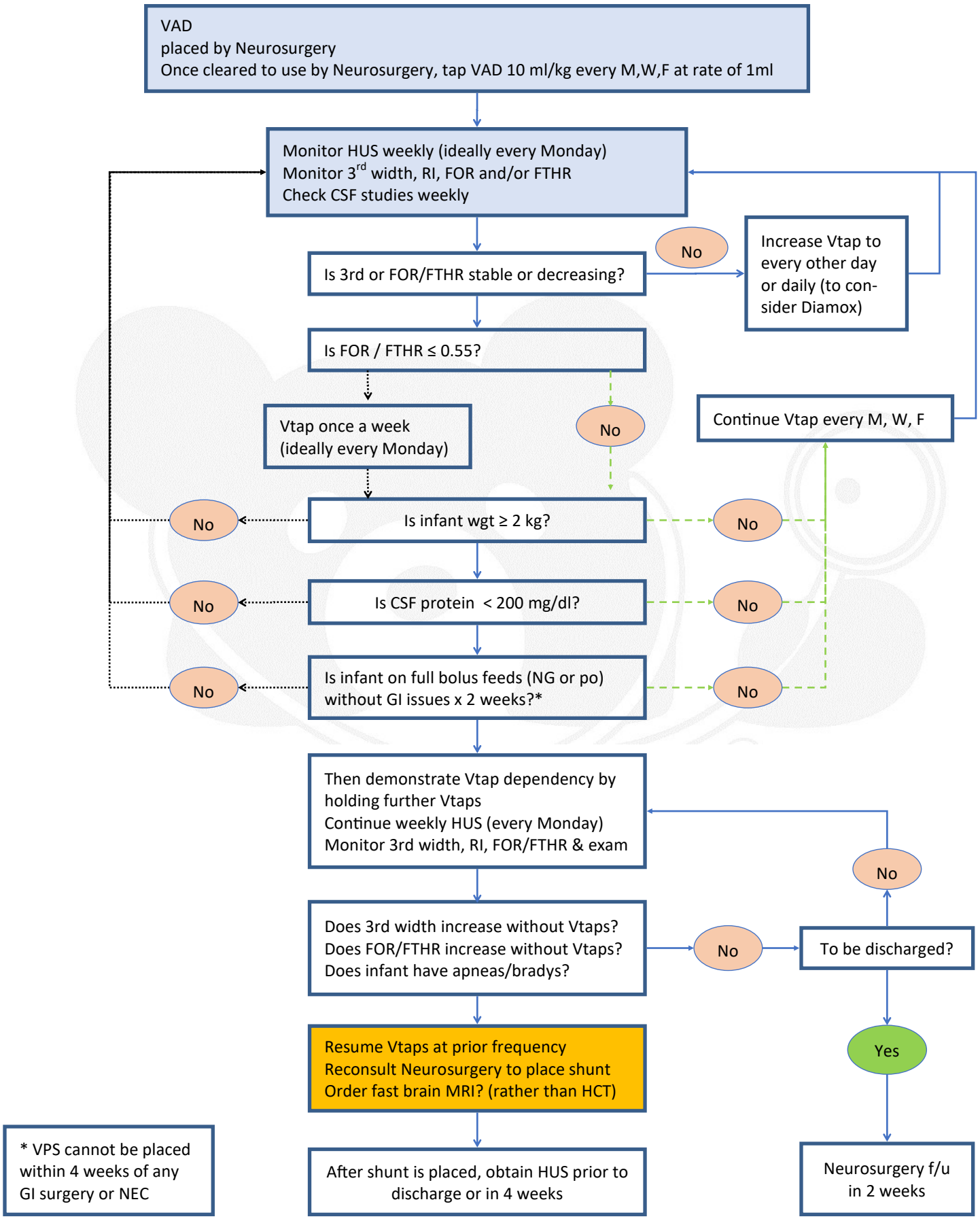
Consult Neurosurgery for VAD placement

DEFINITIONS & NORMS
Ventriculomegaly (VM) = atria ≥ 10mm
IVH grade 2 = blood within ventricles
IVH grade 3 = IVH + VM
RI norms: premie 0.7-0.8; term 0.6-0.7
3rd ventricle width (norm) ≤ 2 mm
*unilateral or bilateral

Children's National Medical Center
Neonatal Neurocritical Care Service

Created 2017
Last revised 3.28.17

VAD Management



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HERPES SIMPLEX VIRUS

I. DEFINITIONS

A. Disseminated disease:
Disease involving multiple visceral organs, including lung, liver, adrenal glands, skin, eye and/or brain

B. Central Nervous System (CNS) disease:
Disease involving central nervous system (e.g. meningoencephalitis) with or without skin lesions

C. Skin, Eye, Mouth (SEM) disease:
Disease limited to the skin, eyes, and/or mouth

II. EXPOSURES

A. Intrapartum exposure:
1. 85% of infections result from intrapartum exposure
2. Disseminated and SEM disease will typically present 10-12 days
3. CNS disease will typically present between 17-19 days

B. Postnatal exposure:
1. Account for approximately 10% of infections and present later

C. Fetal (in utero) exposure:
1. Account for only 5% of infections, with stigmata present at birth

III. CLINICAL MANIFESTATIONS

A. Newborn with multi-system organ failure, including transaminitis without alternative etiology

B. Newborn with maternal history; note AAP Redbook guidelines for management of asymptomatic newborns born to mothers with HSV)

C. Infant with skin lesions, transaminitis, and/or multi-system organ failure

D. It is not customary to “rule-out” HSV for every febrile infant; HSV should be considered in the setting of clinical signs or maternal history:
1. Mucocutaneous vesicles
2. Ill-appearing infant with irritability and lethargy
3. Seizures, focal neuorologic sings or abnormal neuroimaging
4. Abdominal distensions, hepatomegaly or ascites
5. Severe respiratory distress with apnea ore progressive pneumonitis
6. Conjunctivitis
7. Cerebrospinal fluid (CSF) pleocytosis

8. Thrombocytopenia
9. Elevated liver transamases, viral hepatitis or acute liver failure

E. Note the signs of HSV in a premature infant are much more subtle
   1. Skin lesions are present in less than 50% of infants
   2. Lethargy, hypotension, temperature instability and transaminitis are less consistent findings
   3. Respiratory distress and thrombocytopenia were much more common
   4. Diagnostic testing should also include endotracheal and/or pharyngeal secretions in this population in the setting of worsening respiratory distress

IV. DIAGNOSTIC EVALUATION

See subsequent section on HSV testing in neonates

V. TREATMENT

A. Begin empiric acyclovir in any symptomatic patient with suspected HSV

B. Continue empiric therapy until ALL studies, including cultures, are negative; do NOT stop empiric therapy based on PCR alone

C. If diagnostic testing confirms HSV infection, continue IV acyclovir for 14-21 days, followed by suppressive therapy for 6 months with ID consultation

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1. American Academy of Pediatrics. Herpes simplex. In AAP Redbook 2015 edition
2. Caviness AC, Demmler GJ, Swint JM, Cantor SB. Cost-effectiveness analysis of herpes simplex virus testing and treatment strategies in febrile neonates. Arch Pediatr Adolesc Med. 2008; 162(7):665.
3. Kimberlin DW, Baley J. Committee on infectious diseases and Committee on fetus and newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics 2013;131:e635–e646
4. O'Riorda DP, Golden WC, Aucott SW. Herpes simplex virus infections in premature infants. Pediatrics 2006; 118(6).

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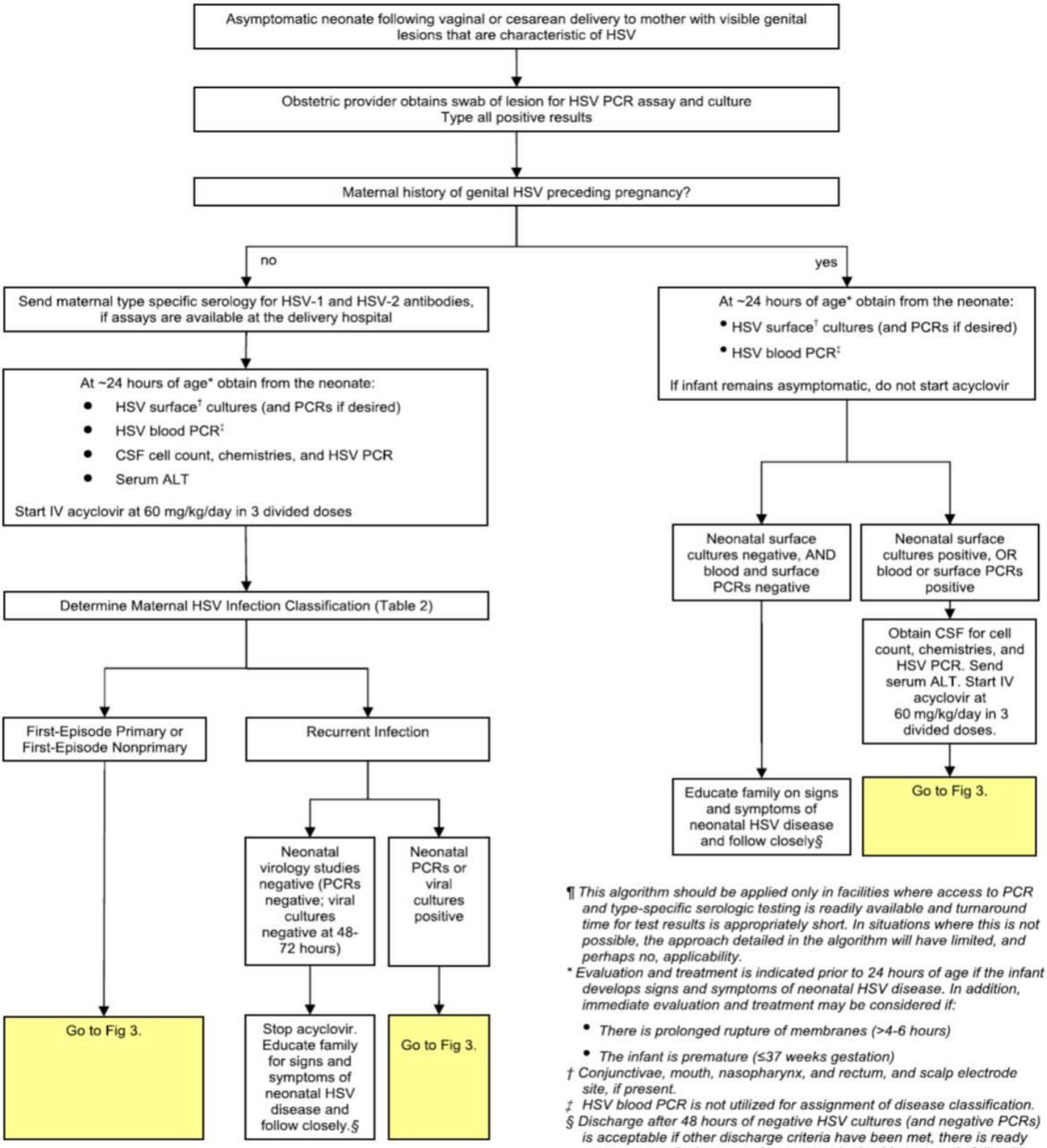

¶ *This algorithm should be applied only in facilities where access to PCR and type-specific serologic testing is readily available and turnaround time for test results is appropriately short. In situations where this is not possible, the approach detailed in the algorithm will have limited, and perhaps no, applicability.*

* *Evaluation and treatment is indicated prior to 24 hours of age if the infant develops signs and symptoms of neonatal HSV disease. In addition, immediate evaluation and treatment may be considered if:*

- *There is prolonged rupture of membranes (>4-6 hours)*
- *The infant is premature (≤37 weeks gestation)*

† *Conjunctivae, mouth, nasopharynx, and rectum, and scalp electrode site, if present.*

‡ *HSV blood PCR is not utilized for assignment of disease classification.*

§ *Discharge after 48 hours of negative HSV cultures (and negative PCRs) is acceptable if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital until HSV cultures are finalized as negative or are negative for 96 hours after being set up in cell culture, whichever is shorter.*

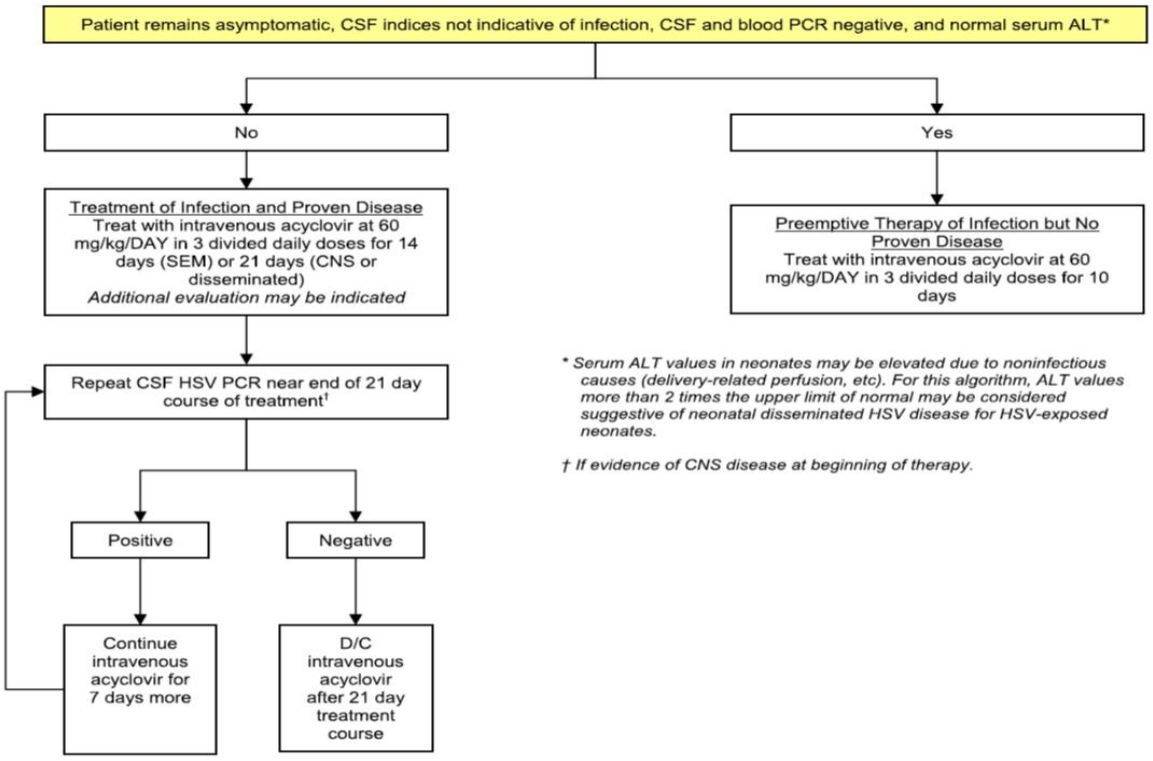

FIGURE 3

Algorithm for the treatment of asymptomatic neonates after vaginal or cesarean delivery to women with active genital herpes lesions. ALT, alan aminotransferase; D/C, discontinue.

HERPES SIMPLEX VIRUS TESTING IN NEONATES

I. DIAGNOSTIC SPECIMENS

A. "Surface" specimens: There are two acceptable methods to obtain mucosal specimens, both of which involve swabbing four sites:
   1. Utilizing a separate VCM transport swab* for each site, swab the conjunctiva with one (and label as such), the nasopharynx with another (and label as such), the oropharynx with a third (and label as such) and a fourth swab for the anus (and label as such). Order both *HSV PCR* and *culture* on all four swabs.
   2. Using a single VCM transport swab, swab the four sites in the following order: First swab the conjunctiva, then the nasopharynx, then the oropharynx, and finally the anus (and label as a combined specimen). Order both *HSV PCR* and *culture* on the single swab specimen.

      **Note – we previously used Eswabs that converts a typical swab specimen into a liquid specimen that greatly expands the spectrum of tests that can be performed on it. However, it is only available for HSV PCR. If we are to do both PCR and cultures, we need to use the VCM transport swab.*

B. Vesicle:
   If a vesicle is present, lift the top off and swab its base with an VCM swab. Send for both HSV PCR and culture.

C. Cerebrospinal fluid:
   1. Obtain from a lumbar puncture and submit in a sterile, leak proof container for CSF Biofire Panel (for rapid detection of meningitis/encephalitis)
      a. Requires 200 microliters of CSF
      b. Testing performed 24x7 and results will be available within 2 hours
   2. Stand-alone CSF HSV PCR is also available, but is only run M, W, F

D. Blood:
   1. Whole blood sent in a lavender EDTA tube for HSV PCR only.
   2. Whole blood sent in a red top tube to for ALT (or send full liver panel)

E. General concepts:
   1. There are no studies in neonatal populations to document that PCR performed on "surface" specimens has equal sensitivity or specificity for detecting active infection compared to viral culture. Thus, culture remains the gold standard for mucosal surface specimens and one should order both HSV PCR ***and*** culture on these specimens.
   2. In contrast, HSV PCR is the "gold standard" for CSF and whole blood, and viral culture should not be sent on those specimens.

F. Test Result Turnaround:
   1. HSV PCR is performed on site at CNMC on Mondays, Wednesdays and Fridays. If the sample is received by the molecular lab before 7 am on a testing day the result

will be available the same day. Otherwise the maximum time till a result is available is 4 days. New CSF Biofire Panel is run daily with 2 hour turnaround time.

2. HSV cultures are sent out to Quest Diagnostics. They utilize the ELVIS system (Enzyme-Linked Virus Inducible System). A negative result is reported in 48 hours after receipt, and the result directly uploaded into Powerchart once released by Quest. If positive, the turnaround time is 3-5 days, to allow for additional confirmatory testing (immunofluorescent staining).

II. ADDITIONAL CONSIDERATIONS (UNUSUAL)

A. If a tissue biopsy of a lesion is performed, contact the microbiology laboratory to obtain M4 media prior to obtaining the biopsy. Place the biopsy directly in the media. Order HSV PCR and culture.

B. If a biopsy for histology is also desired, a separate biopsy should be obtained and placed in formalin.

C. Another option is to obtain a single large punch biopsy and bisect it under sterile conditions, submitting half in the M4 media(for PCR and culture) and half in formalin (for histology).

III. INTERPRETATION OF RESULTS

All neonatal HSV patients should warrant consideration for formal Infectious Diseases consultation, which will include assistance with interpretation of results and subsequent treatment/disposition decisions.

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Roberta DeBiasi, M.D.

AMERICAN ACADEMY™
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Ophthalmic Technology Assessment

Anti-Vascular Endothelial Growth Factor Therapy for Primary Treatment of Type 1 Retinopathy of Prematurity

A Report by the American Academy of Ophthalmology

Deborah K. VanderVeen, MD,[1] Michele Melia, ScM,[2] Michael B. Yang, MD,[3] Amy K. Hutchinson, MD,[4] Lorri B. Wilson, MD,[5] Scott R. Lambert, MD[6]

Purpose: To review the available evidence on the ocular safety and efficacy of anti-vascular endothelial growth factor (VEGF) agents for the treatment of retinopathy of prematurity (ROP) compared with laser photocoagulation therapy.

Methods: A literature search of the PubMed and Cochrane Library databases was conducted last on September 6, 2016, with no date restrictions and limited to articles published in English. This search yielded 311 citations, of which 37 were deemed clinically relevant for full-text review. Thirteen of these were selected for inclusion in this assessment. The panel methodologist assigned ratings to the selected articles according to the level of evidence.

Results: Of the 13 citations, 6 articles on 5 randomized clinical trials provided level II evidence supporting the use of anti-VEGF agents, either as monotherapy or in combination with laser therapy. The primary outcome for these articles included recurrence of ROP and the need for retreatment (3 articles), retinal structure (2 articles), and refractive outcome (1 article). Seven articles were comparative case series that provided level III evidence. The primary outcomes included the effects of anti-VEGF treatment on development of peripheral retinal vessels (1 article), refractive outcomes (1 article), or both structural and refractive or visual outcomes (5 articles).

Conclusions: Current level II and III evidence indicates that intravitreal anti-VEGF therapy is as effective as laser photocoagulation for achieving regression of acute ROP. Although there are distinct ocular advantages to anti-VEGF pharmacotherapy for some cases (such as eyes with zone I disease or aggressive posterior ROP), the disadvantages are that the ROP recurrence rate is higher, and vigilant and extended follow-up is needed because retinal vascularization is usually incomplete. After intravitreal injection, bevacizumab can be detected in serum within 1 day, and serum VEGF levels are suppressed for at least 8 to 12 weeks. The effects of lowering systemic VEGF levels on the developing organ systems of premature infants are unknown, and there are limited long-term data on potential systemic and neurodevelopmental effects after anti-VEGF use for ROP treatment. Anti-VEGF agents should be used judiciously and with awareness of the known and unknown or potential side effects. *Ophthalmology 2017;124:619-633 © 2017 by the American Academy of Ophthalmology*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Pediatric Ophthalmology/Strabismus Panel is to compare the ocular efficacy and safety of intravitreal injection of anti-vascular endothelial growth factor (VEGF) medications with those of laser photocoagulation therapy for treatment of type 1 retinopathy of prematurity (ROP).

Background

Retinopathy of prematurity is a retinal vascular disorder found in premature infants, who have an increased risk of severe disease consistently associated with low gestational age (GA) at birth and low birth weight. Retinopathy of

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prematurity is at least in part an oxygen-regulated retinopathy, and it is thought to develop in 2 phases. Exposure to relative hyperoxia in phase I causes downregulation of growth factors, resulting in retinovascular growth attenuation and vasocessation that leads to hypoxic ischemia and vasoproliferation in phase II.[1–3] Retinopathy of prematurity can progress from vasoproliferation to exudation and to cicatricial traction retinal detachment. Current estimates suggest that of the 13 million premature children born worldwide each year who survive the neonatal period, vision-threatening ROP will develop in more than 50 000.[4]

Although many efforts can be made to prevent ROP, most current treatments target the second phase, after abnormal fibrovascular proliferation occurs. The Cryotherapy for Retinopathy of Prematurity randomized trial demonstrated the efficacy of cryotherapy (vs. observation) as a treatment for threshold ROP (defined as 5 contiguous or 8 interrupted clock hours of stage 3 ROP with plus disease in zone I or II), and it showed a marked reduction in the rates of unfavorable retinal structural outcomes and blindness.[5] The Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial found improved retinal structural and visual outcomes when laser photocoagulation therapy was used for high-risk prethreshold ROP; current clinical treatment guidelines for ROP are based on ETROP recommendations.[6] The ETROP clinical guideline for the ROP severity at which treatment should be considered is defined as type 1 ROP, and it includes any ROP with plus disease or stage 3 without plus disease in zone I, and stage 2 or 3 with plus disease in zone II. However, any retinal ablative treatment is not always effective for type 1 ROP, as reflected in the 6-year ETROP outcomes showing an unfavorable visual acuity outcome (recognition visual acuity of $\leq$20/200) in 25.1% of eyes and an unfavorable structural outcome (retinal fold or detachment involving the macula, retrolental mass, or vitrectomy or scleral buckling surgery) in 8.9% of eyes. Furthermore, both laser treatment and cryotherapy are retinal ablative (destructive) treatments that can be stressful for the infant, require sedation or general anesthesia, and have potentially unwanted ocular side effects.

Although there are many factors involved in the normal growth and protection of retinal blood vessels, VEGF is required for normal angiogenesis, and it plays an important role in the development of ROP.[7] Vascular endothelial growth factor is modulated by relative tissue hypoxia or hyperoxia[8] and is potentiated by insulin-like growth factor 1,[9] which typically rises in the third trimester of fetal development but often is deficient after premature birth. Infants undergoing vitrectomy for severe ROP with retinal detachment have shown elevated intravitreal VEGF levels.[10,11] Similarly, adult eyes with proliferative retinal vascular disorders arising from retinal ischemia, such as diabetic retinopathy, also have elevated VEGF levels.[12] In recent years, there has been increased interest in, and use of, anti-VEGF therapy by intravitreal injection for several retinal vascular disorders, including ROP. In the premature infant population, however, there are concerns about systemic side effects of anti-VEGF agents because VEGF is important for angiogenesis not only in the eyes, but also in other vital organs such as the lungs, kidneys, and brain.[13] Although off-label use of anti-VEGF agents for ROP treatment has been reported, either as monotherapy, in combination with laser photocoagulation therapy, or as salvage therapy, only a few studies provide a direct comparison of ROP treatment methods, and they generally provide limited follow-up data.

Question for Assessment

The purpose of this assessment was to address the following question: How does the efficacy and safety of anti-VEGF therapy compare with that of standard laser photocoagulation for type 1 ROP, specifically with respect to retinal structural outcomes, visual and refractive outcomes, ocular complications, and systemic morbidity?

Description of Evidence

A literature search was conducted last on September 6, 2016, in the PubMed and Cochrane Library databases without date restrictions and was limited to studies published in English. The following search terms were used:

(*Pegaptanib* OR *Macugen* OR *Bevacizumab* OR *Avastin* OR *Ranibizumab* OR *Lucentis* OR *Aflibercept* OR *vegf trap* OR *Eylea* OR *vegf inhibitor* OR *vegf inhibitors* OR *anti-vegf* OR *anti-vegfs* OR *vascular endothelial growth factor inhibitor* OR *vascular endothelial growth factor inhibitors*) AND (*prematurity retinopathies* OR *prematurity retinopathy* OR *retrolental fibroplasia* OR *retrolental fibroplasias* OR *ROP* OR *retinopathy of prematurity* [Mesh] OR *retinopathy of prematurity*) AND (*Laser Therapy* [Mesh] OR *laser therapy* OR *laser therapies* OR *laser ablation* OR *tissue ablation* OR *laser tissue ablation* OR *laser ablative*) NOT (*Child* [Mesh] OR *Child, Preschool* [Mesh] OR *Adolescent* [Mesh] OR *Adult* [Mesh] OR *Aged* [Mesh] OR *Aged, 80 and over* [Mesh] OR *Middle Aged* [Mesh] OR *Frail Elderly* [Mesh] OR *Young Adult* [Mesh]) AND (*Infant, Newborn* [Mesh]).

The search resulted in 311 potentially relevant citations. The first author (D.K.V.) reviewed the abstracts and marked those that potentially met the following inclusion criteria: the research was original; the study population consisted of infants with ROP; the study was a comparative case series or randomized trial; intervention group patients (eyes) were treated with bevacizumab, ranibizumab, or pegaptanib sodium (possibly in combination with laser); control group patients (eyes) underwent laser photocoagulation therapy; patients were followed up until retinal status after acute ROP could be determined; and retinal structure was included as an outcome. Each article was reviewed with respect to severity of ROP, based on the International Classification for ROP[14] considering zone, stage, and presence or absence of plus disease, as well as whether the ROP met contemporary treatment criteria. Some studies analyzed the effectiveness of an anti-VEGF agent as primary therapy for type 1 or threshold ROP, whereas others evaluated the effectiveness of these agents in combination with laser therapy, as salvage therapy after laser

treatment, or in conjunction with planned surgery for repair of retinal detachment. The first author reviewed prospective randomized trials and comparative case series that used anti-VEGF treatment as monotherapy or as a combined therapy compared with laser therapy. Noncomparative case series, single case reports, and commentaries were not included. Review articles were not considered in this assessment.

Thirty-seven articles were selected for full-text review. Most articles (n = 22) were eliminated because they were not comparative case series or randomized trials, and 2 comparative case series were eliminated because the comparison group was not standard laser therapy. The remaining 13 studies were determined to be relevant for the assessment objectives, and they are listed in Table 1.

The methodologist (M.M.) assigned levels of evidence ratings to the studies according to the strength of evidence. A level I rating was assigned to well-designed and well-conducted randomized clinical trials, a level II rating was assigned to well-designed case-control and cohort studies and lower-quality randomized studies, and a level III rating was assigned to comparative case series. No studies met the criteria for level I evidence, 6 articles (from 5 randomized trials) met the criteria for level II evidence, and 7 articles met the criteria for level III evidence. The predefined standardized criteria for rating all Ophthalmic Technology Assessments involving treatment comparisons requires masking when the outcome is subjective for a level I strength of evidence rating. Although it is clear that masking is not possible for this particular Ophthalmic Technology Assessment, having no masking is a source of possible bias in the treatment comparison, regardless of whether masking is possible, and the level of evidence reflects this.

Published Results

Prospective Randomized Trials

All prospective randomized studies were assigned a rating of level II.

In 2011, Mintz-Hittner et al[15] (United States) reported results of the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study.[28] This multicenter study randomized infants who had bilateral stage 3 ROP with plus disease in zone I or posterior zone II to intravitreal bevacizumab (0.625 mg in 0.025 ml) monotherapy or to laser photocoagulation therapy. In this study, 150 infants (300 eyes) were enrolled and 143 infants survived to 54 weeks' postmenstrual age (PMA). The primary outcome was recurrence of ROP that required retreatment by 54 weeks' PMA. RetCam (Clarity Medical Systems, Pleasanton, CA) images were used to document the ROP, and at recurrence, these images were reviewed by the treating and consulting ophthalmologist (without masking) before deciding on additional treatment. Recurrence that required treatment occurred in 4% (6/140 eyes) of the bevacizumab group and in 22% (32/146 eyes) of the laser group. Analysis stratified by zone of ROP showed a significant treatment effect for zone I ROP (recurrence of 6% [2/31 infants] in the bevacizumab group vs. 42% [14/33 infants] in the laser group), but not for zone II ROP. After treatment for zone I disease with bevacizumab, recurrence was seen in 1 eye of 2 patients, and macular dragging occurred in 1 of these eyes. After laser treatment for zone I disease, recurrence was seen in 23 eyes (9 bilateral); macular dragging occurred in 16 eyes and retinal detachment in 2 eyes. After treatment for zone II disease with bevacizumab, recurrence was seen in both eyes of 2 patients, and both eyes of 1 patient showed retinal detachment. After laser treatment for zone II disease, recurrence was seen in 9 eyes of 5 patients, with macular dragging in 6 eyes, but no retinal detachments. This trial was rated level II evidence because of a lack of masked outcome determination. Additional concerns include the following: (1) a change in the primary study outcome from lack of recurrence to a need for retreatment by 54 weeks' PMA; (2) a lack of standardized laser protocol or assessment of the quality of laser treatment and pattern; (3) a higher level of treatment failure (a requirement for retreatment for zone 1 eyes) compared with other study populations, thus potentially biasing the primary outcome in favor of bevacizumab; and (4) concern about generalizability to all populations because of a high percentage of Hispanic infants in this study (85/150 [56.6%]). Furthermore, this study ended without follow-up for most zone 1 eyes that never met retreatment criteria in the bevacizumab group, but probably never fully vascularized.

In 2012, Autrata et al[16] (Czech Republic) reported the results of a prospective comparative study in which 76 infants (152 eyes) with stage 3 ROP with plus disease in zone I or posterior zone II were randomized to receive either intravitreal pegaptanib (0.3 mg in 0.02 ml) and conventional diode laser photocoagulation (group 1; 68 eyes of 34 infants), or diode laser photocoagulation with or without cryotherapy (group 2; 84 eyes of 42 infants). Thus, this study reports results of combination therapy (anti-VEGF treatment plus diode laser photocoagulation) compared with diode laser photocoagulation alone. Outcomes were categorized as retinal anatomic status and rate of recurrence requiring retreatment by 55 weeks' PMA. RetCam images were obtained by the treating ophthalmologist at the time of treatment or retreatment and were reviewed by 2 other ophthalmologists before treatment decisions were made. An unfavorable outcome was defined as the development of stage 4A or worse ROP. Recurrence of stage 3 ROP in at least 1 eye was seen in 14.6% (5/34) of infants in group 1 and in 50% (21/42) of infants in group 2; a favorable anatomic outcome was seen in 89.7% (61/68) of eyes in group 1 and 60.7% (51/84) of eyes in group 2. There was faster resolution of plus disease for eyes in group 1 compared with those in group 2 (mean, 1.3 weeks vs. 2.6 weeks, respectively), shorter time to the growth of retinal vessels into the peripheral retina treated with laser for eyes in group 1 compared with group 2 (mean, 2.2 weeks vs. 3.6 weeks, respectively), and a longer time to recurrence (mean ± standard deviation, 15.1±4.1 weeks for 6 eyes in group 1 vs. 5.9±4.8 weeks for 26 eyes in group 2). Although the rate of recurrence, the rate of the need for retreatment, and the percentage of eyes with unfavorable anatomic outcomes are all higher in this study compared with most cohorts, the added benefit of anti-VEGF therapy is notable. Other limitations of the trial include a lack of standardized laser protocol and assessment of laser quality as well as a lack of a standard reading protocol for images used in making treatment decisions. This trial was rated level II because of its small sample size and a lack of masked outcome determination.

Moran et al[17] (Ireland) reported outcomes of 14 infants with type 1 ROP, all with bilateral stage 3 with plus disease in zone I

Table 1. Studies Meeting Criteria for Ophthalmic Technology Assessment

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Mintz-Hittner et al,[15] 2011 (BEAT-ROP)	II	RCT	150 infants/300 eyes initially enrolled Infants randomized to: IVB (n = 75) or laser (n = 75) 143 infants survived to 54 weeks' PMA; zone I: 64 infants (31 IVB, 33 laser); zone II: 79 infants (39 IVB, 40 laser)	Bevacizumab 0.625 mg (0.025 ml)	Zone I IVB: GA, 24.2±1.3 wks BW, 615.2±139.5 g (34.5±1.4 wks) Zone I laser: GA, 24.3±1.6 wks BW, 657.9±159.5 g (33.7±1.6 wks) Zone II IVB: GA, 24.5±1.2 wks BW, 689.2±111.3 g (35.7±2.1 wks) Zone II laser: GA, 24.5±1.4 wks BW, 680.7±156.8 g (35.8±2.0 wks)	Stage 3+ ROP in zone I or posterior zone II in each eye	54 wks' PMA	Primary outcome was recurrence requiring retreatment by 54 weeks' PMA: Zone I: IVB, 6% (2/131 infants) Laser, 42% (14/33 infants) $P = 0.003$ Zone II: IVB, 5% (2/39 infants) Laser, 12% (5/40 infants) $P = 0.27$	Graded as lower-quality RCT primarily because there was no masking and the outcome was subjective. Also, (1) changed primary outcome during the trial but before data analysis; (2) reported subgroup results (zone I/zone II) without performing a test for interaction.
Autrata et al,[16] 2012	II	RCT	Total: 76 infants/152 eyes Anti-VEGF + laser: 34 infants/68 eyes Laser: 42 infants/84 eyes	Pegaptanib and laser 0.3 mg (0.02 ml)	Anti-VEGF + laser: GA, 24.9±1.3 wks BW, 773±158 g (33.7±1.6 wks) Laser: GA, 25.2±1.4 wks BW, 795±166 g (34.1±1.7 wks)	Stage 3+ ROP; zone I and posterior zone II	Anti-VEGF + laser: mean follow-up, 19.3 mos (5–37 mos) Laser: mean follow-up, 21.5 mos (4–38 mos)	Primary outcome was absence of recurrence of stage 3+: Anti-VEGF + laser, 85.4% (29/34 infants) Laser, 50% (21/42 infants) $P = 0.0197$ Secondary outcome was unfavorable structural outcome at final examination: Anti-VEGF + laser, 10.3% (7/68 eyes) Laser, 39.2% (33/84 eyes) $P = 0.0149$	Combination anti-VEGF + laser (group 1) compared with conventional laser therapy (group 2). Lower-quality RCT. Primary and secondary outcomes not masked. No formal sample size reported. Random assignment method not clear. Study reporting does not meet CONSORT* criteria.

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Moran et al,[17] 2014	II	RCT	14 infants/28 eyes; eyes were randomized to receive IVB in one eye and laser treatment in fellow eye (4 infants bilateral zone I/10 infants bilateral zone II)	Bevacizumab 1.25 mg (0.1 ml)	Mean PMA at treatment, 35 wks	Bilateral stage 3+ ROP in zone I (n = 4) or posterior zone II (n = 14)	2 yrs	Recurrence with retreatment: IVB, 21.4% (3/14 eyes) Laser, 7.1% (1/14 eyes) (*P* value not reported) Ocular and pediatric assessment at 2 yrs, including complete eye examination (with VEP and ERG testing) and pediatric examination (with brain MRI): no abnormalities attributable to effects of IVB	Lower-quality RCT with small sample size and no masking.
Geloneck et al,[18] 2014 (BEAT-ROP)	II	RCT	150 infants/300 eyes (BEAT-ROP): 131 infants/255 eyes eligible for analysis Cycloplegic refractions performed on 109 (83%) infants/211 (83%) eyes	Bevacizumab 0.625 mg (0.025 ml) (BEAT-ROP)	Zone I IVB: GA, 24.3±1.3 wks BW, 625±150 g (34.5±1.5 wks) Zone I laser: GA, 23.9±0.8 wks BW, 648±89 g (33.6±1.6 wks) Zone II IVB: GA, 24.4±1.2 wks BW, 699±116 g (35.5±1.8 wks) Zone II laser: GA, 24.5±1.5 wks BW, 681±150 g (35.8±2.1 wks)	Stage 3+ ROP or aggressive posterior ROP; zone I and posterior zone II (BEAT-ROP RCT)	Mean PMA, 2.5 (0.9) yrs	Cycloplegic refraction, mean (SD): Zone I: IVB, −1.51 (3.42) D (52 eyes) Laser, −8.44 (7.57) D (35 eyes) *P* < 0.001 Zone II: IVB, −0.58 (2.53) D (58 eyes) Laser, −5.83 (5.87) D (66 eyes) *P* < 0.001 Very high myopia (≥−8.0 D): Zone I: IVB, 3.8% (2/52 eyes) Laser, 51.4% (18/35 eyes) *P* < 0.001 Zone II: IVB, 1.7% (1/58 eyes) Laser, 36.4% (24/66 eyes) *P* < 0.001	Lower-quality RCT. Outcome assessment (cycloplegic refractive error by retinoscopy) not masked.

(*Continued*)

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Lepore et al,[19] 2014	II	RCT	13 infants/26 eyes with zone I ROP (3 infants stage 3+, 10 stage 3 no plus) Eyes were randomized to receive IVB in one eye and laser in the other eye 1 infant died; 1 eye progressed to complete retinal detachment before outcome measure (n = 23 study eyes)	Bevacizumab 0.5 mg (0.02 ml)	Infants with zone I stage 3 with plus disease: GA, 25 wks BW, 693 g Infants with zone I stage 3 without plus disease: GA, 25.7 wks BW, 705 g	Type 1 ROP; zone I, stage 3 with or without plus disease	9-mo follow-up Digital fundus photographs (every 3 days after treatment) and FA imaging (every 2 wks until discharge and at 9 mos)	Presence of retinal or choroidal abnormalities on digital fundus photographs or FA imaging All IVB-treated eyes demonstrated abnormalities in the retinal periphery (avascular areas, atypical branching, shunts) or posterior pole (hyperfluorescent lesion, absence of foveal avascular zone), whereas most laser-treated eyes did not	Lower-quality RCT. Small sample size, no masking.
Zhang, et al,[20] 2016 [Epub ahead of print]	II	RCT	50 infants/100 eyes Infants were randomized to receive IVR monotherapy or diode laser therapy	Ranibizumab 0.3 mg (0.03 ml)	IVR: GA, 29.0±1.6 wks BW, 1220±320 g Laser: GA, 28.3±1.8 wks BW, 1060±240 g	Type 1 ROP; zone II (stage 2 or 3 with plus disease)	6 mos	Regression of plus disease and ROP, recurrence of ROP, complications Significantly greater recurrence rate in IVR group (26 eyes of 13 infants [52%]) vs. laser group (2 eyes of 1 infant did not show initial regression and required retreatment [4%]); $P = 0.001$ No complications in either group	Lower-quality RCT. No sample size justification, no masking. Potential lack of generalizability; all zone II eyes and all patients were Han Chinese.
Lee et al,[21] 2010	III	Comparative case series	Total: 15 infants/30 eyes IVB + laser: 8 infants/16 eyes Laser: 7 infants/14 eyes	Bevacizumab 0.5 mg (0.02 ml)	IVB + laser: GA, 25.7 wks BW, 820.6±190.5 g (39 1/7 wks) Laser: GA, 26.9 wks BW, 933.1±355.9 g (36 3/7 wks)	Moderate to severe stage 3+ ROP	8-wk follow-up after treatment	Effects on development of peripheral retinal vessels: Time to resolution of plus disease (wks): IVB + laser, 1.0±0 (n = 8 infants) Laser, 2.3±0.8 (n = 7 infants) $P = 0.002$ Time to vascularization of peripheral retina (wks): IVB + laser, 2.0±0.5 (n = 8 infants) Laser, 2.9±0.7 (n = 7 infants) $P = 0.02$ No significant or systemic complications in either group	Combination therapy (IVB and laser) compared with laser alone. Comparative case series with small sample size and noncomparable treatment groups.

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Harder et al,[22] 2013	III	Comparative case series	Total: 25 infants/49 eyes IVB: 12 infants/23 eyes Historical laser cohort: 13 infants/26 eyes	Bevacizumab 0.375 mg (n = 9) or 0.625 mg (n = 3)	IVB: GA, 25.2±1.6 wks BW, 622±153 g Laser: GA, 25.3±1.8 wks BW, 717±197 g	Stage 3+ ROP in zone I or posterior zone II	1 yr (11.4±2.3 mos corrected age)	Cycloplegic refraction, mean (SD): IVB, −1.04±4.24 D (n = 23 eyes) Laser, −4.41±5.50 D (n = 26 eyes) *P* = 0.02	Comparative case series with small sample size. Treatment groups reasonably well matched; analysis adjusted for BW, GA, and gender. Seems laser group taken from period just before IVB use began. IVB = consecutive cases.
Hwang et al,[23] 2015	III	Comparative case series	Total: 28 infants/54 eyes IVB: 11 infants/22 eyes Laser: 17 infants/32 eyes	Bevacizumab 0.625 mg (0.025 ml)	IVB: GA, 24.2±1.0 wks BW, 668.1±127.3 g (35.1 wks) Laser: GA, 24.8±1.2 wks BW, 701.4±118.8 g (36.1 wks)	Type 1 ROP; zone I or posterior zone II	At least 6 mos IVB: 21.7 wks Laser: 34.5 wks	Rate of recurrence: IVB, 14% (3/22 eyes) Laser, 3% (1/32 eyes) Complications: Retinal detachment (1 laser eye); macular ectopia (5 laser eyes) Refraction at last follow-up/after GA: Overall: IVB, −2.4±3.5 D at 22.4 mos (n = 20 eyes) Laser, −5.3±5.4 D at 37.1 mos (n = 29 eyes) Zone I: IVB, −3.7±3.3 D (n = 14 eyes) Laser, −10.1±10.5 D (n = 4 eyes) *P* = 0.41	Comparative case series with small sample size.

(*Continued*)

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
								Zone II: IVB, 0.6±1.7 D (n = 6 eyes) Laser, −4.7±4.6 D (n = 25 eyes) *P* = 0.002	
Isaac et al,[24] 2015	III	Comparative case series	Total: 25 infants/45 eyes IVB: 13 infants/23 eyes Diode laser: 12 infants/22 eyes	Bevacizumab 0.625 mg (0.025 ml)	IVB: GA, 25.2±1.4 wks BW, 722±131 g (37.6±1.7 wks) Laser: GA, 25.0±1.1 wks BW, 674±175 g (36.7±2.6 wks)	Type 1 ROP; zone I or posterior zone II	At least 6 mos	Structural outcome at 1 yr corrected age: neither group developed unfavorable structural outcomes. VA (mean ± SD logMAR) at corrected age: IVB, 0.99±0.38 (n = 15 eyes) at 11.1 mos Laser, 0.71±0.36 (n = 18 eyes) at 12.1 mos *P* = 0.34 Refractive error (mean ± SD) at corrected age: IVB, −3.57±6.19 D (n = 23 eyes) at 10.8 mos Laser, −6.39±4.41 D (n = 22 eyes) at 11.3 mos *P* = 0.33 Number of follow-up visits 9 mos after treatment: IVB, 16±6 Laser, 6±3 *P* < 0.0001	Comparative case series with small sample size. Treatment groups were reasonably comparable on measured characteristics; no apparent severe confounding.
Gunay et al,[25] 2016	III	Comparative case series	134 infants/264 eyes IVB: 55 infants IVR: 22 infants Laser: 57 infants	Bevacizumab 0.625 mg (0.025 ml) or Ranibizumab 0.25 mg (0.025 ml)	IVB: GA, 27.3±2.2 wks BW, 1005±411 g (34.8±1.9 wks) IVR: GA, 28.0±2.9 wks BW, 1196±467 g (35.6±1.6 wks) Laser: GA, 28.2±2.5 wks	Type 1 ROP	IVB: 19.4±6.4 mos IVR: 19.0±4.8 mos Laser: 20.7±6.9 mos	Resolution after single treatment: 100% in all groups Recurrence of ROP: IVB, 5.5% IVR, 50% Laser, 1.8% Retreatment of ROP: IVB, 5.5% IVR, 13.6%	Comparative case series, noncomparable groups.

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Gunay et al,[25] cont.					BW, 1119±337 g (36.0±1.4 wks)			Laser, 0% Presence of high myopia (zone I, zone II): IVB, 23.8%, 5.9% IVR, 14.3%, 12.5% Laser, 71.4%, 6% $P = 0.019$, $P = 0.77$	
Gunay et al,[26] 2016 [Epub ahead of print]	III	Comparative case series in infants with BW >1500 g and high-risk characteristics	36 infants/71 eyes IVB: 15 infants Laser: 21 infants	Bevacizumab 0.625 mg (0.025 ml)	IVB: GA, 32.3 wks BW, 1908 g (36.9 wks) Laser: GA, 32.0 wks BW, 1816 g (38 wks)	Zone II stage 3+, or aggressive posterior disease	IVB: 18 mos (range, 11–33 mos) Laser: 20 mos (range, 8–47 mos)	Unfavorable structural outcome: no eyes in either group had unfavorable structural outcome	Comparative case series with small sample size.
Mueller et al,[27] 2016 [Epub ahead of print]	III	Comparative case series	54 infants/108 eyes IVB: 37 infants/74 eyes Laser: 17 infants/34 eyes	Bevacizumab 0.625 mg (0.025 ml)	Posterior zone I (n = 4 infants):† GA, 24.0 wks BW, 461 g (33.7 wks) Posterior zone II (n = 29 infants):† GA, 24.9 wks BW, 642.5 g (35.4 wks) Peripheral zone II (n = 21 infants):† GA, 25.4 wks BW, 575 g (40.1 wks)	Type 1 ROP; posterior zone I, posterior zone II, or peripheral zone II stage 3+	12–15 mos of age	Time to complete regression of active ROP (median days): Posterior ROP: IVB, 12 (IQR, 9–15) Laser, 57 (IQR, 28–63) $P = 0.002$ Peripheral ROP: IVB, 25 (IQR, 13.5–34.5) Laser, 24 (IQR, 12–45) $P > 0.05$ Recurrence of ROP: IVB, 12% of infants Laser, 0% of infants Visual acuity (cycle/degree) and refractive error (SE diopters). No statistically significant differences between IVB and laser for posterior or peripheral ROP	Comparative case series with small sample size.

BEAT-ROP = Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study; BW = birth weight; CONSORT = Consolidated Standards of Reporting Trials; D = diopter; ERG = electroretinography; FA = fluorescein angiography; GA = gestational age; IQR = interquartile range; IVB = intravitreal bevacizumab; IVR = intravitreal ranibizumab; logMAR = logarithm of the minimum angle of resolution; MRI = magnetic resonance imaging; PMA = postmenstrual age; RCT = randomized controlled trial; ROP = retinopathy of prematurity; SD = standard deviation; SE = spherical equivalent; VA = visual acuity; VEGF = vascular endothelial growth factor; VEP = visual evoked potential.

*Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.

†Median values.

or posterior zone II ROP, who were randomized to receive bevacizumab (1.25 mg in 0.1 ml) in 1 eye and diode laser therapy in the other eye. In addition to early retinal status after treatment, these infants had complete eye and pediatric medical and developmental examinations at 1 and 2 years of age. Pediatric examinations included assessment of systemic diagnoses and developmental status, and magnetic resonance imaging of the brain was obtained for all infants. When possible, visual evoked potentials and electroretinography were performed. Recurrence requiring retreatment occurred for 3 eyes in the bevacizumab group and for 1 eye in the laser group; all eyes had a favorable structural outcome. Retreatment occurred earlier for the eye that received laser (at 37 weeks) than for the eyes that received bevacizumab (at 50, 51, and 52 weeks). The authors concluded that the pediatric and ophthalmic assessments at 2 years of age showed no adverse ocular or systemic events that could be attributed to bevacizumab therapy. No details of functional outcome measures were reported. Limitations of this study include small sample size, lack of distinction between zone I and II disease, and recurrence that was not well defined. This trial was rated level II because of its small sample size and a lack of masked outcome determination.

In 2014, Geloneck et al[18] (United States) published the refractive outcomes for eyes of infants enrolled in the BEAT-ROP study. Of the 150 infants enrolled, 137 survived (there were 6 deaths in the bevacizumab group and 7 deaths in the laser photocoagulation group). Eyes undergoing intraocular surgery were excluded from analysis (19 eyes, 6 bilateral), leaving 255 eyes of 131 infants for analysis. Refractions determined by cycloplegic retinoscopy were available for 83% of the eyes, and infants were examined at a mean age of 2.5±0.9 years. For eyes treated for zone I disease, the mean spherical equivalent (SE) was −1.51±3.42 diopters (D) for the group of 52 eyes that received bevacizumab compared with −8.44±7.57 D for the group of 35 eyes that received laser treatment. For eyes with zone II disease, the mean SE was −0.58±2.53 D for the group of 58 eyes that received bevacizumab compared with −5.83±5.87 D for the group of 66 eyes that received laser treatment. Very high myopia (≥−8.0 D) was seen more frequently among eyes undergoing laser treatment (51.4% zone I, 36.4% zone II) compared with eyes receiving bevacizumab (3.8% zone I, 1.7% zone II). Because high myopia after laser therapy is attributed in part to alterations in anterior segment development, the authors concluded that less impact on ocular growth may be seen with bevacizumab therapy. This trial report was rated level II evidence because it lacked a masked outcome determination.

In a 2014 publication, Lepore et al[19] (Italy) reported on retinal structural outcomes based on digital fundus photography and fluorescein angiography of 13 infants with type 1 ROP in zone I who were randomized to receive 0.5 mg (0.02 ml) bevacizumab in one eye and laser photocoagulation therapy in the other eye, using digital fundus photographs and fluorescein angiography. All infants had stage 3 ROP in zone I at the time of treatment. Plus disease was present in 6 eyes of 3 infants, and all other eyes had stage 3 ROP without plus disease. Infants were followed up for 9 months after treatment, except for 1 infant who died at 3 months of age. Two eyes that received laser therapy progressed to retinal detachment (1 at stage 5, 1 at stage 4A). At 9 months, all eyes receiving bevacizumab had a favorable anatomic outcome, but showed 1 or more of the following abnormalities on fluorescein angiography: abnormal retinal vascular branching, peripheral retinal shunt vessels, a persistent avascular retina, the absence of a foveal avascular zone, posterior hyperfluorescent lesions, or a linear choroidal filling pattern. Some of the laser-treated eyes also demonstrated these abnormalities as well as the expected peripheral atrophic retinochoroidal lesions. This trial was rated level II because of its small sample size and a lack of masked outcome determination.

In 2016, Zhang et al[20] (China) reported outcomes of a prospective randomized trial for 50 infants who had bilateral type 1 ROP in zone II who were randomized to receive either intravitreal ranibizumab (0.3 mg in 0.03 ml) or diode laser photocoagulation. All infants had stage 2 or 3 ROP with plus disease. The main outcomes assessed were regression of ROP and plus disease, recurrence requiring treatment, and complications. All infants were followed up for 6 months. In the ranibizumab group, all eyes showed initial regression, but 26 eyes of 13 infants (52%) demonstrated a recurrence and underwent laser photocoagulation. The mean time to retreatment for this group was 12.6±7.9 weeks. At the last follow-up, eyes treated with ranibizumab still did not show complete vascularization to the ora serrata. In the laser group, both eyes of 1 patient did not show an initial response; the patient was considered to have experienced a recurrence (4%) and received ranibizumab injections 1 week after the laser treatment. There were no complications in either group. The difference in recurrence rates was statistically significant ($P = 0.001$), so the authors did not endorse ranibizumab therapy for type 1 ROP in zone II. They also mention that the outcomes may not be generalizable to other populations because all infants were of Han Chinese ethnicity. This study was rated level II because: (1) it lacked information on randomization administration, including whether it was concealed; (2) the outcome determination was unmasked; and (3) there was no sample size calculation to justify the choice of sample size.

Comparative Case Series

All comparative case series were rated as providing level III evidence.

In 2010, Lee et al[21] (Korea) reported on the effects of combination therapy on the development of peripheral retinal vessels using bevacizumab (0.5 mg in 0.02 ml) and diode laser photocoagulation versus diode laser photocoagulation alone. This was a retrospective comparative case series of infants with bilateral moderate to severe ROP. Eight patients (16 eyes) with ROP that was considered to have more vascular activity received combination therapy, whereas 7 patients (14 eyes) with less-active disease received diode laser photocoagulation only. Patients who received combination therapy showed more rapid resolution of plus disease, faster regression of fibrovascular tissue, and earlier vascularization into the peripheral retina. There are several limitations to this study in addition to its retrospective nature and small sample size: (1) the severity of ROP was clinically dissimilar between groups; (2) no specific information was provided about the ROP zone or presence of plus disease; (3) the amount of laser treatment was not specified; and (4) the measurement of the response was not standardized. There were also clinical differences between the groups in terms of GA, birth weight, and age at treatment (the combination group had a lower GA and birth weight and an older age at the time of treatment).

Nonetheless, this was an early comparative case series that showed results of laser photocoagulation in combination with an anti-VEGF agent for treatment of patients that were considered to have more severe ROP.

In 2013, Harder et al[22] (Germany) performed a retrospective, nonrandomized, comparative study of refractive outcomes for a consecutive series of infants who had received intravitreal bevacizumab compared with a historical cohort of infants who underwent argon laser photocoagulation therapy. There were 12 children in the study group and 13 in the historical control group. There was no statistically significant difference between the groups in mean GA (25.2±1.6 weeks vs. 25.3±1.8 weeks) or mean birth weight (622±153 g vs. 717±197 g). In the study group, 9 infants received 0.375 mg bevacizumab and 3 children received 0.625 mg bevacizumab; the dosage was determined by the practice preference of the treating ophthalmologist. All eyes in this study met type 1 ROP treatment criteria. In the study group, 3 infants had acute posterior type 1 ROP and both eyes of the remaining 9 infants, as well as all of the control group eyes, had classic threshold ROP as defined in the Cryotherapy for Retinopathy of Prematurity study. One infant in the study group received intravitreal bevacizumab in 1 eye and argon laser therapy in the other eye; however, the eye that received laser therapy required retreatment with bevacizumab, so that eye was not included in the refractive analysis. The anatomic results were favorable in all bevacizumab-treated eyes; 1 eye in the control group showed a stage 4B retinal detachment (and the eye excluded from refractive analysis showed a macular fold). At a mean age of 11.4±2.3 months after birth, less myopia was seen in the study group (−1.04±4.24 D) compared with the control group (−4.41±5.50 D). Additionally, a higher degree of astigmatism was associated with laser treatment. Limitations of this study, in addition to the small sample size and retrospective analysis, include the use of a historic cohort with clinically dissimilar birth weights and dissimilar severities of ROP, the use of different bevacizumab doses, and a lack of detail about the laser protocol.

In 2015, Hwang et al[23] (United States) performed a retrospective review of all eyes that underwent primary treatment of type 1 ROP with either bevacizumab (0.625 mg in 0.025 ml) or diode laser treatment and had at least 6 months of follow-up. There were 22 eyes (11 patients) in the bevacizumab group and 32 eyes (17 patients) in the laser group. The groups showed similar GA at birth, birth weight, and age at treatment, but a longer follow-up period was noted for the infants treated with laser (34.5 weeks for the laser group vs. 21.7 weeks for the bevacizumab group). The main outcomes were rate of recurrence requiring retreatment or retinal detachment, complications, and refraction at last follow-up. In the bevacizumab group, recurrence was seen in 14% of eyes compared with 3% of laser-treated eyes; all recurrences were in zone I eyes in both groups. No complications were seen in the bevacizumab group, but in the laser group, 1 eye experienced stage 5 retinal detachment and 5 eyes demonstrated macular ectopia. Refraction data were available for 93% of the cohort. More myopia was seen in the laser group compared with the bevacizumab group (mean SE, −5.3 D at 37.1 months vs. −2.4 D at 22.4 months, respectively). Eyes treated with laser for zone I disease also demonstrated more myopia (−10.1 D for the laser group vs. −3.7 D for the bevacizumab group) compared with zone II eyes (−4.7 D for the laser group and +0.6 D for the bevacizumab group). Although the mean spherical power and degree of myopia were significantly greater in zone II ROP eyes treated with laser compared with those treated with bevacizumab, there was no significant difference between the groups for zone I eyes. Limitations of this study include the small sample size, the retrospective nature of the study, the comparison of groups with dissimilar zones of ROP, and the dissimilar lengths of follow-up.

Isaac et al[24] (Canada) performed a retrospective review of infants undergoing treatment for type 1 ROP over a 4-year period that included patients with at least 6 months of follow-up. The primary outcome was retinal status at a corrected age of 1 year. Thirteen infants (23 eyes) received bevacizumab (0.625 mg in 0.025 ml) and 12 infants (22 eyes) received diode laser therapy. A favorable anatomic result was obtained in all eyes. No statistically significant difference was found in visual acuity measures, and although a higher prevalence of myopia in the laser-treated eyes was found, this did not reach statistical significance. There was a significant increase in the number of examinations required for infants who had bevacizumab injection compared with the infants who had diode laser therapy (mean, 16±6 visits vs. 6±3 visits, respectively). Although this small retrospective study has limitations, the demonstration of the significant difference in follow-up examinations that were needed, even with successful treatment, is noteworthy.

Gunay et al[25,26] (Turkey) published 2 comparative case series in 2016. The first study[25] included 264 eyes of 134 infants with type 1 ROP or aggressive posterior ROP at 2 large referral centers. It evaluated resolution and recurrence rates after anti-VEGF therapy using either bevacizumab (55 infants; dose, 0.625 mg), ranibizumab (22 infants; dose, 0.25 mg), or diode laser photocoagulation (57 infants). Patients were followed up for up to 1.5 years adjusted age for refractive and biometry measurements. Eyes that received supplemental anti-VEGF therapy for failed laser treatment were excluded. All eyes in this study showed an initial response to treatment, but recurrence of ROP was seen in 3 of 55 infants in the bevacizumab group (5.5%), 11 of 22 infants in the ranibizumab group (50%), and 1 of 57 infants in the laser group (1.8%). Whereas all of the infants with recurrence in the bevacizumab group required bilateral retreatment, only 3 of the 11 with recurrence in the ranibizumab group required bilateral retreatment, so there was no significant difference in retreatment rates between the groups receiving anti-VEGF therapy. The mean time to recurrence was 14 weeks for bevacizumab-treated eyes and 9 weeks for ranibizumab-treated eyes. No complications were noted for any of the groups, but 1 eye of a patient treated with laser photocoagulation demonstrated a stage 4A retinal detachment that did not progress to require treatment. At the last follow-up, the prevalence of emmetropia was significantly higher in the groups that received anti-VEGF therapy compared with the laser-treated group (50.9% of the bevacizumab group, 45.5% of the ranibizumab group, and 16.3% of the laser group). The presence of zone I ROP at treatment was associated significantly with the presence of myopia and high myopia across the treatment groups.

The second study by Gunay et al[26] reviewed outcomes for 36 infants with a birth weight of more than 1500 g who required ROP treatment. Treatment was performed for type 1 ROP in 30 infants and for aggressive posterior ROP in 6 infants. Diode laser photocoagulation was performed in 21 infants (58.3%), all of whom had anterior zone II ROP, and intravitreal bevacizumab treatment was given to 15 infants (41.7%), all of whom had either aggressive posterior ROP in zone I or type 1 ROP in

posterior zone II. Infants were followed up for a minimum of 8 months, and the mean follow-up was 19.9 months for the laser photocoagulation group and 17.9 months for the bevacizumab group. All eyes in both groups showed a good response to therapy, with no complications or recurrences reported, although treatment choice was influenced by the posterior location of ROP. Limitations of this study include the small sample size and the retrospective nature of the analysis, as well as the inclusion of clinically dissimilar treatment groups. However, the authors' focus was to show that in some countries, severe ROP can still develop in heavier preterm infants, sometimes as a result of underlying systemic conditions or variability in early neonatal care, which national ROP screening guidelines should take into consideration. The authors concluded that both anti-VEGF agents were useful for halting ROP; that recurrence of ROP after ranibizumab treatment was more common, but also more likely to regress spontaneously; and that both anti-VEGF agents allowed for more normal refractive development compared with eyes receiving laser therapy.

In 2016, Mueller et al[27] (Germany) reported on retinal, visual, and refractive outcomes for a cohort of German infants who underwent treatment for type 1 ROP. In this retrospective study, 54 patients were identified who underwent ROP treatment with either intravitreal bevacizumab (37 infants; dose, 0.625 mg) or diode laser photocoagulation (17 infants). There was some preference for eyes with posterior disease to be given anti-VEGF therapy; thus, 28 of 33 infants (56/66 eyes) with zone I or posterior zone II ROP received intravitreal bevacizumab and 5 of 33 infants (10/66 eyes) with zone I or posterior zone II ROP received laser photocoagulation. Of the 21 infants with more peripheral zone II ROP, intravitreal bevacizumab was given in 9 (18 eyes) and laser treatment was performed for 12 (24 eyes). Patients were followed up to 12 to 15 months of age, and retinal anatomic status, grating visual acuity, and refractions were obtained. The time to complete regression of ROP was significantly less for eyes with posterior ROP that received bevacizumab (median, 9 days) compared with laser-treated eyes (median, 57 days), although there was no difference for peripheral zone II eyes. Recurrence of ROP was noted in 7 infants (12%) at a median of 12.7 weeks after bevacizumab treatment, and 5 required retreatment (with laser). No recurrences were seen in laser-treated eyes. Ocular complications included exudative retinal detachment in both eyes of 1 patient who underwent laser photocoagulation for posterior zone II disease, macular dragging in 1 eye of another infant after laser treatment for posterior zone II ROP, and culture-negative keratitis with permanent corneal opacity in 1 eye of an infant who received bilateral bevacizumab injections. One child in the bevacizumab group died 3 weeks after ROP treatment as a result of cardiorespiratory failure with severe bronchopulmonary dysplasia. The ROP treatment method had no significant impact on grating visual acuity scores or refractive error. There was a lower SE (more myopia) in eyes treated for posterior disease compared with eyes treated for peripheral zone II disease. The main limitation of this study is the clinical dissimilarity of ROP between the groups, with anti-VEGF therapy preferred for posterior disease.

There have been a few large noncomparative case series using anti-VEGF monotherapy,[29–31] but these studies did not meet the criteria for full review for this Ophthalmic Technology Assessment.

Conclusions

Anti-VEGF agents for ROP are an emerging treatment option that is becoming used more frequently,[32,33] and review of the recent literature suggests that the short-term efficacy and ocular safety are similar to those of laser photocoagulation therapy. The advantages of using anti-VEGF agents include less time to administer treatment (resulting in possibly less stress for the infant), faster improvement in plus disease and regression of ROP, less treatment-related destruction of the peripheral retina, and a lower likelihood of myopia, high myopia, and astigmatism. The disadvantages of anti-VEGF therapy include a longer required follow-up as a result of delayed or incomplete vascularization, significant rates of recurrence and the potential need for later retreatment, and the possibility of developmentally abnormal or atypical retinal vascular patterns. The long follow-up period required after anti-VEGF therapy also creates a burden on families and the medical system to ensure that late recurrences or complications do not arise.

With respect to the severity of ROP, there seem to be several potential advantages for primary treatment with anti-VEGF agents for eyes with zone I ROP or eyes with aggressive posterior ROP. However, there is no clear advantage over laser photocoagulation for eyes with more peripheral zone II ROP, and there is no clear advantage for first-line combination therapy. The rapid response and involution of ROP that can be obtained with anti-VEGF treatment compared with laser treatment can be of particular advantage for aggressive posterior ROP. Although treatment of zone I eyes with anti-VEGF treatment can allow some retinal vascular development over time, most zone I eyes treated with anti-VEGF will never completely vascularize and may still need retreatment after 55 weeks' PMA (the standard end point for several studies considered in this review).

The rate of ROP recurrence is not insignificant with anti-VEGF therapy, but it is somewhat variable among study populations. The BEAT-ROP study showed a lower recurrence rate for zone I eyes that received bevacizumab compared with laser therapy, but one criticism of this study was the unusually high retreatment rate for the eyes that had undergone laser therapy. Most other studies have shown that, when there is a difference, there is a higher recurrence rate with anti-VEGF therapy compared with laser therapy, though not all recurrences require retreatment. Recurrence after bevacizumab monotherapy was characterized by Mintz-Hittner et al[34] in a series of 241 infants who received treatment for zone I or posterior zone II ROP and who were followed up at least to 65 weeks' PMA. In this series, 8.3% of infants required retreatment for recurrence of ROP, with greater risk noted for babies with aggressive posterior ROP, lower birth weight, and extended duration of hospitalization (a surrogate for systemic illness). Recurrences occurred both from the fibrovascular complex present at the initial treatment and at the advancing edge, and were noted at up to 70 weeks' PMA. In a comparative case series reviewed for this report, Gunay et al[25] found a higher rate of ROP recurrence in eyes treated with ranibizumab compared

with bevacizumab, but there was no difference in retreatment rates. Chen et al[31] performed a comparative case series of 72 eyes (37 patients) treated with intravitreal bevacizumab (0.625 mg) or ranibizumab (0.25 mg) for type 1 ROP, and followed up the infants to 1 year of age. Recurrence was not defined except for the need to retreat, and only 1 eye in the bevacizumab group did not respond initially and underwent laser treatment. However, 2 other small comparative case series using intravitreal bevacizumab (0.625 mg) or ranibizumab (0.25 mg) reported high rates of ROP recurrence requiring retreatment in eyes treated with ranibizumab compared with those treated with bevacizumab (83% vs. 0%[35] and 40% vs. 9.5%[36]). It is clear from all of these studies that there is a significant risk of ROP recurrence after anti-VEGF therapy for ROP. There is also the risk of delayed and incomplete retinal vascularization (particularly for zone I eyes), which significantly prolongs the period needed to follow up and manage acute ROP after anti-VEGF treatment, compared with the follow-up time needed to manage acute ROP after laser photocoagulation therapy.

No level I studies have yet addressed the longer-term ocular, visual, systemic, or neurodevelopmental effects of anti-VEGF treatment. Bevacizumab used for ROP treatment can be detected in the serum within 1 day of intravitreal injection, and there is a corresponding decline in serum VEGF levels.[37] Intravitreal bevacizumab results in low VEGF serum levels for at least 8 weeks[38] and up to 12 weeks after the treatment.[39] Intravitreal ranibizumab also can lower serum levels of VEGF by 1 day after treatment, but this effect is short lived and serum VEGF levels recover to baseline within 1 week of treatment.[39,40] The potential effects of lowering systemic VEGF levels on other developing organ systems in a premature infant are unknown. Determining whether anti-VEGF therapy has a clinically evident effect would be difficult, because the presence of treatment-warranted ROP is known to be associated with comorbidities and poor neurodevelopmental outcomes in the first place. Hence, a very large patient population would be needed for such a study to be powered correctly to sort out confounding variables.

Nevertheless, systemic safety remains a concern, and neurodevelopmental outcomes at 2 years of age for children who received intravitreal anti-VEGF treatment have been measured by a few groups using the validated and standardized Bayley Scales of Infant Development (BSID) test. Araz-Ersan et al[41] evaluated series of 13 infants treated with combination intravitreal bevacizumab (0.625 mg) and laser therapy for ROP, compared with a birthweight- and gestational age-matched control group of children who had received laser treatment for ROP. They found no difference in the mean cognitive, language, or motor scores on the BSID III test. In another study, Lien et al[42] studied BSID scores at 24 months of age in 61 infants who had received either bevacizumab (0.625 mg) monotherapy, laser monotherapy, or a combination of bevacizumab and laser therapy (required for salvage therapy). The patients who required combination (salvage) therapy had a higher incidence of mental or psychomotor impairment, but there was no difference between the groups that had either modality as monotherapy. The authors concluded that because of the retrospective nature and lack of randomization for this study, the cause for this difference could not be determined. However, they speculate that poorer outcomes could be related to exposure to more surgical procedures and anesthesia, earlier age at treatment, and more cases of zone I disease in the combination therapy group. Morin et al[43] evaluated neurodevelopmental data from infants in the Canadian Neonatal Network and Canadian Neonatal Follow-Up Network. The neurologic examination and the BSID III test results of 125 infants treated for ROP (27 with bevacizumab) were compared. The group of infants who had received bevacizumab showed a statistically lower median motor composite score, and the odds of having a severe neurodevelopmental disability (BSID score <70, severe cerebral palsy, hearing aids, or bilateral blindness) was 3.1 times higher with bevacizumab versus laser treatment. However, this comparison was adjusted for many infant variables but not ROP severity, and there was a significantly greater proportion of patients with zone I disease in the bevacizumab group. Additionally, aside from having zone I disease, treatment choice could have been biased toward using bevacizumab in those infants with a worse overall medical condition, which has been shown to be associated with greater neurodevelopmental impairment. Finally, in the BEAT-ROP trial,[15] there was concern that 5 of 7 early deaths (mostly resulting from respiratory failure) occurred in children treated with bevacizumab, although by the time of the 2-year follow-up publication,[18] this difference in mortality was no longer seen (there were 6 deaths in the bevacizumab group and 7 deaths in the laser group).

Future Research

Evidence is lacking on the long-term safety of anti-VEGF agents, the best anti-VEGF agent to use for ROP treatment, the optimal dose for each agent, and the potential long-term systemic effects. For this Ophthalmic Technology Assessment, we found significant variability in or lack of standardized classifications of treatment, use of different agents and dosing, variable follow-up periods, lack of standardized and masked assessment of treatment outcomes, and significant variation in efficacy of treatment among populations. Other areas to consider for further study and when considering implementation of anti-VEGF treatment in clinical practice are the potential effects of ethnic or genetic background in different populations, differences in early exposures and neonatal care, and effects of regional bias toward treatment preference and need for close follow-up after treatment, particularly in areas with limited resources. The 13 articles reviewed for this assessment were from 9 different countries (United States, Czech Republic, Ireland, Italy, China, Korea, Germany, Canada, and Turkey), which demonstrates that there is likely significant diversity in the above-mentioned variables. This should be considered when applying study results to regional clinical practice.

Further evidence for efficacy, safety, and dosing of anti-VEGF agents is forthcoming. Most studies to date have used bevacizumab, perhaps because of wider availability and

lower cost, with various doses. The Pediatric Eye Disease Investigator Group, in collaboration with the National Eye Institute, currently is conducting a prospective phase 1 multicenter trial aimed at determining the lowest effective bevacizumab dose for treatment of type 1 ROP.[44] This study also will collect serum levels of VEGF and bevacizumab after intravitreal injection, which may aid in understanding the effects of dosing on systemic bevacizumab and VEGF circulation in the short term in premature infants. Ranibizumab is of interest because it has a vitreous half-life that approaches that of bevacizumab, but after reaching systemic circulation, the elimination half-life is a few hours rather than weeks and results in a negligible effect on serum VEGF levels. Although this could be a distinct advantage for the treatment of ROP, the efficacy of ranibizumab for ROP treatment with respect to recurrences or long-term ocular outcomes is not available. A prospective multicenter trial of ranibizumab for ROP is underway in Germany (Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity [CARE-ROP]; clinicaltrials.gov identifier, NCT02134457) and in the United States (RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity [RAINBOW]; clinicaltrials.gov identifier, NCT02375971).

Finally, questions remain about late systemic and neurodevelopmental effects.[45] Challenges will include following up a large cohort for long-term data collection to sort out the impact of this treatment within a population that is already at high risk of experiencing later neurodevelopmental abnormalities. Until these questions have been addressed more fully, clinicians should exercise caution and offer anti-VEGF therapy only for type 1 ROP treatment in patients with zone I or posterior zone II disease after carefully weighing the benefits and risks and discussing treatment options with parents.

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Abbreviations and Acronyms:
BSID = Bayley Scales of Infant Development; **CARE-ROP** = Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity; **D** = diopter; **ETROP** = Early Treatment for Retinopathy of Prematurity; **GA** = gestational age; **PMA** = postmenstrual age; **RAINBOW** = RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity; **ROP** = retinopathy of prematurity; **SE** = spherical equivalent; **VEGF** = vascular endothelial growth factor.

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VITAMIN A

I. DESCRIPTION

Vitamin A is a fat-soluble vitamin involved in the regulation and promotion of growth and differentiation of many cells, and maintains the integrity of the epithelial cells of the respiratory tract.[1] Vitamin A is also required for innate and adaptive immunity.[2] Retinol, the primary form of circulating Vitamin D, and retinol-binding protein, the transport protein for retinol, are lower in premature infants than in term infants.[3]

II. USE

To reduce the risk of chronic lung disease in low-birth-weight neonates

A. Criteria for Use[4]
   1. Birth weight less than 1 kg
   2. Mechanical ventilation or supplemental oxygen at 24 hours of age and within 24-96 hours of birth

III. PHARMACOKINETICS[5]

A. Distribution: Large amounts concentrate for storage in the liver

B. Metabolism: Converted in the small intestine to retinol; further metabolized in the liver

C. Elimination: In feces via biliary elimination

IV. DOSING AND ADMINISTRATION[4]

Vitamin A 5000 international units IM three times a week for 12 doses

V. ADVERSE REACTIONS[1]

A. Elevated intracranial pressure

B. Vomiting

C. Bone and joint pain

D. Mucocutaneous lesions

E. Hepatic dysfunction

VI. MONITORING[4]

A. When to draw levels: Only if concern for toxicity

B. Goal levels: 20-80 mcg/dl[6]

C. Timing of levels: Prior to next dose

References

1. Darlow BA, Graham PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD000501. DOI: 10.1002/14651858.CD000501.

2. Stephensen CB. Vitamin A, infection, and immune function. *Annu Rev Nutr.* 2001;21:167-192.

3. Shenai JP, Chytil F, Jhaveri A, Stahlman MT. Plasma vitamin A and retinol-binding protein in premature and term neonates. *J Pediatr*. 1981;99(2):302-305.

4. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. *N Engl J Med.* 1999;340:1962-1968.

5. Pediatric & Neonatal Lexi-Drug OnlineTM, Hudson, Ohio: Lexi-Comp, Inc.; January 29, 2011.

6. Pearson E, Bose C, Snidow T, et al. Trial of vitamin A supplementation in very low birth weight infants at risk for bronchopulmonary dysplasia. *J Pediatr.* 1992;12:420-427.

Revised: June, 2016
Katherine Pham, Pharm.D.

TRAINEE ROLES & RESPONSIBILITIES

I. RESIDENT RESPONSIBILITIES

Second and third year residents will bear the primary responsibility of covering a panel of patients, to include the following:

- Admitting new patients
- Obtaining consent for treatment and procedures
- Pre-rounding and patient presentation on rounds - All infants should have a brief physical exam each morning. Do not be afraid to handle the infants and do not rely on notes or other people for the exam.
- Placing of orders
- Performing various procedures, including endotracheal intubation, blood draws, lumbar puncture, etc.
- Supervising medical students – medical students will be assigned a patient with a resident until their abilities can be evaluated.
- Communicating with families (on rounds, night call, via telephone) and participating in family meetings when possible

II. NEONATOLOGY FELLOW

Our fellows will be more than happy to answer questions, help with procedures and teach. They can be reached anytime on the fellow Ascom phones at x8743 and x8655. They are not expected to be direct patient care givers in place of residents or NNP's/PAs. At times of emergencies both attendings and fellows will help.

III. NIGHT CALL

Every night there is a fellow on with the resident and NNP/PA. The NNP/PA will cover their patients and report to the fellow any concerns. The resident will take primary call for the resident teams' patients, and then discuss medical management with the fellow.

IV. PROCEDURES

Any procedure on any infant should be tried a maximum of 2 times before calling for a more experienced person. These include drawing blood, starting IV's, lumbar punctures, suprapubic taps, or arterial sticks. Depending on the type of procedure being performed, pain control is an important element, and should be managed via non-pharmacologic measures (swaddling, oral sucrose) or with analgesics if needed.

All procedure attempts, whether or not successful, should be documented, citing details such as body location, "time out", indication, number of attempts and complications. Whenever possible parents should be notified and updated regarding anticipated procedure prior to

procedure attempt. All parents should be notified and updated after all procedures, and a communication note added in the medical record.

A. Endotracheal intubation.
Infants with respiratory failure requiring intubation should be performed with the use of fentanyl for analgesia, and atropine to prevent reflex bradycardia. Attempts made by a resident should be supervised by a LIP (fellow/NNP/PA). A procedure and parent communication note must be documented in the medical record.

B. Chest tube insertion/needle thoracentesis.
Neonatology or Surgery Fellow/Attending must supervise any chest tube placement or needle thoracentesis. There must be a note or an x-ray that documents that there is a pneumothorax, or pleural effusion. Confirmation of proper side placement must be documented with a "time-out", i.e. the nurse must confirm with the doctor that the chest tube should be placed, and is being placed in the left/right side. This "time-out" should be documented in the procedure note for the medical record.

C. Pericardiocentesis.
A pericardial effusion should be confirmed by echocardiogram or ultrasound (US). Ideally, pericardiocentesis should be performed under echocardiogram or US guidance by either cardiology fellow/attending, or NICU fellow/attending/NNP/PA.

D. Percutaneously inserted central catheters (PICC).
There is a designated PICC Line team consisting of the Fellows, NNPs/PAs, transport RNs, and specific staff RNs who have undergone specialized competency training. All procedures related to PICC lines (placement, adjustment, removal) must be performed by a PICC team member. A procedure and parent communication note must be documented in the medical record.

E. Peripheral arterial line placement (PAL).
The need for continuous hemodynamic monitoring and frequent blood draws are indications for arterial line placement. Determination of the need for an arterial line must be made by the attending physician. Common sites for peripheral arterial line placement include the radial, ulnar, posterior tibial and dorsalis pedis arteries. Cannulation of the ulnar artery should be performed with caution and with permission from the attending physician. Documentation of adequate collateral flow should be made by performing an Allen's test. Central arterial sites including the axillary, brachial and femoral arteries should be avoided in the neonate due to risk of ischemic compromise and lack of adequate collateral supply. A procedure and parent communication note must be documented in the medical record.

F. Umbilical line placement.
Central venous and arterial access in the neonate may be obtained via umbilical vein (UV) or umbilical artery (UA) placement in the first few days of life. This may be performed by the

resident with fellow or NNP/PA supervision. Correct placement should be confirmed with an x-ray and documented in the medical record.

G. Bedside surgical procedures.
On occasion, infants will have bedside surgical procedures performed (ECMO cannulation, exploratory laparotomy, ROP laser surgery, PDA ligation). In such cases, anesthesia is managed by the NICU fellow and/or attending through the use of analgesics and paralytic agents (fentanyl 5-10ug/kg x 2-3 doses, vecuronium 0.1mg/kg x 1-2 doses). Appropriate respiratory and blood pressure management must be provided. A NICU fellow and/or attending must be present for the entire duration of the procedure, and documented as a procedure note in the medical record.

Revised: June, 2016
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Mariam Said, M.D.

Standard Precautions and Postnatal Care for Newborns Exposed to a Sexually Transmitted Infection (STI*)

*STIs include, but are not limited to, Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Syphilis, and Hepatitis B

Standard Precautions include the use of personal protective equipment (gown, gloves, +/- face mask and eye shield if risk of splashing into eyes/mouth) and should be used on all patients when there is potential exposure to secretions or bodily fluids.

For newborns with perinatal STI exposure:

Bathe within 3-4 hours of life:

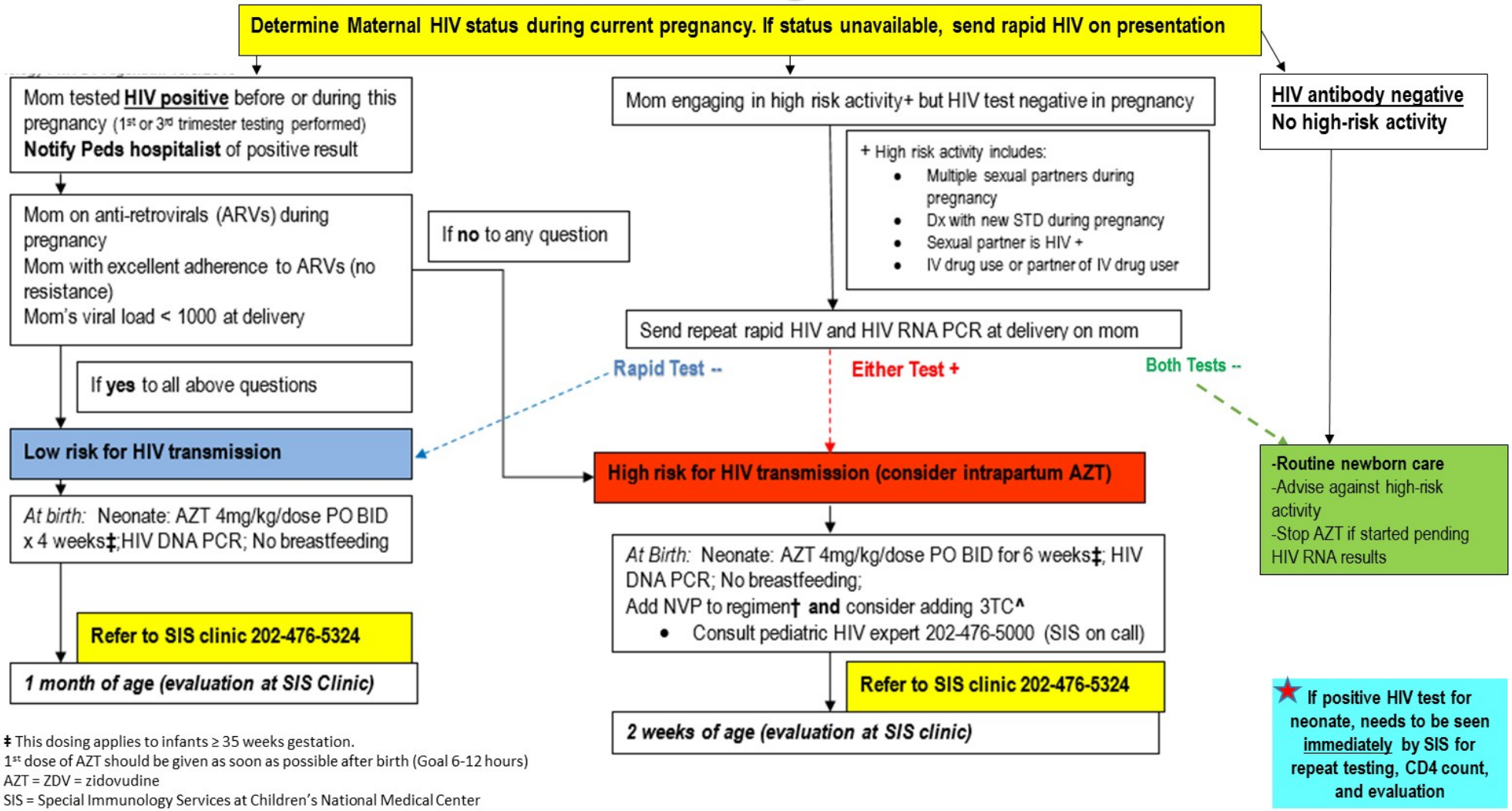
- If medically stable including normal vital signs
- ***Prior to administration of injections***. If unable to bathe prior to injections, **notify the Pediatric hospitalist** and clean the site x 3 with Chloraprep (gestational age >30 weeks) or betadine
- Using standard precautions

Administer routine medications:

- Erythromycin eye ointment (within 1 hour of birth)
- Hepatitis B vaccine (see algorithm)
- Vitamin K (within 6 hours of birth)

References:
1. U.S. Preventative Services Task Force Recommendations, July 2011
2. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5416a1.htm
3. http://www.cdc.gov/ncbddd/vitamink/facts.html

HIV Perinatal Management Protocol



‡ This dosing applies to infants ≥ 35 weeks gestation.
1st dose of AZT should be given as soon as possible after birth (Goal 6-12 hours)
AZT = ZDV = zidovudine
SIS = Special Immunology Services at Children's National Medical Center

Recommended Neonatal Zidovudine (ZDV/AZT) Dosing for Prevention of Perinatal Transmission of HIV			
Initiate as soon as possible after delivery for all HIV-exposed infants, preferably within 6-12 hour			
Gestational Age At Birth	PO Dosing	IV dosing (if unable to take PO)	Duration
≥35 weeks	4 mg/kg/dose PO BID	3 mg/kg/dose q 12 hours	Birth through 4-6 weeks*
≥ 30 to < 35 weeks	2 mg/kg/dose PO BID Advance to 3 mg/kg/dose at age 15 days	1.5 mg/kg/dose q 12 hours Advance to 2.3 mg/kg/dose at age 15 days	Birth through 6 weeks
<30 weeks	2 mg/kg/dose PO BID Advance to 3 mg/kg/dose after age 4 weeks	1.5 mg/kg/dose q 12 hours Advance to 2.3 mg/kg/dose after age 4 weeks	Birth through 6 weeks

*A 6-week course is recommended, though a 4-week course may be considered if the mother has received ART during pregnancy with viral suppression < 1000 copies, and no concerns for maternal adherence

† NVP (nevirapine) dosing:

- Band dosing:
  - BW 1.5 – 2kg: 8mg/dose PO ***(not per kg)***
  - BW > 2kg: 12mg/dose PO ***(not per kg)***
- 3 doses: 1st dose within 48 hours of birth,
  2nd dose 48 hours after 1st dose
  3rd dose 96 hours after 2nd dose

^ 3TC (lamivudine) dosing – for full term infants: 2mg/kg/dose PO BID x 2 weeks

Special Immunology Services (SIS) consult: call hospital operator 202-476-5000, ask for Special Immunology Physician on call

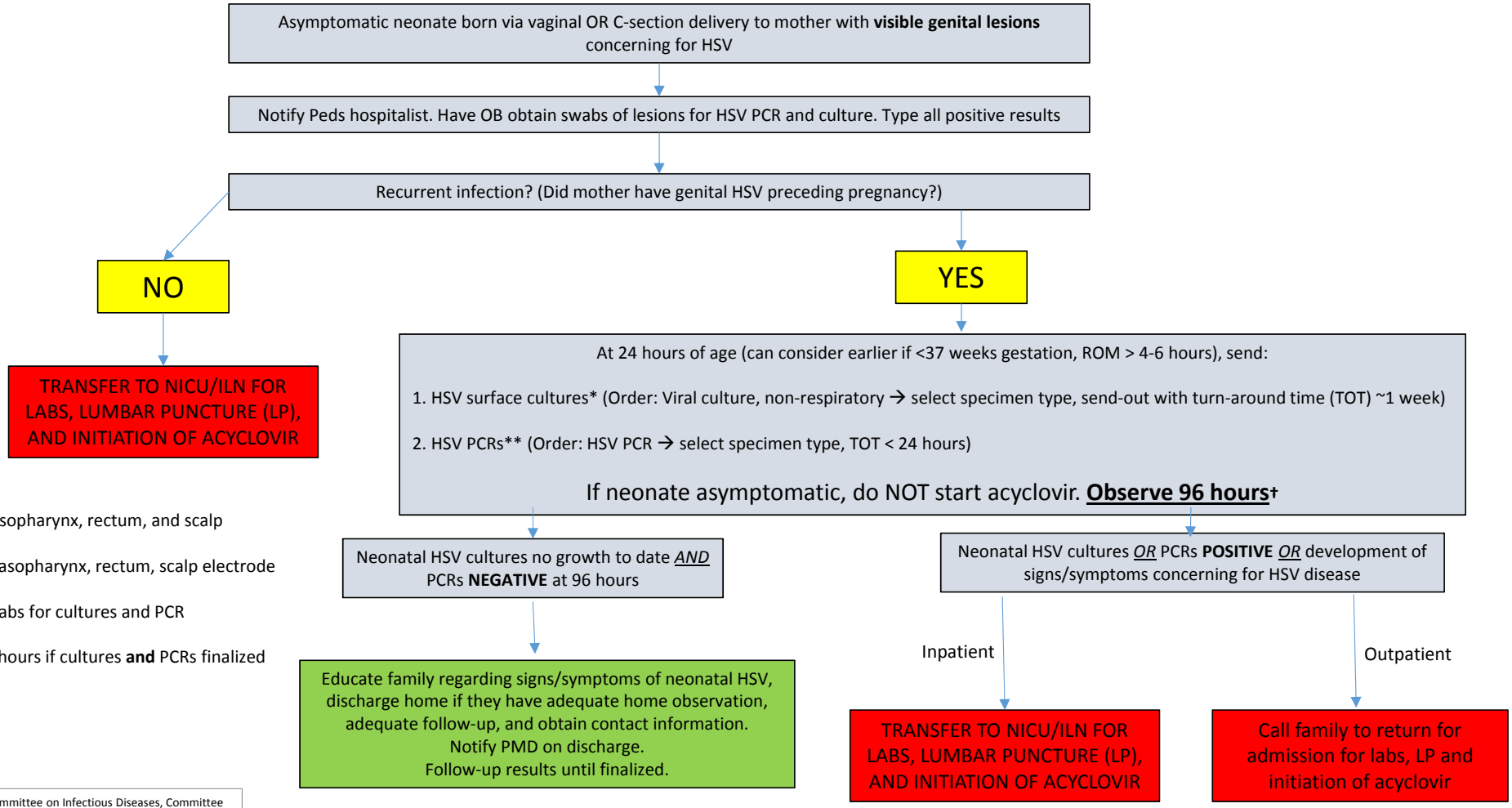
SIS clinic coordinator: 202-476-5324 or 202-476-4705 (confidential voicemail)
National Perinatal HIV Hotline: 1-888-448-8765

MWH/Stafford Hospital:

1. RN should review documentation regarding maternal HIV status and notify the pediatric hospitalist if mother is HIV+ or results not available. If records not available, send rapid HIV testing on mother.
2. Pediatric Hospitalist should discuss with OB provider regarding mode of delivery and need for intrapartum antiretroviral therapy/prophylaxis for HIV+ mothers. Also recommend to OB to send rapid HIV and HIV RNA PCR testing upon delivery on high-risk mothers who previously tested negative on antibody screening.
3. Pediatric Hospitalist should notify pharmacy regarding any medication needs (for Stafford, AZT may need to be delivered from MWH pharmacy)
4. All providers should use Standard Precautions when handling the newborn
5. Testing should be sent for HIV-1 DNA PCR on baby:
   a. If known/suspected maternal HIV-2 infection, send HIV-1 and HIV-2 DNA PCR
   b. The correct order is NOT in Soarian. Call the lab regarding send-out and paperwork that needs to be completed. Order as miscellaneous/send out
   c. Test information: HIV-1 DNA, Qualitative PCR [8401X]; Test Code: 3525; 0.5-1 mL blood in lavender (EDTA) top from Quest Diagnostics (not available at Mayo) www.questdiagnostics.com/testcenter/BUOrderInfo.action?tc=3525&labCode=AMD
   *If unavailable, discuss with Special Immunology re: sending HIV-1 RNA as alternative (HAART can interfere with RNA results)

References:
1. https://aidsinfo.nih.gov/
2. Connor, Edward M., et al. "Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment." New England Journal of Medicine 331.18 (1994): 1173-1180.
Adapted from Children's National Medical Center Special Immunology

Herpes Simplex Virus (HSV) Perinatal Management Protocol

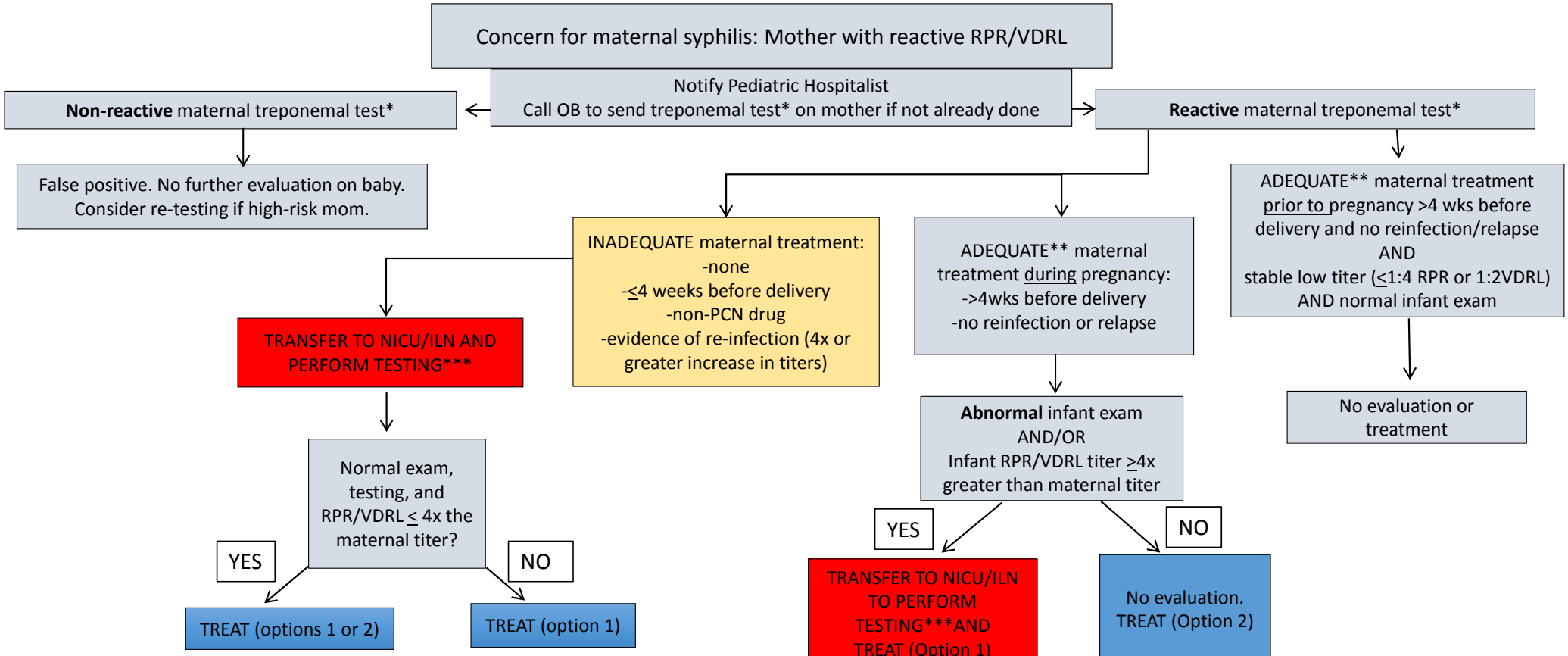


*conjunctiva, mouth, nasopharynx, rectum, and scalp electrode (if present)
conjunctiva, mouth, nasopharynx, rectum, scalp electrode (if present) **and blood
Will require separate swabs for cultures and PCR

†Can discharge after 48 hours if cultures **and** PCRs finalized and negative

Reference: Kimberlin DW, Baley J, Committee on Infectious Diseases, Committee on Fetus and Newborn. *Guidance on management of asymptomatic neonates born to women with active genital herpes lesions.* Pediatrics 2013, 131: e365-646.

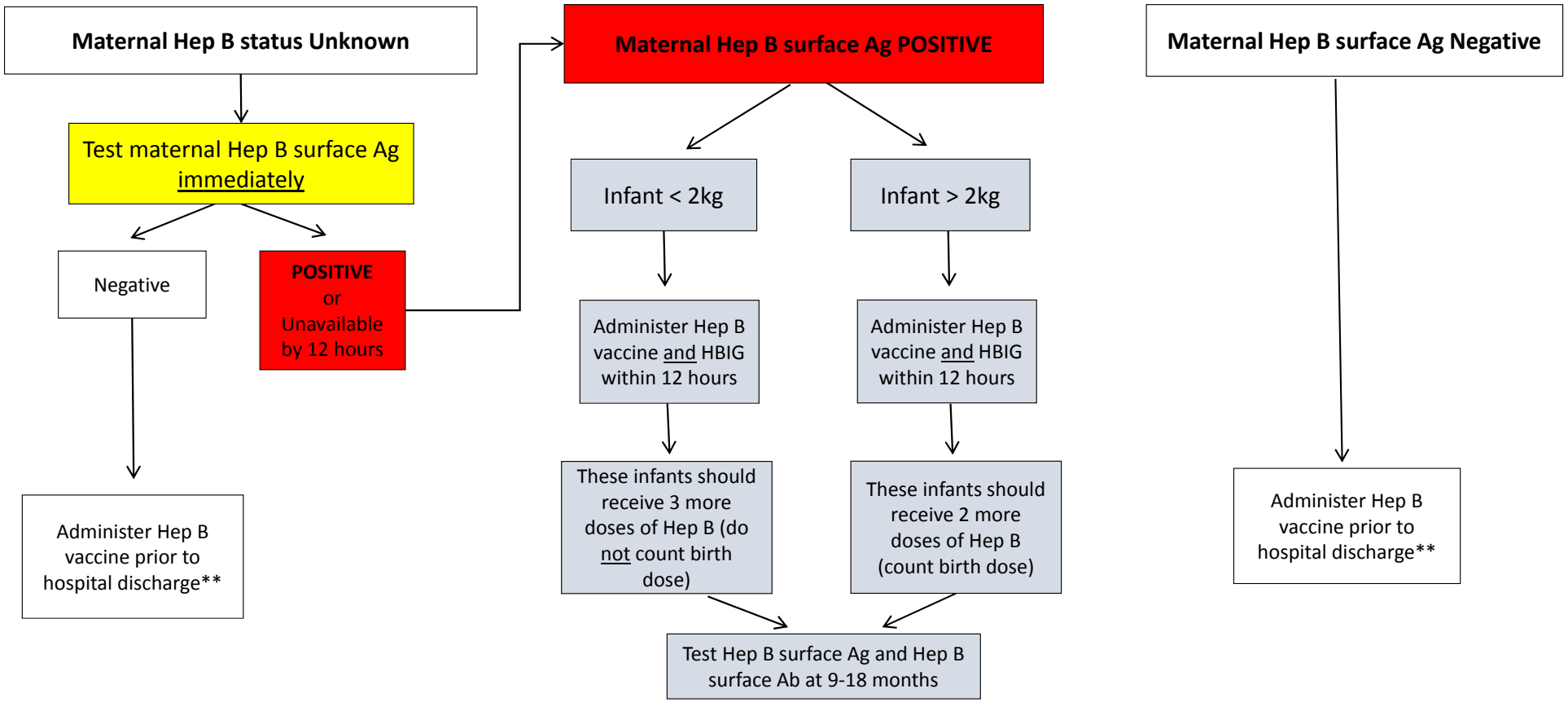
Syphilis Perinatal Management Protocol



***Treponemal test: FTA-ABS, TP-EIA, TP-PA, or MHA-TP**
****Adequate treatment= PCN G benzathine 2.4million U IM x1 (for primary or early latent syphilis); PCN G benzathine 2.4million U IM Q1week x3 weeks (for late latent syphilis) AND titers decrease, remain the same, or rise a max of 2-fold (ex: 1:8 to 1:16).**
*****Testing in NICU/ILN: CBC and CSF evaluation (cell count, protein, quantitative VDRL). Consider CXR, long-bone XR, eye exam, LFTs, neuroimaging, and ABR hearing testing.**
Treatment:
Option 1= Aqueous Penicillin G 50,000 Units/kg IV x 10 days (Q12hrs if ≤7 days; Q8hrs if >7 days old) OR IM Procaine Penicillin G 50,000 Units/kg x10 days.
Option 2= Benzathine Penicillin G 50,000 Units/kg IM x1
-NOTE: 4x a titer equals 2 dilutions. 1:16 is 4x greater than 1:4

Reference: American Academy of Pediatrics [Syphilis]. In: Kimberlin, DW, Brady, MT, Jackson, MA, Long, SS, eds. *Redbook: 2015 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL.

Hepatitis B Perinatal Management Protocol



Hep B vaccine= 0.5mL. HBIG= 0.5mL– to be administered IM at a different site than Hep B vaccine.

***Some experts recommend not administering HBIG to infants >2kg with mothers of unknown Hep B status unless mothers test positive for HepBsAg (Hepatitis B surface antigen).**

****Hep B vaccine may be delayed until after hospital discharge in rare circumstances only for infants >2kg whose mother is HepBsAg negative. Document mother's testing in infant's chart if Hep B vaccine is deferred.**

NOTE: It is OKAY for mothers with Hepatitis B to breastfeed, as it adds no additional risk of transmission when Hep B vaccine and HBIG are given.

Reference: American Academy of Pediatrics [Hepatitis B]. In: Kimberlin, DW, Brady, MT, Jackson, MA, Long, SS, eds. *Redbook: 2015 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL.

SKIN TO SKIN CARE

I. GENERAL INFORMATION

Since the Kangaroo Mother Care (KMC) method was established in Colombia in 1978, parent-infant skin-to-skin contact (SSC) has been introduced all over the world, based on evidence of positive effects it has on infants and their families, both in low income and in affluent societies; empowering parents to be active in their role as caregivers of NICU infants.

The American Academy of Pediatrics recommends "Birth Kangaroo Care"; where the newborn is placed in skin-to-skin contact with the mother within one minute after birth and up to the first feeding, if the baby doesn't require life support. In 2003, the World Health Organization published practical guidelines for application of skin-to-skin in all types of hospitals and health care facilities. In 2010 the International Network of Kangaroo Mother Care recommended universal application of KMC/SSC in a high tech environment.

The tight bundling skin-to-skin provides is enough to stimulate the baby in different ways. Vestibular stimulation from the parent's breathing and chest movement, auditory stimulation from the parent's voice and natural sounds of breathing and the heartbeat, touch by the skin of the parent, the wrap, and the natural tendency to hold the baby.

Different modalities of SSC have been adopted around the world (1), according to the needs of various settings. This diversity includes exclusive and non-exclusive breastfeeding, breast or gavage feedings, completely or partially naked, continuous (≥ 20 hours per day) or intermittent (for short periods once or a few times per day and for a variable number of days) SSC with variable duration of exposure, and early-or-not hospital discharge

Intermittent skin-to-skin can be done in the NICU. It is usually used for varying, shorter periods of time, which can be offered to less stable and technology-supported infants; and can be performed by both parents. Intermittent skin-to-skin is widely offered to parents for benefits such as enhancing attachment, parental self-esteem, breastfeeding, and involving both parents in the care of their at-risk infant, thus transforming the parents' care of their babies from preoccupation to occupation. Lastly, skin-to-skin offers a practical and cost-effective method of humanizing the NICU experience.

II. BENEFITS OF SKIN-TO-SKIN IN THE NICU

Admission to the NICU for prematurity and/or neonatal sickness often results in separation of mother and baby. This can interrupt the process of attachment and can increase maternal stress levels. Mothers who have had the opportunity to provide skin-to-skin for their infants describe feelings of being needed, increased confidence in familiarizing with their infants, and a sense of fulfilling their role as a mother (2, 3). Skin-to-skin for LBW infants have shown to reduce mortality, severe illness, infection and length of hospital stay(4-6). Cardiorespiratory and temperature stability, sleep organization and duration of quiet sleep, neurodevelopmental outcomes, breastfeeding and modulation of pain responses appear to be improved for infants who have received skin-to-skin (5). Significant improvement in breast milk production and longer breastfeeding duration are related with skin-to-skin contact (1, 7, 8). Increased parent satisfaction has also been reported in association with skin-to-skin and mothers show enhanced attachment behaviors and describe an increased sense of their role as a mother during and after skin-to-skin (9).

A variety of physiological parameters have been assessed to ascertain the safety of skin-to-skin for sick preterm infants. A meta-analysis in 2016(7) of 124 studies comparing SSC to conventional care, found that SSC was associated with 36% lower mortality (RR 0.64; 95% CI 0.46-0.89), decreased risk of neonatal sepsis (RR 0.53, 95% CI 0.34-0.83), hypothermia (RR 0.22; 95% CI 0.12-0.41), hypoglycemia (RR 0.12; 95% CI 0.05-0.32), and hospital readmission (RR 0.42; 95% CI 0.23-0.76) and increased exclusive breastfeeding (RR 1.50; 95% CI 1.26-1.78). Newborns receiving SSC had lower mean respiratory rate and pain measures, and higher oxygen saturation, temperature, and head circumference growth.

Skin-to-skin was found not to be related with an increase in the frequency or duration of apneic episodes or increases in oxygen consumption. Most studies have been conducted with stable, non-ventilated preterm infants, but stability during skin-to-skin is also reported for those receiving assisted ventilation (7). Some centers routinely and successfully provide skin-to-skin care for infants with chest tubes and on ventilators, including high-frequency oscillatory ventilation (6).

III. BENEFITS FOR THE INFANT

A. Mortality

Overall, in a meta-analysis published in January 2016 in Pediatrics, skin-to-skin was associated with a 23% lower risk of mortality at each study's latest follow-up time, compared with conventional care (7) . Among 11 studies reporting mortality, during the first 45 days of life, there was 21% decrease in mortality with SSC (95% CI, 0.57-1.10; I2 = 77%), whereas the 7 studies reporting mortality at 3, 6, or 12 months of age showed 41% lower mortality in the SSC groups compared with controls (95% CI 0.43-0.82; I2 = 0%).

B. Sleep and neurobehavioral maturation

Studies on the impact of skin-to-skin for preterm infants' behavior and sleep pattern have reported uniform results in infants with various degrees of prematurity(10). When in the kangaroo position, the infant quickly calms down and often falls asleep. The infant sleeps more, it is sleep is peaceful, breathing is regular, and active sleep and arousal decrease (3, 7). Peaceful sleep episodes also occur when the infant is held by the father.

Some studies found increased frontal brain activity during both quiet and active sleep, which is thought to be predictive of improved neurobehavioral outcomes (5, 11). Other studies using electroencephalography and polysomnography data indicate more mature sleep organization, with increased total and quiet sleep, decreased REM sleep and arousals from sleep, and an improvement in sleep cycling. They also appeared more alert and observant when awake and spent less time crying. Crying and irritability while the infant is in skin-to-skin contact are rare. Overall, infants in the kangaroo position are calmer and cry less (12). The following mechanisms would explain this particular effect of the kangaroo position:

1. Maternal heart sounds may induce sleep in the infant. SCC position lets the baby listen continuously to those sounds transmitted through the mother's chest wall. The infant is also exposed to soft, rhythmical swinging resulting from the mother's regular movements while breathing.
2. Fewer arousal episodes occur while preterm babies sleep in the prone position.

3. Nesting preterm babies in a peaceful environment seems to decrease the number of arousal episodes. The support for the kangaroo position enable keeping the infant comfortably positioned (nested) between their mother's breasts.

Infants receiving skin-to-skin, demonstrated better autonomic regulation and maternal–infant interactions at term gestation (11) as well as higher scores on the Bayley Scales of Infant Development–Second Edition at 6 or 12 months of age. In one study 117 infants were followed up to 10 years of age, and the authors reported that those who received skin-to-skin showed attenuated stress response, improved autonomic functioning, better-organized sleep, and better cognitive control (5, 13).

C. Temperature
Compared with conventional care, SSC was associated with 78% lower risk of hypothermia (n= 9; 95% CI, 0.12 to 0.41; I2 = 71%) and 23% lower risk of hyperthermia (n = 3; 95% CI, 0.59 to 1.01; I2 = 0%).(7)

D. Non-pharmacologic management of procedural pain
Newborn infants can perceive pain. Preterm and/or sick newborns can have many painful and stressful procedures. The long term negative effect of these painful stimuli has been properly documented (14). Pharmacological analgesia particularly opiates, while necessary and clearly beneficial, are associated with many risks, especially during prolonged use. Given these concerns, it is important to optimize effective non-pharmacological measures for controlling pain, particularly before reiterative painful stimuli.

There is evidence which shows that keeping the baby in the kangaroo position during a painful procedure reduces physiological alterations, decreases autonomic indicators of pain, and shows no evidence of harmful effects (14, 15). Cortisol concentrations are also found to be reduced in preterm infants during SSC offers gentle stimulation across the auditory, tactile, vestibular and thermal sensory systems, which may modulate the perception of pain. SSC is one of the non-pharmacological measures recommended by the Canadian Pediatric Society and the American Academy of Pediatrics for reducing pain associated with bedside procedures in the NICU (6).

E. Nosocomial infections
Decreases in nosocomial infections secondary to SSC is most significant in developing rather than developed countries. Early SSC likely increases the chance of the infant being colonized with maternal flora rather than the flora in the nursery, which may include antibiotic-resistant organisms and MRSA. Because SSC is only undertaken between individual infant-mother dyads, it should not increase the spread of infection from one infant to another during infectious outbreaks (5). In stabilized LBW infants, SSC was associated with a statistically significant reduction in severe infection/sepsis at latest follow up (7).

F. Breast milk use
The benefits of breast milk for the preterm infant are well-known and include decreased incidence of infections and necrotizing enterocolitis, feeding tolerance, improved growth and neurodevelopmental outcome. SSC increased the likelihood of exclusive breastfeeding at hospital discharge or 40 to 41weeks postmenstrual age by 50% (3). SSC is associated with a longer duration of breastfeeding, higher volumes of milk expressed, higher exclusive breastfeeding rates, and higher percentage of breastfeeding

at the time of NICU discharge. Mothers of SSC infants were more likely to be breastfeeding at discharge, or 40 - 41 weeks', corrected gestational age, and at 1 – 3 months follow up than mothers in the control group (5, 7).

G. Autonomic maturation and vital signs
Compared with conventional care, SSC was associated with a non–statistically significant reduction in risk of apnea among 6 studies of LBW infants <2000 g (RR 0.39; 95%CI, 0.13 to 1.14; I2 = 42%). On average, newborns receiving SSC had a respiratory rate 3 breaths per minute slower (n = 12; 95% CI, −5.15 to −1.19; I2 = 75%) and oxygen saturation 0.9% higher than controls (n = 14; 95% CI, 0.35 to 1.45; I2 =92%) (7).

H. Hypoglycemia
SSC was found to be strongly protective against hypoglycemia in LBW Infants (RR 0.12; 95% CI, 0.05 to 0.32; I2 = 0%) (7).

I. Infant growth
There is no direct evidence that the SSC per se, continuously or intermittently, leads to better somatic growth results in preterm and/or low birth weight babies, when compared to properly fed and managed babies in a neutral thermal environment, and with a comparable health status. There is clear evidence that it has no negative effect on weight gain. When babies in the kangaroo position are compared to babies cared in suboptimal environments that do not ensure a neutral thermal environment, the kangaroo position has been associated with better short and medium term growth, and somatic development (12).

Since it provides a neutral thermal environment, the kangaroo position enables an adequate use of calories ingested for growth. If the physical location where the baby is kept provides an appropriate, neutral thermal environment (adequate fully functional incubators), usually no significant difference is observed in the rhythm and quality of somatic growth experienced by babies in the kangaroo position (12).

At least two studies have documented that babies in skin-to-skin have a higher cranial growth as compared to babies exposed to control maneuvers (12).

J. End stage care
Some neonatal units suggest that parents of critically ill babies, especially when they are to be weaned from artificial support, may carry their babies until they die. This contact may be reassuring to families and may help in the bereavement process. The fact that the parent holding the baby is actively involved in terminal care and may feel he/she is contributing something positive to their child and may be particularly valued. Many individuals also advocate that it is an intimate, appropriate way to say goodbye to their children. Nevertheless, no specific evidence supporting these statements was found.

IV. BENEFITS FOR MOTHERS

A. Improves parent–infant interaction/attachment.

B. Increases psychological well-being and improves psychological adaptation and recovery after preterm delivery or unexpected sick full term.

C. Promotes recovery from postpartum depression.

D. Salivary cortisol decreases in mothers who practice SSC.

E. Mother's feeling of being needed by or comfortable with her infant.

F. Promotion of participation of the mother and father in the infant's care, strengthens the family role in the care of a fragile infant, and decreases feelings of helplessness.

G. Mothers report less stress and more satisfaction with NICU care, and both parents are more responsive to their infant's cues.

V. BENEFITS FOR FATHERS

A. The new baby is familiar with the father's voice and it is believed that contact with the father helps the infant to stabilize and promotes father to infant bonding.

B. Helps fathers of preterm infants gain confidence in the paternal role.

C. Facilitates role attainment, allowing fathers to feel in control and are contributing to their babies. As active agents in their infant's care, some fathers stayed with the infant during the whole hospital stay, others were at the neonatal intensive care unit all day long. Despite the un-wished-for situation, they adapted to their predicament and spent as much time as possible with their infants (16).

VI. PROCEDURE

A. General considerations
The care of preterm and sick newborn infants requires a location which allows control of the infant's temperature, observation and monitoring of the infant, and the infant's availability to parents and staff. Good temperature balance minimizes infant energy loss, which has effects on preterm infants' survival and growth. The stable infant's primary care location is the kangaroo position on mother, father, or a substitute designated by the family, without any unjustified restrictions, continuously or during most of the 24 hours per day. Assessment of infant stability is based on occurrence and severity of desaturation and bradycardia, and overall medical condition, and during the first week of life (especially in extremely preterm infants), on weight loss and elevated serum sodium levels (17).

B. Parent Information
All parents should be informed about benefits of SSC for infants and parents, about practical application, and when SSC can commence. Continued information and follow-up of given information should be offered on an on-going basis. It is an advantage that both parents are present when information is given, so they can give each other mutual support in their participation and develop cooperation in the infant's care. The core component in this information is provision of the infant's care in the kangaroo position, how they can gradually take over their infant's care, and their access to assistance and support by nurses. Parents should also receive information on how to read/interpreter cardiovascular monitor before holding the baby (17).

C. Infant position
The infant should be dressed with only a diaper and always kept upright, placed prone

with their body and cheek against the caregiver's chest ("frog" position). The head should be turned to the side. Although the caregiver may keep the baby positioned with his/her arms, it is impossible to remain as such indefinitely. The baby should be maintained in the position using a device that can keep them in contact with the chest with little or no support from the caregiver's arms, and that is flexible enough to permit adequate movements, both respiratory or other (5).

D. Timing
For infants born at 26 weeks and below, SSC can often commence during the first week of life, but the appropriateness of a SSC session must be assessed each time by the attending neonatologist or LIP based on the infant's current medical condition. The SSC session should continue for at least 2 hours, unless the infant's condition deteriorates. Special caution should be taken to prevent hazards, such as accidental extubation (which also may occur during repositioning in the incubator) (8).

E. Patient selection
1. Ideal candidates
    a. Term and preterm neonates hemodynamically stable with at least one parent or caregiver willing to participate
2. Contraindications
    a. Unstable or very sick newborns with wide blood pressure swings and/or significant bradycardia, apnea or oxygen desaturation with handling that is associated with prolonged recovery.
    b. Mechanical ventilation for acute disease.
    c. Treatment with vasopressor drugs.
    d. Presence of umbilical artery catheter, thoracic or abdominal drainage.
    e. Abdominal wall and neural tube defects that are to be kept sterile prior to surgery.
    f. Newly postoperative infants in whom stability is not yet determined.
3. Caregiver contraindications
    a. Contagious rash
    b. Hyperthermia
    c. Hypothermia
    d. Skin wounds on the chest
    e. Non-controlled epilepsy
    f. Poorly controlled mental illness
    g. Evidence of ongoing illicit drug use
4. Relative contraindications
    a. Neonates with birthweight < 750 grams or < 26 weeks gestation in the first week of life, unless after careful medical assessment
    b. Neonates with significant jaundice near exchange transfusion levels requiring continuous, intensive phototherapy
    c. Neonates in their first week after major surgery

F. Steps
1. Caregivers should freely manifest their willingness to implement the kangaroo position once they have been adequately informed, and their doubts and concerns have been carefully attended to. It is necessary to confirm such willingness after the caregiver has experienced the kangaroo position.
2. If the infant's mother had a caesarean birth, the father can hold their baby in skin-to-skin contact while the mother recovers and can visit the NICU.

3. Provide a comfortable chair and a mirror (to observer baby while on skin-to-skin).
4. The temperature probe should be secured to monitor infant's temperature
5. Endotracheal suction if necessary and allow recovery time prior to transfer to the caregiver.
6. If the baby is intubated or with central lines, the nurse transferring the baby should ask for extra help supporting lines and endotracheal tube.
    a. A nurse should be available to provide direct supervision and assists with any equipment attached i.e. respiratory tubing, IV fluids lines, SpO2 and/ ECG leads.
    b. Nurse secures the respiratory tubing. Despite physiologic stability during skin-to-skin care, it is important that the infants have continuous cardiovascular monitoring. Evaluate correct head positioning for airway patency as well as the stability of the endotracheal tube, arterial and venous access devices, and other life support equipment.
    c. The tubing and lines should be secure with tape on furniture or caregiver's clothing.
    d. In case infant instability persists after controlling or adjusting kangaroo position and oral/nasal or endotracheal suctioning, SSC should be interrupted.
7. Parents must be informed that a preterm baby needs some time to adapt when transferred from an incubator to kangaroo care as well as when returning to the incubator.
8. Most nursing procedures can be performed during SSC, including oral/nasal or endotracheal suctioning, feeding tube insertion, parenteral nutrition administration, and IV injection.
9. There is no maximum time limit for the session, provided the mother enjoys the experience and the baby remains stable. Ideally, allow an infant to remain out for at least one hour to allow for recovery time (from the transfer process) and allow for one full sleep cycle.
10. Mobile phones and earphones are not advisable in order to avoid distraction from the SSC experience.
11. When SSC cannot be implemented, parents must be informed about how to minimize the negative effects of prolonged separation from their baby. Gentle containing touch, proprioceptive sense stimulation, face-to-face visual contact, talking, reading, singing soothing lullabies, and olfaction stimuli are good options.
12. Parents must be coached to recognize signs of stress in their baby in order to avoid sensitive and sensorial hyper-stimulation (15-16).

G. Transfer back to incubator or crib

SSC session usually ends when the parent requests for it to end. Nevertheless, sometimes the session could be suddenly interrupted if the parent is no longer available or becomes sick or if the infant becomes unstable in spite of effective intervention provided by the nurse to restore baby stability.

When SSC ends, same cautions must be observed for the transfer of the baby from the kangaroo position to the incubator or crib.

1. Modes of transfer:
   Hold the infant with still hands in a flexor position (flexed arms and legs), paying attention to head.
   A sheet or a cape can be used during both transfer and SSC session
2. Pay close attention to maximal prevention of infant hypothermia and destabilization.

3. When the infant has respiratory support, the nurse disconnects airway tubing during transfer and reconnects it as soon as infant is in position. The tubing and lines should be secure with tape.

VII. SUMMARY

In conclusion SSC is protective against a wide variety of adverse neonatal outcomes and has not shown evidence of harm. This safe, low-cost intervention has the potential to prevent many complications associated with preterm birth and may also provide benefits to full-term newborns (5).

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NEONATAL SEPSIS

I. GENERAL INFORMATION

Sepsis in the neonate is typically categorized into either early-onset (within the first 72 hours of life) or late-onset (> 72 hours of life) in the hospitalized newborn. This definition has evolved from past characterizations of early-onset sepsis (EOS) occurring within the first 7 days of life[1]. The overall incidence of neonatal EOS in the United States is estimated at 0.98 per 1000 live births, and increases to a rate of 10.96 per 1000 live births among VLBW infants (<1500 grams). Mortality rates are approximately 3% for full term infants, and as high as 30-54% for extremely preterm infants[2].

The newborn infant, in particular the premature infant, is more susceptible to bacterial infection than is the older child. This relates to differences in humoral and cellular immunity, and in the effectiveness of the phagocytic, chemotactic and opsonization systems.

Premature infants are born with poorly functional immune system; as a result they are at increased risk of infections. Infection rates are high in premature infants treated in intensive care units, with the highest rates of around 30% occurring in extremely premature infants. Bacterial and fungal sepsis is a major cause of morbidity and mortality in neonates. Mortality from sepsis declined steadily until the early 1980s, but since then it has remained constant at near 15%. This plateau of mortality most likely reflects the poor host defenses of premature infants. Neutrophil leukocytes are important defenses against bacterial infection, and in neonates both neutrophil production and function are immature. Neutropenia occurs in up to 35% of preterm neonates and in 50% of all infants born to mothers with pregnancy induced hypertension. The development of sepsis together with neutropenia carries a high mortality of 39%, and two out of three septic infants with neutropenia die.

Because of these shortcomings in the ability to resist bacterial infection, the newborn can be quickly overwhelmed by a variety of organisms. Therefore, aggressive early treatment is indicated in suspected bacterial infection. The approach usually involves empiric treatment while awaiting confirmation of diagnosis.

II. ETIOLOGY

A. Common Perinatal/Neonatal Infections:
   1. Group B Streptococcus (most common)
   2. Gram negatives — Escheria coli (K_1 antigen most virulent) & Klebsiella pneumoniae
   3. Ureaplasma urealyticum
   4. Listeria monocytogenes
   5. Occasionally other groups of Streptococcus (S. viridians & S. pneumoniae)
   6. Pseudomonas aeruginosa, Staphylococcus aureus
   7. Viral — cytomegalovirus (CMV), herpes, enterovirus
   8. Anaerobic organisms (rare)

B. Nosocomial/Chronic Infections
   1. Staphylococcus epidermidis
   2. Candida albicans, Candida parapsillosis, Malassezia furfur
   3. Staphylococcus aureus
   4. Enterococcus
   5. Pseudomonas aeruginosa

6. Cytomegalovirus
7. Anaerobic organisms should be considered if necrotizing enterocolitis is an associated diagnosis

NOTE: NICU outbreaks have been reported with virtually every organism. Strong suspicion and knowledge of current hospital organisms and their sensitivities will help guide therapy.

III. CLINICAL SIGNS OF SEPSIS

A. Physical Exam:
   1. Temperature instability - hyper- or hypothermia
   2. Respiratory distress - apnea, cyanosis, hypoxia
   3. Hemodynamic instability - shock, poor perfusion
   4. Lethargy, irritability
   5. Feeding intolerance (poor feeding, emesis, abdominal distension)
   6. Diarrhea

B. Laboratory Findings
   1. Metabolic disturbances - hypo- or hyperglycemia, acidosis
   2. Hyperbilirubinemia (particularly direct fraction)
   3. Leukopenia or leukocytosis (with increased immature WBC)
   4. Thrombocytopenia

NOTE: Symptoms of meningitis are almost indistinguishable from those of sepsis. Common symptoms of CNS involvement may include: full fontanelle, irritability, lethargy and seizures.

IV. NEONATAL GROUP B STREPTOCOCCUS (*S. agalactiae*)

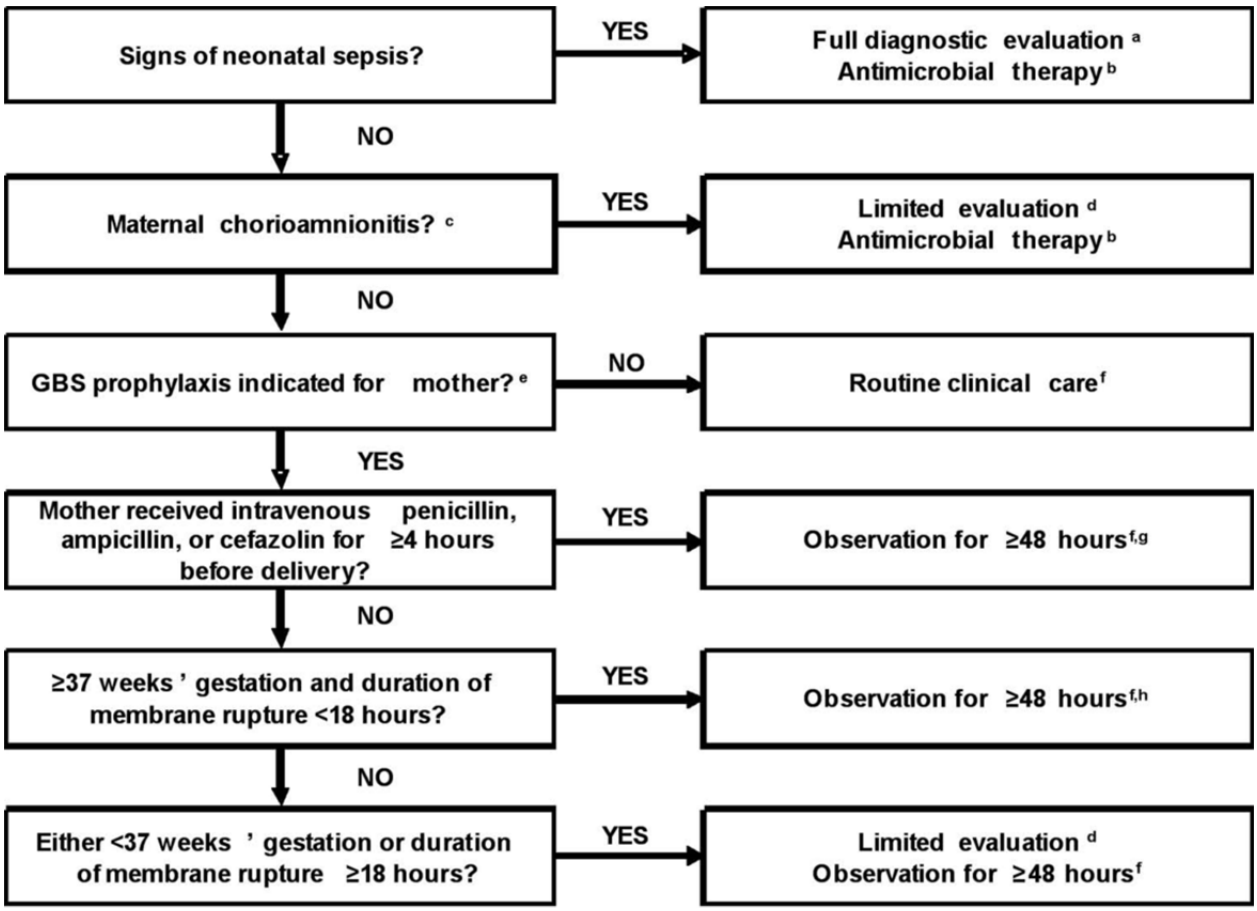
Characteristic	**Early**	**Late**
Time of onset	0-6 days Usually first 24 HOL	7-89 days Usually 3-4 weeks of age
Transmission	Vertical from mother to fetus	Community, nurseries?
Presentation	Severe, fulminant systemic infection (respiratory distress, apnea, shock pneumonia) Meningitis 5-10% of cases**	Occult bacteremia Meningitis ~30% of cases**
Mortality	Preterm: 20% Term: 2-3%	Preterm: 5-6% Term: 1-2%
Serotypes	Variable Type III predominant in early-onset meningitis	Type III predominant in late-onset disease

**50% survivors of early- or late-onset meningitis have long-term neurologic sequealae, including encephalomalacia, cortical blindness, cerebral palsy, visual impairment, hearing deficits, learning disabilities

A. Other manifestations of Group B Strep disease
   a. Pneumonia

b. Osteomyelitis
c. Septic arthritis
d. Necrotizing fasciitis
e. Adenitis
f. Cellulitis

B. Management of Neonates for Prevention of Early-Onset Group B Streptococcal (GBS) Disease (extracted from Red Book® 2015)



[a]Full diagnostic evaluation includes complete blood cell (CBC) count with differential, platelets, blood culture, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient stable enough to tolerate procedure and sepsis is suspected).

[b]Antimicrobial therapy should be directed toward the most common causes of neonatal sepsis, including GBS and other organisms (including gram-negative pathogens), and should take into account local antimicrobial resistance patterns.

[c]Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically, and some of the signs are nonspecific.

[d]Limited evaluation includes blood culture (at birth) and CBC count with differential and platelets (at birth and/or at 6–12 hours of life).

[e]GBS prophylaxis indicated if one or more of the following: (1) mother GBS positive at 35 to 37 weeks' gestation; (2) GBS status unknown with one or more intrapartum risk factors, including <37 weeks' gestation, rupture of membranes ≥18 hours or temperature ≥100.4°F (38.0°C), or intrapartum nucleic acid amplification test results positive for GBS; (3) GBS bacteriuria during current pregnancy; (4) history of a previous infant with GBS disease.

[f]If signs of sepsis develop, a full diagnostic evaluation should be performed and antimicrobial therapy should be initiated.

[g]If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, if there is a knowledgeable observer and ready access to medical care.

[h]Some experts recommend a CBC with differential and platelets at 6 to 12 hours of age.

V. UREAPLASMA UREALYTICUM

A. Introduction:
Over the years, the *Ureaplasma* have been implicated in infertility, spontaneous abortions, stillbirths and premature births. Infection in the newborn is closely associated with chorioamnionitis. Unfortunately it is hard to culture and obstetricians do not perform routine cultures.

B. Clinical presentation:
There is evidence that *Ureaplasma* can be responsible for CNS infection and pneumonias in infants and may be associated with the rapid development of chronic lung disease in infants in intensive care. PPHN due to *Ureaplasma* has been described in large infants. The rate of positive placental cultures has been as high as 40% in infants < 1000 gm. and up to 16% in those > 2500 gm.

C. Evaluation:
Ideally small infants (<1200 gm) should have a tracheal aspirate taken on admission, so that when the question comes up as to whether we should treat or not, a culture might have returned.

D. Management:
Treatment consists of Erythromycin for a 7-10 day period.

VI. POLICY AND PROCEDURES

A high level of suspicion for bacterial infection should be maintained in the intensive care nursery at all times. Infants with suggestive signs or symptoms must be carefully examined, appropriate laboratory studies done, and if bacterial infection cannot be confidently excluded, a sepsis work-up should be done and IV antibiotic therapy begun.

A. Evaluation:
1. Blood Cultures from central line, peripheral venous and/or arterial puncture
2. Urine culture – suprapubic tap or catheter specimen; do not send bagged urine for culture.
3. C-reactive protein (CRP) levels – may be useful trending tool, though a normal value does not exclude infection
4. Lumbar puncture for cerebro-spinal fluid analysis and culture
5. Culture of any skin lesion
6. Tracheal aspirate for culture with gram stain if change in secretions is suggestive of infection
7. Tracheal culture for ureaplasma if suspected
8. Chest X-ray / Abdominal X-ray
9. Viral Cultures as necessary, particularly during known out-breaks (RSV, rotavirus)

B. Laboratory Tests
    1. Total white blood cell and band count (Band/total count > 0.2 usually significant)
    2. Leukocyte Counts (< 5000/cu mm very significant)
    3. Platelet Counts (< 100,000 significant)
    4. Other: Directigen for GBS (Blood and CSF)

C. Therapy — General Concepts

Therapy must be directed at the most likely organisms. In general, it has been suggested that Ampicillin and Gentamicin be started as drugs of choice in newborns where the organism is unknown. If a nosocomial infection is suspected, therapy should be discussed with the fellow or attending. Usually Staphylococcus epidermidis coverage is indicated. When the organism is known, broad coverage may not be necessary. If a central line is present, you should discuss with the attending/fellow about giving antibiotics through the line.

The length of therapy will, in general, be decided by the fellow or attending. With proven sepsis, the length is usually 7-10 days following cessation of symptoms. With meningitis, it is usually 14-21 days. If all cultures are negative at 72 hours, antibiotics should be discontinued. If antibiotics are continued despite negative culture, the exact reasons for doing so should be documented in the medical record. This decision should result from discussion with the attending.

If the infant is already on antibiotics and either does not respond to these or has additional symptoms, another work-up should be done and review of antibiotic coverage discussed with the attending physician.

D. Complications of Sepsis
    1. Shock
    2. Hypoglycemia
    3. Hyponatremia (with or without SIADH)
    4. Hypoadrenal-like state (low Na, high K)
    5. DIC
    6. Acidosis

E. Therapy — Adjuvant therapy and supportive care

    1. Septic Shock:
        a. Volume Resuscitation with 0.9% NS 10-20cc/kg or blood products - PRBC, fresh frozen plasma 10-20 cc/kg
        b. Vasoactives (Lexicomp, 2016)
            i. Dopamine - Continuous IV infusion: 1-20 mcg/kg/minute
                1. The hemodynamic effects of dopamine are dose-dependent:
                2. Low dosage: 1-5 mcg/kg/minute, increased renal blood flow and urine output
                3. Intermediate dosage: 5-15 mcg/kg/minute, increased renal blood flow, heart rate, cardiac contractility, cardiac output, and systemic blood pressure
                4. High dosage: >15 mcg/kg/minute, alpha-adrenergic effects begin to predominate, vasoconstriction, increased blood pressure

            ii. Dobutamine – Continuous IV infusion: 2-20 mcg/kg/min (max 40

mcg/kg/min)

1. Stimulates myocardial $beta_1$-adrenergic receptors resulting in increased contractility and heart rate
2. Stimulates both $beta_2$- and $alpha_1$-receptors in the vasculature
3. Little effect on pulmonary vasculature and does not require release of endogenous norepinephrine like Dopamine

iii. Epinephrine - Continuous IV infusion: Initial 0.05 to 0.2 mcg/kg/min; usual range: 0.05 to 0.5 mcg/kg/min

1. Stimulates alpha-, $beta_1$-, and $beta_2$-adrenergic receptors resulting in relaxation of smooth muscle of the bronchial tree, cardiac stimulation (increasing myocardial oxygen consumption), and dilation of skeletal muscle vasculature
2. Small doses can cause vasodilation via $beta_2$-vascular receptors; large doses may produce constriction of skeletal and vascular smooth muscle
3. Note that doses <0.3 mcg/kg/minute generally produce beta-adrenergic effects and higher doses (>0.3 mcg/kg/minute) generally produce alpha-adrenergic vasoconstriction

c. Steroids

i. Hydrocortisone can be used to support refractory hypotension / shock, particularly in adrenal insufficiency
ii. Stress dosing typically used

d. Intravenous Immunoglobulin (IVIG) therapy

Most of the studies that have evaluated the effectiveness of intravenous immunoglobulin (IVIG) in the treatment of neonatal sepsis have been neither randomized nor blinded and have involved only small number of patients. Although efficacy has not been clearly established, the findings of these trials suggest that IVIG may be valuable in combination with antibiotics in selected cases. Neonatal sepsis may rapidly progress to shock and death, even in patients receiving appropriate antibiotics. This is usually due to the deficiency of pathogen-specific opsonic antibody. IVIG preparation containing high level of opsonic antibodies to organisms responsible for neonatal sepsis may serve to correct this deficiency.

In general, IVIG preparations contain low titers of antibodies against group B streptococcus (GBS) and Escherichia coli which are the most common bacterial sepsis in neonatal period therefore at present, the data do not support the routine use of IVIG in neonatal sepsis.

Other considerations for IVIG administration:

- Sepsis with absolute neutropenia
- Isoimmune thrombocytopenia
- Maternal and neonatal idiopathic thrombocytopenic purpura
- Serum IgG levels < 200 mg/dl

Criteria for screening serum IgG levels

Very-low-birth-weight (VLBW) infants

Short bowel syndrome and ileostomies

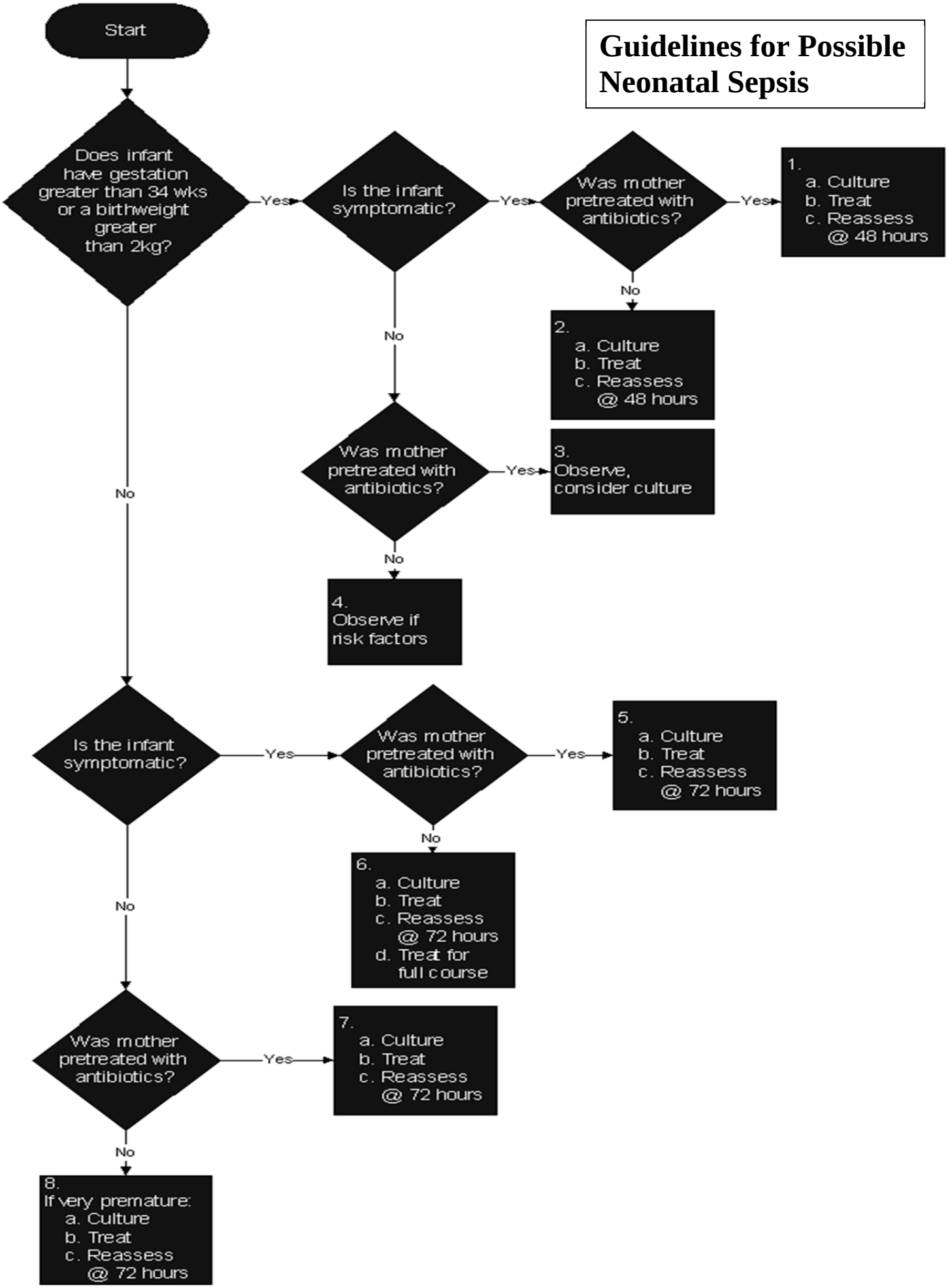
i. Dosage
IVIG dose may vary from 200-500 mg/Kg as a single dose for low IgG levels with further follow-ups as necessary. In septic neonates and/or thrombocytopenia the dose may be given daily for 3-5 days. Maximum single dose should not exceed 750 mg/Kg. Hospital stores may be low so the pharmacy should be contacted prior to ordering IVIG.

ii. Adverse effects
Hypotension and anaphylaxis. If either occurs, the rate of infusion should be decreased or stopped until resolved, then resumed at a slower rate as tolerated.

2. Respiratory failure
   a. Supportive care (VT, CPAP, vent, HFOV)
   b. iNO if indicated

3. Monitoring
The infant in shock should have an arterial line for the measurement of blood gases, a venous line for administration of fluids and medications and an indwelling bladder catheter if oliguria is present.

Guidelines for Possible Neonatal Sepsis



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RETINOPATHY OF PREMATURITY

I. GENERAL INFORMATION

Retinopathy of prematurity (ROP) is defined as a growth of abnormal blood vessels on the retina, seen primarily in the premature infant. The eye is rapidly developing during gestational weeks 28-40. The blood supply to the retina starts at the optic nerve at about 16 weeks. Blood vessels grow out from there toward the edges of the retina until the time of birth. When a baby is born prematurely, this normal vessel growth stops and new abnormal vessels begin to grow. There seems to be a barrier to the normal growth of vessels creating a line beyond which the precursors of the vessels cannot pass (Stage I). It is postulated that the retina anterior to this line does not have an adequate oxygen supply causing the release of chemical signals that stimulate new vessel growth. This new vessel growth can form arterio-venous shunts at the location of the barrier (Stage II). This shunt gradually enlarges, becoming thicker and more elevated. The new vessels are accompanied by fibroblasts, which produce fibrous scar tissue (Stage III). This ring of scar tissue can contract and pull on the retina, with eventual retinal detachment (Stage IV). The International Classification of Retinopathy of Prematurity (*The International Classification of Retinopathy of Prematurity Revisited. An International Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol. 2005; 123: 991-999*), is used to standardize our descriptions of ROP, so that therapies and outcome data can be approached in a standard fashion. This is discussed later in this section.

II. RISK FACTORS

Risk factors related to the development of ROP appear to be multifactorial in nature. Many conditions or stimuli, both prenatal and postnatal are responsible for the development of ROP.

A. Prematurity: ROP is a disease primarily of the premature infant.

B. Supplemental oxygen: High levels of oxygen (PaO2, not FiO2) have been associated with the development of ROP. This is why we monitor pulse oximetry and blood gases closely in the premature population, keeping the oxygen level as low as possible to reduce the risk of ROP. In most cases keeping the arterial oxygen level between 50-60 torr &/or the saturations between 88 and 94%, will meet these criteria. Although it is known that high arterial oxygen levels are a risk for the development of ROP, there is evidence that it is not only oxygen, but also carbon dioxide levels. Of more concern may be the large swings in PaO_2 and $PaCO_2$ levels, as we can see in the very ill premature infant.

C. Race: In the CRYO-ROP study, black infants were found to be less likely to develop ROP and less likely to go on to threshold ROP than white infants. Other racial groups appeared to have a similar risk of ROP as compared with white infants.

D. Comorbidities: Twin gestation, intraventricular hemorrhage (IVH), hydrocephalus, poor weight gain before first ROP screening, and unstable clinical course requiring cardiorespiratory support.

We have traditionally thought of ROP as a disorder caused by exposure of premature infants to noxious stimuli encountered after birth. However, we are learning that some of the factors that precipitate ROP are not within our control, and may occur before birth. Full blown threshold

ROP has been seen within a day or two of life, implying that the retinopathy was already well under way prior to birth. It is suspected that as many as one third of cases of ROP are caused by prenatal rather than postnatal conditions.

III. SCREENING

A. All infants ≤ 30 weeks GA and/or infants with ≤ 1500 grams birth weight are screened for ROP beginning as early as 31 weeks PMA. ROP needing treatment can occur between 33 and 43 weeks PMA.

B. According to American Academy of Pediatrics, first ROP eye exam should occur according to the following:
   1. Infants ≤27 weeks gestation will receive their first eye exam at 31 weeks corrected gestational age.
   2. Infants born between 28-30 weeks gestation will receive their first exam at 4 weeks of life (DOL 28). If infant is set to be discharged before 1st exam please have baby seen for ROP eye exam before discharge.

C. Table from National Policy Statement[2] Modified for CNHS[3]

	Age at Initial Exam (wks)	
GA at Birth	Postmenstrual	Chronologic
22*	31	9
23*	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
Older GA at High Risk		4

*Evidence for 22-23 GA from CNMC data; older GA or very low birth weight determined high risk will generally be seen by PMA 35 weeks at CNHS.

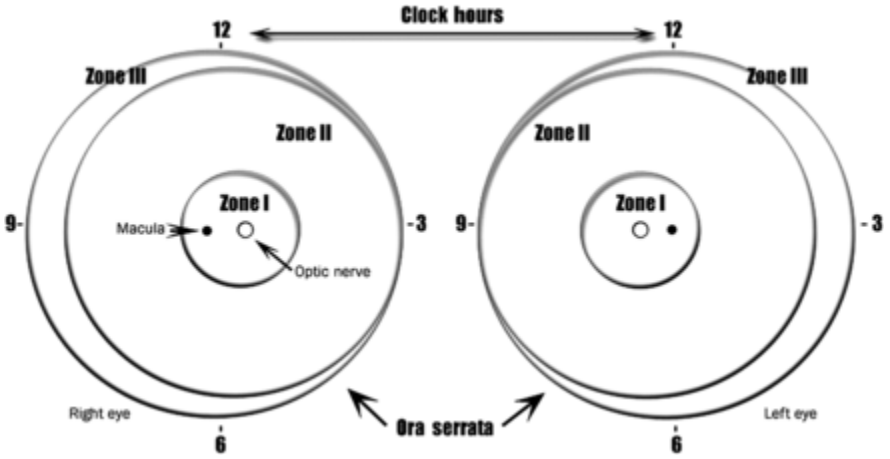
[2]National Policy Statement: American Academy of Pediatrics Policy Statement: Screening examination of Premature Infants for Retinopathy of Prematurity. Section of Ophthalmology, American Academy of Pediatrics, American Academy of Ophthalmology, American Association of Pediatric Ophthalmology and Strabismus Pediatrics 2013;131:189–195.

[3]CNHS NICU data on 22 and 23 GA infants revealed extremely premature infants ≤ 25 weeks GA develop ROP requiring treatment between 33 and 43 weeks PMA. At CNHS, the cumulative probability of receiving laser therapy approached 46% when GA was 23 weeks; 30% when GA was 24 weeks, and 18% when GA was 25 weeks.
Risk and Clinical Course of Retinopathy of Prematurity in 78 Infants Gestational Age 22 to 25 weeks. Miller MM, Revenis ME,Lai MM, Meleth AD, Jeffress ES, Carrera A, Cheng YI, Sills AM, McCarter R.: Journal of AAPOS, 2014.

IV. PRESENTATION

The International Classification of Retinopathy of Prematurity (ICROP): This system allows the examiner to define ROP with several distinct criteria: *location, extent, stage, and plus disease.*

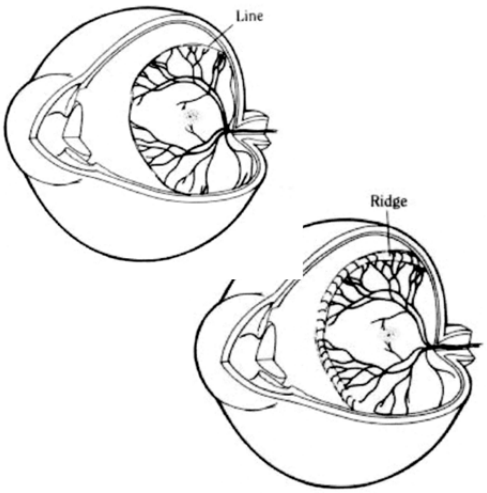
A. Location: the location of ROP refers to the location relative to the optic nerve. The retinal vessels normally start their growth at the optic nerve and gradually move toward the edge of the retina. Vessels that are farther from the optic nerve (or closer to the edge of the retina), e.g., Zone II-III, are more mature and less concerning. Location is standardized by dividing the retina into 3 zones. Zone I is an area centered on the optic disc and extending from the disc to twice the distance between the disc and the macula. Zone II is a ring concentric to Zone I, which extends to the nasal ora serrata (edge of the retina on the side of the eye toward the nose). Zone III is the remaining crescent of retina on the temporal side. See Figure.



B. Extent: The extent of ROP is how many clock hours of the retina are involved. For example, if there is retinopathy extending from 1:00 around to 5:00, the extent of ROP is 4 clock hours. (See above Figure)

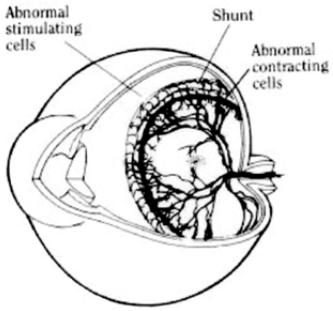
C. Stage: SROP begins with mild changes, progressing to severe. The stage of ROP describes how far along in this progression the vessels have reached and reflects severity.

1. Stage 1 is characterized by a demarcation line between the normal retina nearer the optic nerve and the non-vascularized retina more peripherally.

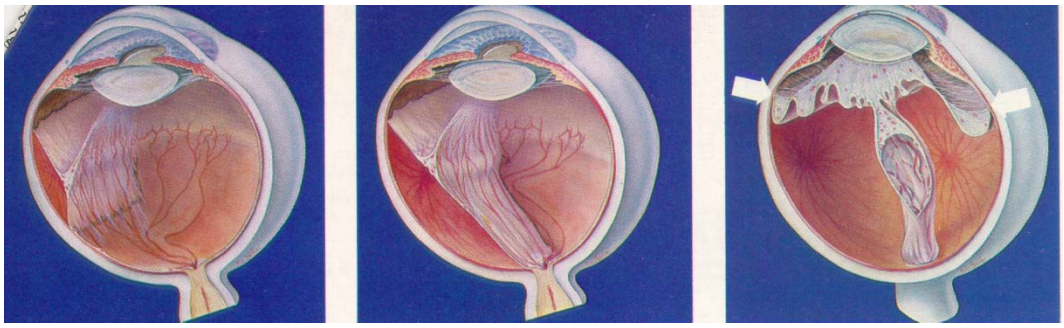


2. Stage 2 ROP has developed to a ridge of scar tissue with new vessels in place of the demarcation line; the white line now has width and height.

3. Stage 3 has increased size of the vascular ridge, with growth of fibrovascular tissue on the ridge, extending out into the vitreous.



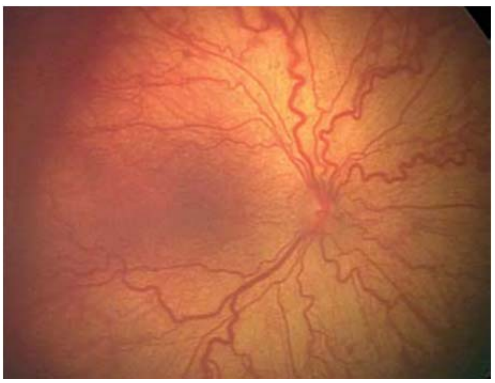
4. Stage 4 includes partial retinal detachment. The scar tissue associated with the fibrovascular ridge contracts, pulling the retina away from the wall of the eye.
   a. Stage 4A, the detachment does not include the macula; vision may be good.
   b. In Stage 4B, the macula is detached, and the visual potential is markedly decreased. ***Intraocular surgery with vitrectomy and laser may be offered*.**



Stage 4a Stage 4b Stage 5

5. Stage 5 includes complete retinal detachment, usually resulting in blindness.

D. Plus Disease: Plus disease describes vessels which are dilated and tortuous near the optic nerve in at least 2 quadrants (1/2 the vessels at the disc). Plus disease is a very important criteria that indicates ROP needs treatment.



E. Aggressive Posterior ROP (AP-ROP): Is a rapidly progressing variant of ROP that will need exams more often than weekly and may require emergent treatment. Extremely low GA infants are more likely to have AP-ROP at PMA of 33-34 weeks and therefore, the initial ROP screening exam must occur according to schedule.

V. FOLLOW-UP EXAMS

A. Repeat exams will be scheduled on an individual basis.

B. If mild retinopathy is found, the exam is repeated every 2 weeks.

C. If advancing or posterior ROP (zone 1 any stage, posterior zone 2 any stage; Zone 2 stage 3 without plus) repeat the exam within 8 days. The patient should remain in the hospital until ROP has begun to regress.

D. NO infant can be discharged with stage 3 ROP or Plus disease without direct permission of the screening ophthalmologist.

E. Continuation of ROP screening after discharge must be arranged and the family informed (with signed discharge sheet) before discharge. ROP outpatient care is a critical part of discharge planning. (Large law suits have occurred nationally when families have failed to keep outpatient ROP appointments and lost vision.)

VI. TREATMENT

Many infants with mild ROP will resolve without treatment. These infants usually develop normal central vision. However, some infant who undergo regression may have late complications of ROP, including strabismus (crossed eyes), amblyopia (lazy eye), myopia (near-sightedness), glaucoma, and even late onset retinal detachment from localized traction. In addition, premature infants are at risk of vision reduction from optic nerve atrophy from IVH or ICP and may have central nervous system anomalies that predispose to non-ROP causes of impaired vision. For this reason, parents are given information about ROP and vision in the premature infant at the time of initiation of ROP screening and also sign a second form at the time of NICU discharge with eye appointment scheduled to insure follow-up eye care is obtained.

A. Type 1 ROP
During ROP screening (inpatient or after discharge), the screening ophthalmologist in consultation with the retina specialist will determine when “Type 1 ROP” is present which requires treatment.

The definition of *Type 1 ROP* is detailed in the AAPOS/AAP policy statement (summarized below). Due to the risk of blindness**,** treatment is offered for Type 1 ROP disease. Treatment may need to be performed more than once.

1. Type 1 ROP:
Zone 1: Any stage with plus disease
Zone 1: Stage 3 without plus disease
Zone 2: Stage 2 or Stage 3 with plus disease

A. Laser treatment remains the most common type of ROP treatment. The purpose of the

treatment is to place laser spots in the avascular retina adjacent to active ROP and to fully cover the avascular retina with laser spots (evenly spaced spots to full painting with laser). While laser treatment turns off ROP activity in many cases, it does destroy the avascular retina and reduces peripheral vision.

With laser therapy, infants often require escalation in respiratory support so that adequate sedation can be given for the procedure (including, on occasion, intubation; anticipated respiratory support should be determine by the NICU Attending and Fellow.) The laser procedure is done at the patient's bedside at CNHS. Coagulation deficiencies may need blood product pretreatment. The neonatology team is responsible for writing orders and administering sedation, in addition to monitor patient bedside during the procedure. As with all procedures, there is consenting and time out. Laser safety is used with screen and goggles. Depending on number of laser spots, treatment time can range from 15 minutes to 1.5 hours. Each treatment case will require extensive conferencing for set up and coordination. Treatment is performed by the consulting retina specialist who will come to CNHS for confirmatory consultation and treatment. The ROP nurse will coordinate the treatment plan communications to the family and NICU team in coordination with the ophthalmology attending, treating retina specialist, bedside nurse and ophthalmology fellow. Infant will be seen 1 week after laser surgery and on a regular basis after that to monitor the regression of ROP. Re-treatment may be necessary if ROP begins to progress again to Type 1 disease. Patient will be followed as an outpatient in ophthalmology clinic to optimize vision outcome.

Other treatment options include Anti- VEGF injections, scleral buckle and vitrectomy if laser therapy does not work. These are discussed below:

B. Intravitreal Injection of Bevacizumab (Avastin) is given at the bedside with topical anesthetic by defined protocol developed with pharmacy (0.625 mg in 0.025 ml; note: the written order is for Bevacizumab 1.25mg/0.05 mL because ½ is wasted to fill the needle.) The injection is performed by the consulting retina specialist or ROP ophthalmologist.

   The American Academy of Pediatrics states that Avastin may be used as treatment for infants diagnosed with zone 1, stage 3+ but it has not been approved by the FDA for ROP treatment. A detailed informed consent must be reviewed with parents specifically before treating with Avastin because they should be aware of the possible risks of using a therapy where the long term effects have not yet been seen.

   The reoccurrence of ROP that can occur after treatment with Avastin has a much longer time frame then with laser. After Avastin, recurrence of ROP occurs at 16 ± 4.6 weeks (possibly up to PMA 65 weeks so both inpatient and outpatient ROP care is critical) while after laser recurrence occurs at 6.2 ± 5.7 weeks. Close follow up requires a commitment from the medical professional that performs the treatment and from the parents so that adequate follow up visits are made in a timely manner. A benefit of using Avastin is that normal peripheral retina growth may occur after treatment unlike with laser treatment where permanent damage is made to the peripheral retina.

C. Scleral buckle may be used when laser therapy and/or Avastin are not effective. This involves placing a silicone band around the equator of the eye and tightening it to produce a slight indentation on the inside of the eye. This keeps the vitreous gel from pulling on the scar tissue and the retina and allows the retina to flatten back down onto

the wall of the eye. This band must be removed months or years later since the eye continues to grow. This therapy is usually reserved for Stage 4 and 5 ROP patients.

D. Vitrectomy involves making several small incisions into the eye to remove the vitreous and replace it with a saline solution to maintain the shape and pressure of the eyeball. Laser may be given during the operation. After the vitreous has been removed, the scar tissue on the retina can be peeled back or cut away, allowing the retina to relax and lay back down against the eye wall. Gas may be injected to flatten the retina, but this is difficult in infants because positioning may be needed. Vitrectomy may be used for Stage 4 or worse ROP.

VII. ROP TEAM RESPONSIBILITES AND PROCEDURES

The primary ROP Team is the ROP RN, the screening attending ophthalmologist and the ROP outpatient coordinator, but all members of the medical team must participate to give good ROP care.

A. Ophthalmology Attending:
   1. Contact Clinical Coordinator regarding examination day. Exams are done on the day most convenient for the ophthalmology service, typically on Tuesday or Wednesday.
   2. Provide ROP information sheet for the parents at the time of the initial examination.
   3. Perform indirect ophthalmoscopy.
   4. Complete the consult note specifying stage, zone and clock hours.
   5. Speaking with the parents if the eye(s) is(are) abnormal or designating ROP nurse to discuss with family and being available for additional discussions as needed.
   6. Determine the timing of repeat examinations.
   7. Treat acute disease by contacting retinal consultant to reexamine infant and perform treatment if in agreement that Type 1 disease.
   8. Establish long-standing relationships with the families of children who have residual cicatrix from their ROP.
   9. Discussing the findings of the ROP exam and plans for follow/up with the baby's physician.

B. Ophthalmology Fellow (or designate on call)
   1. Attend ROP rounds to gain extensive knowledge of ROP screening and care.
   2. Be present for ROP treatments by the retina consultant
   3. Facilitate complex communications with the families about ROP and treatment consents and support communications by ROP RN.
   4. Prepare notes in Power-chart for ROP patients.
   5. Order dilation drops for scheduled ROP patients for current week.

C. Neonatology Attending
   1. Review the weekly list of patients requiring ROP exams.
   2. Review the findings on the ROP exam, assure proper followup is assigned and discuss findings with parents if severe; review findings with resident, so they can discuss with the parents on routine cases

D. NICU Resident/NP/PA:
   1. Place consult orders in Cerner requesting ROP consult for high risk infants (≤30 weeks gestation and/or ≤1500 grams birth weight)

2. Speak with the parents about the outcome of the exam, and if the retina is still immature, that a repeat exam is necessary
3. Be aware of scheduling when initial and repeat exams are due
4. Be aware that eye drops should be ordered for patient prior to the exam (may be done by ophthalmology fellow or NICU practioner)
5. Check Vitamin E level in premature infants with ROP, if on oral feeds to make sure the level is at least normal (10-20) mgm/ml)
6. Orders
    a. ROP consults: place order upon admission for high-risk infants
    b. Dilation drops: Generally, Cyclomydril is given one drop to each eye and repeated once in 5 minutes. Cyclomydril is a specially formulated dilation drop for the premature infant. Other dilation drops may be too strong and will only be substituted in special situations (for instance: failed dilation or pre-laser treatment).
    c. Other ophthalmologic exams: Cerner consult request needs to be filled out completely with the appropriate information if non-ROP consults are needed, e.g. evaluation for possible Toxoplasmosis, fungal infection, etc. The ROP ophthalmologist will generally not be available for other types of consults during the designated ROP session unless special exception is made after discussion with ROP RN or ophthalmologist.
7. Discharge
    a. NICU resident/NNP/PA must go over the ROP Discharge Information Sheet, making sure the parent(s) understand the importance of keeping this f/u appointment. The infant could go BLIND if the appointment is missed. **The ROP Discharge form MUST be signed by the parent.** Compliance with signing of the form is monitored. The "best" phone number should be listed on this form. Several law suits have occurred because parents do not keep appointment, and when finally seen, the infant has progressed to blindness. We want to insure best ROP care for our families.
    b. Please do not transfer or discharge infants with the following criteria without discussing with the ophthalmology attending on service for ROP screening that week.
        i. Zone 1 any level of disease (e.g immature, any staging or any hemorrhage)
        ii. Zone 2 ROP and less than PMA 36 weeks
        iii. PLUS disease present on exam
        iv. Post Avastin injection

E. ROP Nurse:
1. Enter new patients into the ROP program to determining timing of first exam
2. Prepare for ROP rounds by obtaining BW, GA, post-conceptional age (PCA) and any pertinent medical history (e.g.: IVH, hydrocephalus, twin-twin transfusion, etc.)
3. Provide a list of patients requiring ROP exams to the attending neonatology weekly and review this list of patients with the neonatology attending prior to exams
4. Make eye speculums/depressors available for exams
5. Schedule exams in the computer program based on ophthalmology recommendations

F. Bedside Nurse:
1. Administer eye drops at the time directed by ROP nurse
2. Assist ophthalmology fellow/attending with the eye exam
3. Chart the date of exam and the follow-up as indicated

G. Unit Clerk:

1. Notify bedside nurse when the ophthalmologist or ophthalmology RN calls to let the staff know when they are coming, so the RN will know when to start instilling eye drops for the exam

H. Retina Consultant:
   1. The retina consultant is assigned month long coverage for ROP and will respond to and provide ROP consultation regarding need for treatment in a timely manner
   2. Will plan and discuss treatment options with families and the ROP team.

VIII. HELPFUL CONTACT INFORMATION

ROP Nurse- Inpatient Clinical Coordinator
Caitlin Forsythe
Ascom x 1040
Desk x 5328
Email : cforsyth@childrensnational.org

Outpatient Clinical Coordinator for ROP
Kerrisa Gordon
Desk X4636
Email: KeGordon@childrensnational.org

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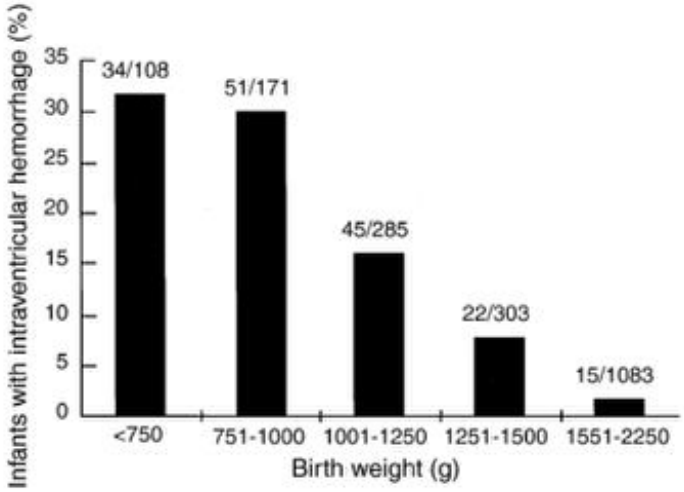
Caitlyn Forsythe, R.N.

PREMATURITY RELATED BRAIN INJURY

I. INTRAVENTRICULAR HEMORRHAGE (IVH)

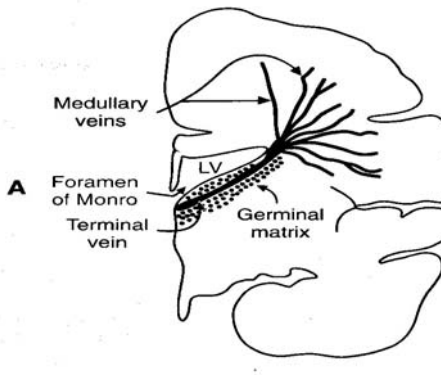
A. Incidence

Historically (1980s and prior) IVH the incidence was 40-50%. More recently (late 1980's to present), the incidence has decreased, now **20-25%.** It is rare but not unknown in full-term infants (up to 3.5%). Incidence is inversely related to gestational age and birth weight.



From Volpe: *Neurology of the Newborn, 5th Ed,* 2008

B. Site of Origin



Subependymal germinal matrix adjacent to lateral ventricle; occurs most commonly at the head of the caudate nucleus (at the caudo-thalamic notch); smaller preemies may have hemorrhage into the choroid plexus.

C. Pathogenesis: multifactorial but risk factors include:

1. Anatomical
   a. Poor endothelial integrity of capillary network

b. Arterial supply to the germinal matrix (GM) = vascular endzone vulnerable to ischemic injury
c. High metabolic demand (cellular proliferation) further susceptibility to ischemia

2. Impaired autoregulation of cerebral blood flow
Systemic blood pressure and cerebral blood flow changes occur with hypoxia, hyperoxia, hypocarbia or hypercarbia- large and rapid swings in these parameters can predispose to IVH. Hyperosmolar solutions (e.g. NaHCO3) and bolus solutions can also predispose to IVH. Major changes in intrathoracic pressure (pneumothorax) are highly associated with IVH.

3. Hematologic
Platelet dysfunction and coagulation disturbances.

D. Timing
Majority occur within the first 5 days of life and seldom after 2 weeks.

Postnatal day	Percent of infants with GM-IVH
1	50
2	25
3	15
>= 4	10

E. Clinical Presentation
Most hemorrhages are clinically silent; a few are *catastrophic* with deterioration within minutes to hours; some occur in a *saltatory* manner over hours to days with more subtle neurologic/respiratory changes. Falling hemoglobin/hematocrit may be an indicator.

F. Diagnosis
Because of the frequency of hemorrhage in the premature infant and the lack of reliably-associated clinical symptoms, all infants less than 1500 gms at birth should undergo routine screening with cranial ultrasound (CUS). See CUS protocol below.

G. Grading
Ultrasound findings on parasagittal view are described by Papile classification (originally developed to describe CT findings).
Grade I: Subependymal Hemorrhage (SEH) only
Grade II: SEH plus intraventricular hemorrhage (IVH) filling less than 50% of lateral ventricle
Grade III: IVH plus ventriculomegaly and blood filling greater than 50% of lateral ventricle
"Grade IV": Parenchymal hemorrhage with or without IVH and ventriculomegaly; usually asymmetric in distribution; now understood to be Periventricular Hemorrhagic Infarction (PHI) from venous congestion of medullary veins NOT extension of bleeding into parenchyma.

H. Treatment

1. Prevention: avoid rapid swings in BP, PaCO2, hyperosmolar solutions, particularly in first 3 days of life.
2. Correct coagulopathy and thromobocytopenia (goal plt >100K).
3. Post-hemorrhagic hydrocephalus (PHH): Intraventricular hemorrhage may produce acute ventriculomegaly or long-term hydrocephalus requiring surgical intervention. See Part IV for PHH management guidelines.

I. Outcome and Follow-up
All patients with IVH/PVL are followed in the Developmental Follow-up Clinic. *Motor deficits common, also cognitive, visual and auditory.

Severity of Hemorrhage	Mortality rate (%)	Progressive Ventricular dilatation (% of survivors)	Incidence of definite neurological sequelae (%) *
Grade I	5	5	5
Grade II	10	20	15
Grade III	20	55	35
Grade IV	50	80	90

II. PERIVENTRICULAR LEUKOMALACIA (PVL)

A. Definition
White matter damage (focal necrosis), usually symmetrical in periventricular region

B. Risk factors
Similar to IVH (cerebral autoregulation, vascular integrity, vascular endzone with risk for ischemia), but *different pathological entity*

C. Pathology
Key feature is vulnerability of periventricular oligodendrocytes to:
1. Ischemia/ reperfusion
2. Hypocarbia
3. Sepsis (chorio), inflammation, cytokines
4. Reactive oxygen species

D. Diagnosis
US detection is difficult early (subtle ventricular asymmetry or parenchymal echogenicity), but cystic lesions develop by 4-6 weeks and can be well visualized by US. MRI has higher sensitivity for PVL/white matter injury.

E. Outcome
Usually results in spastic diplegia but also cognitive/ behavioral, visual defects

III. PRETERM NEUROIMAGING PROTOCOL

*Note no universally accepted national/international protocols exist regarding routine surveillance by CUS or MRI in preterm infants. CNHS guidelines are developed based on institutional consensus regarding available guidelines/data (see Ment, Woodward in references).

I. Screening
   1. Screen all infants less than 1500 grams at birth with CUS on day 3 of life. Consider performing earlier in micro-preemie with catastrophic presentation if indicated for direction of care.
   2. For negative CUS, repeat at day 7 and 14 of life. If still negative and no new indications arise, repeat at 4-6 weeks of life to evaluate for PVL. Thereafter, consider monthly in sick preterm infants with prolonged hospitalization for intermittent surveillance until term MRI can be performed (see below)

II. Monitoring
For positive CUS: re-scan weekly (sooner if clinical suspicion for extension of bleeding if scan will be used to direct care) until IVH/PHH stable or resolved on at least 2 consecutive scans; then repeat monthly in sick infants, sooner if clinically indicated (i.e. more than 1.5 cm growth in head circumference or apneic/bradycardic events of unclear etiology).

III. MRI
For all ELBW <1000g infants, and babies with known IVH/PVL or other neurological concerns, consider term equivalent MRI as it has higher sensitivity for white matter injury than US (Woodward et al). This should be performed in stable, feeding, term-corrected (>38 wks PMA) infants WITHOUT sedation. If exam is not performed during NICU stay, outpatient exams can be considered but need to be scheduled as "neonate, feed and bundle, non-sedate exam." For patients who fail non-sedate exams, it should be determined by the attending whether the risk/benefit ratio warrants scheduling the exam with sedation (i.e. in low risk patient outpatient MRI may be deferred with close developmental follow-up).
   1. Procedure
      a. Order non-contrast brain MRI in Cerner *specifying both gestational age at birth and corrected age at time of scan, as well as other pertinent clinical history (e.g. h/o IVH by CUS)*
      b. Notify Charge RN for scheduling.
      c. Dedicated NICU time slots nightly at 8pm and Sunday mornings.
      d. If an urgent exam is needed, LIP should communicate with neuroradiology/ MRI staff to schedule outside of these times.
      e. Once patient is scheduled, bedside RN should adjust feeding schedule to 30-45 minutes prior to exam. Patient will be swaddled, immobilized and imaged during sleep.
      f. DO NOT ORDER NPO/SEDATION without discussion with fellow/attending.

IV. MANAGEMENT OF POST-HEMORRHAGIC HYDROCEPHALUS (PHH)

A. Monitoring
   1. Physical examination: All infants will be monitored for signs of progressive ventricular dilation on daily basis by a medical staff with the following:
      a. Daily head circumference (HC) in centimeters plotted on the appropriate percentile for gestational age; abnormal growth is if the HC crosses two centiles at any time point (i.e. growth > 1.5 cm/week).

b. Anterior fontanel palpation in a sitting position while calm; classified into either soft, bulging, or tense (Kaiser and Whitelaw, 1987).
c. Metopic suture splay in cm just above the glabella (1.5 cm below the tip of the anterior fontanel) (Figure-1).

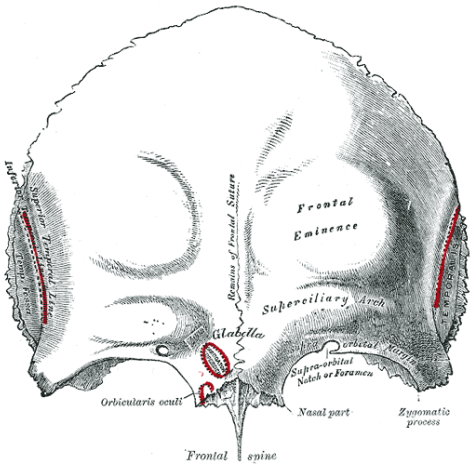
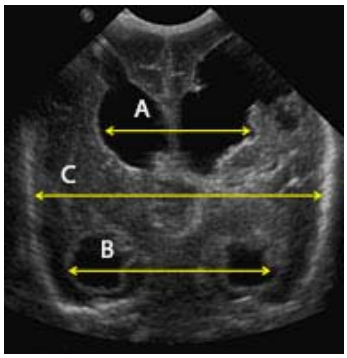


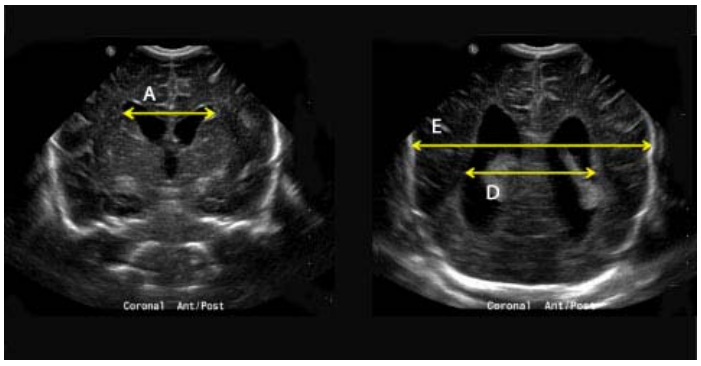
Figure 1. Metopic suture splay

d. The presence of either apnea or bradycardia longer than 30 seconds that could not be explained by other medical reasons.

2. CUS: The size of the dilated lateral ventricles will be reported using multiple methods:
   a. The fronto-temporal horn ratio (FTHR) and fronto-occipital horn ratio (FOR) (Antes et al., 2013; O'Hayon et al., 1998), (Figures 3 -4): The normal FTHR and FOR are <**0.50** and are independent of age. Mild to moderate ventricular dilation if FTHR or FOHR between **0.55 – 0.60.** A change in the ratios of **>0.1** regardless of time period could be significant.



FTHR= A+B/2C



FOR = A+D/2E

   b. Other CUS measures have been described and are summarized below, however the FTHR and FOR are most reliable and will be primarily used in management decisions (Levene, 1981; Davies et al., 2000)

CUS Measure	**Normal values: Mean (SD)**

Ventricular index (VI)	9 mm (1)
Anterior horn width (AHW)	Left: 1.7 (0.98) Right: 1.52 (0.81)
Thalamo-occipital diameter (TOD)	Left: 18.1 (4.3) Right: 16.5 (3.9)
Third ventricular width (3rd)	1.24 (0.32)

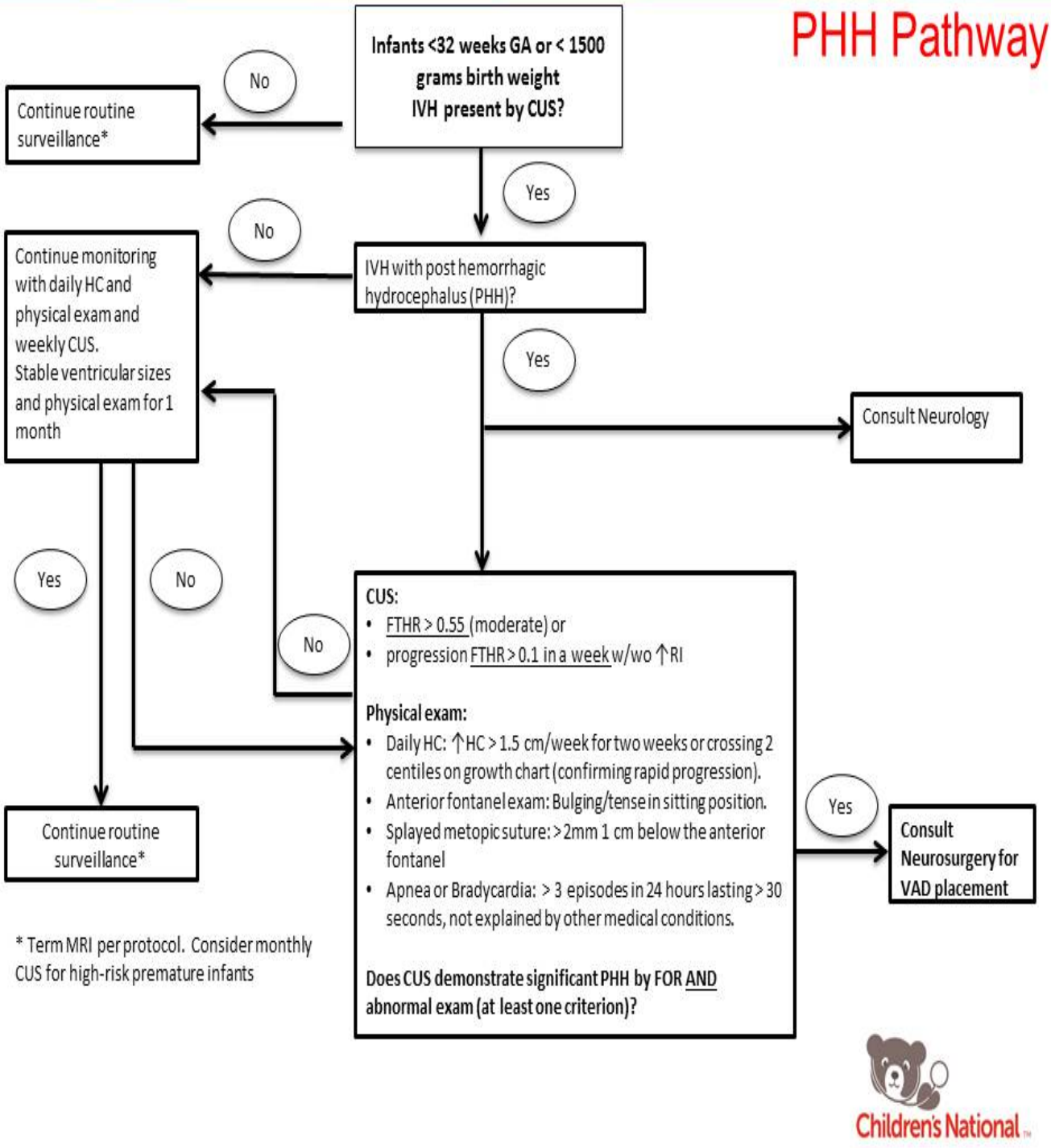
B. Management

Significant PHH is defined by the following criteria (1) the presence of at least one physical exam finding indicating significant PHH and (2) continuous progression of the FTHR (~ 0.1 change in the ratio) over one week period or FTHR > 0.55 (indicating moderate PHH).

Neurosurgery consult should be obtained for significant PHH and if no medical contraindications (sepsis, NEC, severe RDS, coagulopathy), placement of a ventricular access device (VAD) will be considered.

1. VAD management
    a. Continue daily physical exam and weekly CUS assessment to gage adequacy of CSF diversion.
    b. Initiate VAD taps when cleared by neurosurgery. Usually remove 10 ml/kg once a day and escalated as necessary (Tian et al., 2012).
    c. The VAD is accessed by qualified personnel only (attending, nurse practioner, neonatology fellow) with appropriate training and after thorough clean prep, wearing sterile gloves and a mask. The baby is placed in the lateral position on the side opposite of the VAD. Using sterile technique, the skin around the VAD is prepped with chlorhexadine or betadine per unit protocol. The VAD is punctured with a 25 butterfly needle and a syringe is used to slowly remove the amount of fluid. The fontanel is palpated before and after the tap.
    d. Once a week fluid samples are sent for cell count, protein, glucose, and aerobic/anaerobic culture and gram stain.
    e. The VAD is tapped until the infant's ventricles stabilize or decrease in size on weekly CUS or a ventriculo-peritoneal shunt (VPS) is placed. VPS are placed in infants who continue to require removal of fluid and have no contraindications to the shunt procedure- i.e. adequate gestational age/size, CSF is non-bloody/low protein, tolerating enteral feeds.

PHH Pathway


Infants <32 weeks GA or < 1500 grams birth weight IVH present by CUS?
No
Continue routine surveillance*
Yes
IVH with post hemorrhagic hydrocephalus (PHH)?
No
Continue monitoring with daily HC and physical exam and weekly CUS. Stable ventricular sizes and physical exam for 1 month
Yes
Consult Neurology
Yes
No
No
CUS:
• FTHR > 0.55 (moderate) or
• progression FTHR > 0.1 in a week w/wo ↑RI
Physical exam:
• Daily HC: ↑HC > 1.5 cm/week for two weeks or crossing 2 centiles on growth chart (confirming rapid progression).
• Anterior fontanel exam: Bulging/tense in sitting position.
• Splayed metopic suture: > 2mm 1 cm below the anterior fontanel
• Apnea or Bradycardia: > 3 episodes in 24 hours lasting > 30 seconds, not explained by other medical conditions.
Does CUS demonstrate significant PHH by FOR AND abnormal exam (at least one criterion)?
Yes
Consult Neurosurgery for VAD placement
Continue routine surveillance*
* Term MRI per protocol. Consider monthly CUS for high-risk premature infants
Children's National

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PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

I. GENERAL INFORMATION

Persistent pulmonary hypertension of the newborn (PPHN) is a term used for infants who have increased pulmonary vascular resistance post-delivery, resulting in a continuation of their fetal right-to-left shunts, i.e., the foramen ovale and ductus arteriosus (see Figures 1 & 2). As blood shunts away from the lungs as seen in Figure 2, severe hypoxia develops. This hypoxia worsens the increased vascular resistance further. This "cycle" (see Figure 3) can be extremely difficult to break. Therefore management of these infants has to be a team effort, with the bedside nurse and respiratory therapist fully aware of the physician's plans. Although it is routine for respiratory therapy and nursing to make some changes in oxygen or ventilator settings based on the daily respiratory care plan, in these infants, blood gases need to be shown to the physician. The pediatric resident should discuss blood gas results with the Neonatal Fellow and/or Attending before making changes on the ventilator.

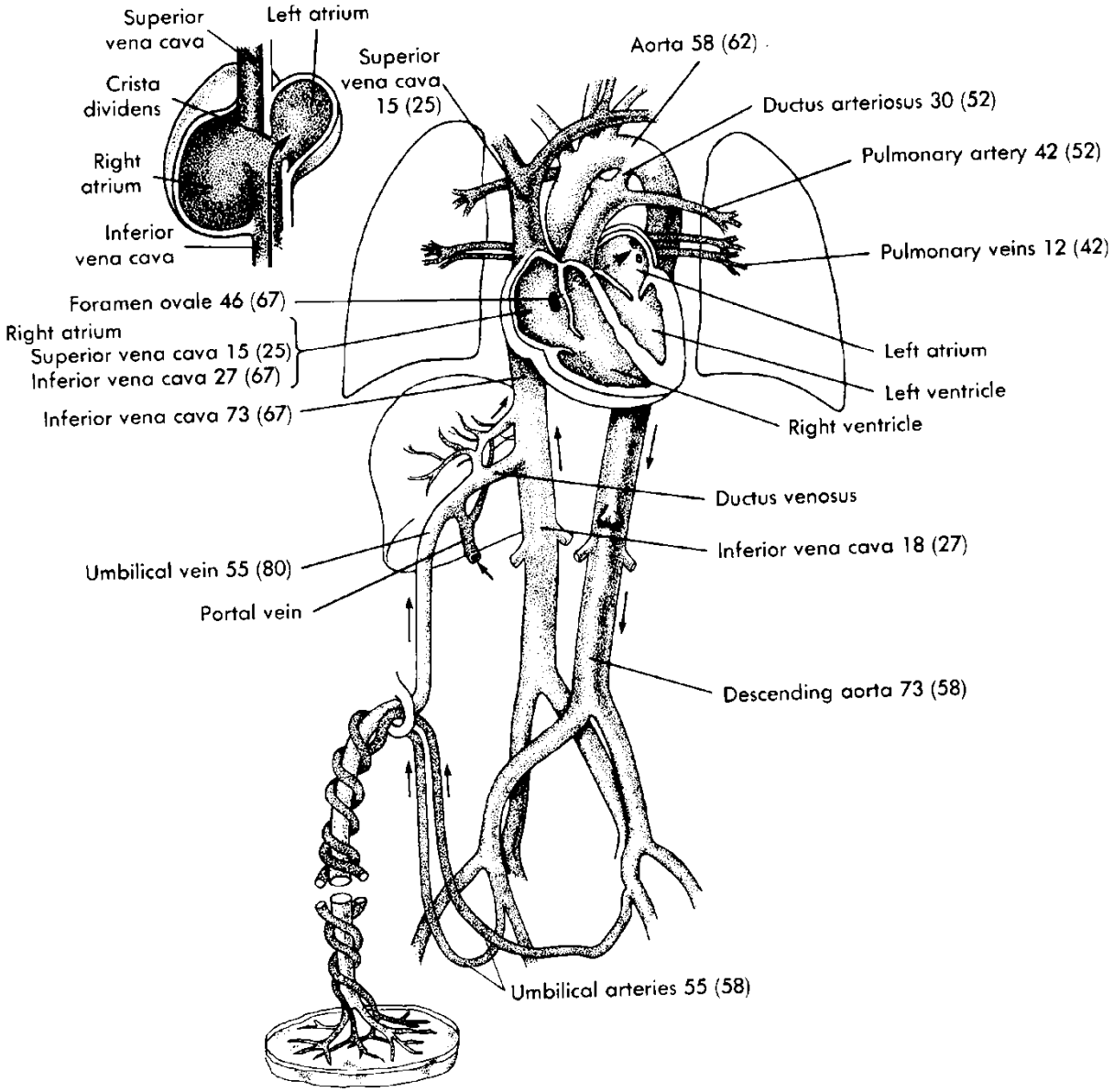
PPHN can present as an isolated entity, called idiopathic PPHN, or with other disease processes including, meconium aspiration syndrome (MAS), sepsis, pneumonia, severe asphyxia, congenital diaphragmatic hernia (CDH), and others. The exact etiology for this physiologic state is unknown, but probably differs per disease state. There appear to be 3 forms:

A. Secondary to an acute event:
   An acute event which results in asphyxia or hypoxia, such as in MAS, sepsis, cord accidents, et al, may result in PPHN by causing increased vascular resistance.

B. Secondary to a chronic event:
   Chronic events in utero, such as hypoxia or asphyxia from placental abnormalities (usually difficult to determine from the clinical history) may result in vascular re-modeling. It is postulated that these events cause structural changes in the vascular bed with increased muscular wall thickness, resulting in an increase in vascular resistance. Not only is there a decrease in cross-sectional area resulting in increased vascular resistance, but it also appears that these vessels can acutely contract and obstruct outflow in these vessels in response to a stimulus like hypoxia/asphyxia. Obstructed vessels have been noted in pathology specimens of patients who have died of PPHN.

C. Abnormal development:
   The hypoplastic pulmonary bed, as in diseases such as CDH or pulmonary hypoplasia from other causes, the lung has a decreased number of air sacs and on the vascular side, a decrease in the cross sectional area of the vascular bed. This can result in severe pulmonary hypertension. Some of these infants may have irreversible pulmonary hypoplasia, but clinically it is impossible to predict which patient has irreversible lung hypoplasia.

The Fetal Circulation
Figure 1



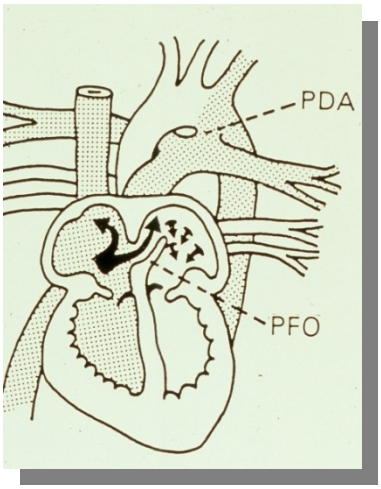


Figure 2: Right to left shunts at the patent foramen ovale and the patent ductus arteriosus

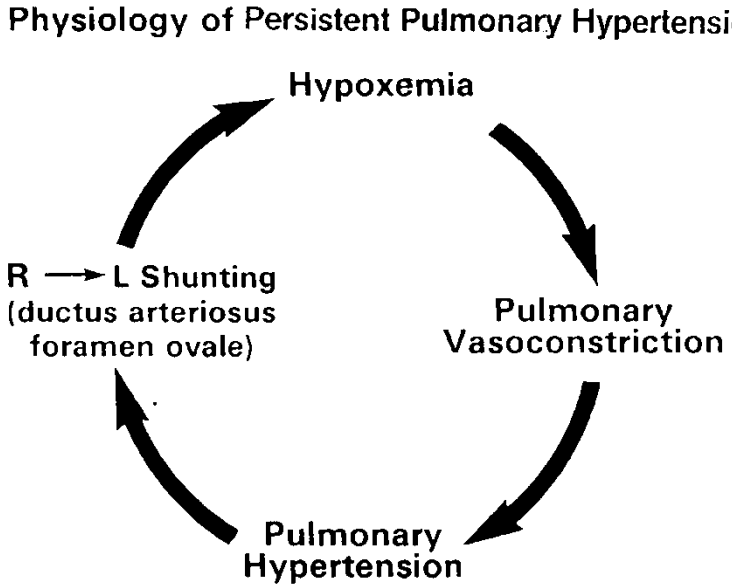


Figure 3: The physiology of increased pulmonary vascular resistance in the newborn. Right to left shunting results, causing worsening hypoxia. Hypoxia increases the pulmonary vasoconstriction. A difficult cycle to break.

II. DIAGNOSIS

Since this is a physiologic diagnosis, one must evaluate physiologic events outlined below before making the diagnosis of PPHN:

A. The infant with PPHN may show clinical signs of the "flip-flop" phenomenon. This is a picture of major swings in oxygenation caused by very small changes in ventilator or oxygen settings.
B. Pre (right radial or temporal artery) and post ductal (umbilical, tibial, or dorsalis pedis artery) blood gases may show a difference. As noted in Figure 2, this only means that there is a shunt at the PDA, which does indicate PPHN. If the shunt is primarily at the PFO level, pre and post ductal blood gases will be the same, but you still have PPHN. Therefore, if there is a difference of at least 15 torr between pre and post ductal ABGs, it is a positive test for PPHN, but if there is no difference, it does not rule out PPHN.
C. Hyperoxia/hyperventilation test: if the baby is placed on a FiO_2 of 100% the PaO_2 may not significantly increase as it will for pneumonia, i.e., reacting like a cardiac patient. Usually, if the patient is placed on a FiO_2 of 100% with the $PaCO_2$ decreased to 20-25 torr, the PaO_2 will increase at least by 15-20 torr. If it does not, consider heart disease and not PPHN.
D. The ultimate diagnosis is through the use of echocardiographic studies, although, even these can be confusing. If the patient is stable with PaO_2 >100, the echo may not show shunting at that time period. If the infant had been examined when the oxygen was low, there would be significant shunting. Therefore one must always evaluate the other signs/symptoms as well as the echo when making the diagnosis of PPHN.

III. TREATMENT GUIDELINES

A. General treatment concepts
   1. Keep Hematocrit $\geq$ 35-40
   2. Keep blood pressures (especially systolic) normal or slightly elevated; hypotension should be treated immediately
   3. Correct electrolyte abnormalities

B. Hypotension therapy in PPHN is considered an emergency
   1. Volume
      - Bolus with 10 cc/kg
      - NS preferred
      - Blood/FFP/albumin (5%) may be used in specific instances
   2. Dobutamine:
      - Beta-one (B_1) inotropic agent
      - No pulmonary hypertensive side effects
      - 2-20 micrograms/kg/min
   3. Dopamine:
      - B_1 & Alpha adrenergic inotropic agent
      - >8-10 micrograms/kg/min is in the alpha effect of the drug and can increase pulmonary artery pressure as a side effect
      - You can attempt dobutamine/dopamine combo to keep dopamine <10 mcg/kg/ml
   4. Epinephrine:
      - Alpha & beta adrenergic inotropic agent
      - 0.1 to 0.5 mcg/kg/min, can transiently titrate up to 1 mcg/kg/min – discuss maximum

dose with attending
- Increases myocardial oxygen requirements, heart rate, and myocardial contractions; increases systemic vascular resistance, increasing blood flow to skeletal muscles, brain, liver, and myocardium; decreases renal blood flow by 40%

5. Isuprel:
   - B_1 B_2 inotropic/chronotropic effect with peripheral vasodilation
   - Must be able to increase cardiac output or you may get decreased BP due to drop in peripheral vascular resistance
   - Tachycardia in the newborn is a common event and may limit its use
6. Milrinone:
   - Selective phosphodiesterase III inhibitor
   - Positive ionotropic effect – increases cardiac output
   - Vasodilator, both pulmonary and systemic
   - Use should be only be after discussion with the attending

C. Respiratory management

Always reevaluate the patient on a daily basis to determine if PPHN is still a factor in the disease state. Most infants resolve their PPHN by 5 days of age. <u>All attempts to not hyperventilate should be taken</u>. Patients referred from another institution with low pCO_2s need to be managed carefully with pCO_2s increased gradually to not cause an acute hypoxic event (fellow/attending should be involved in blood gas management).

1. Blood Gases:
   a. PaO_2 - 50-80 torr
   b. Pulse oximetry:
      - Pre-ductal sats 88-95
      - Pre and post ductal pulse oximetry measurement should be done to determine shunting at the duct level

   a. $PaCO_2$ - 40-55 torr
      - $PaCO_2$'s < 35 should be avoided $PaCO_2$'s in the 20 torr range have been associated with high-frequency hearing loss & lung injury.

   c. pH - pH 7.28- 7.35
2. Measurement of metabolic status
   a. Lactate levels – monitor at least q4hrs; combined with marginal saturations &/or blood pressure stability, a rising lactate is an indication for need for ECMO
   b. Cerebral NIRS – continuous monitor – if <60 on maximal therapy, consider ECMO
3. <u>Nitric oxide (iNO)</u> should be used when PPHN has been diagnosed (see iNO protocol)
   a. The use of iNO has to be approved by the Attending Physician
   b. Start dose: 20ppm
   c. Methemoglobin (Met Hb) must be measured every 4 hours until stable, then daily while on iNO
   d. Rebound PPHN can occur with weaning; weaning should be discussed with the Neonatal Fellow or Attending.
4. <u>Air leak:</u> Always be alert for air leak

5. Daily Management:
   a. Day 1-2: <u>Only make one change at a time</u>, i.e., one of the following:
      - decrease pO_2 by 1-2 torr only
      - decrease IMV by 2 only
      - decrease pressure limit by 1 (cmH_2O)

- Note: PL effects both T_V and MAP, i.e., ventilation and oxygenation, so if chest movement is not indicating over ventilation after finding optimal PL, do not change PL for the first 24 hours.
- Always evaluate for over distension especially after 24-48 hrs as lung compliance may have improve; decrease PL or MAP (HFOV) if this is occurring
- If rebound occurs with iNO wean, try increasing the FiO_2 back to 100% and wean slowly over several hours.

b. Days 5-10:
- primary disease may be parenchymal lung disease and not PPHN, so attempt to maximize "gentle ventilation" methods
- increase pCO_2 to 45-60 range

c. At any point:
- if all therapeutic attempts do not increase pO_2 then consult the ECMO team

PPHN OF THE NEWBORN (PPHN): MANAGEMENT APPROACH TO PROMOTE PULMONARY VASODILATION AND IMPROVE PULMONARY BLOOD FLOW

GOAL	METHOD
Vasodilate Pulmonary Vascular Bed	
Oxygenation	PaO_2 50-80, Post ductal; Pre-ductal sats 88-95
Ventilation	$PaCO_2$ 40-55 range
Metabolic alkalosis	No longer recommended
Vasodilator Therapy	*iNO - Start 20ppm MetHg should be monitored q 4hr, then daily
Maintain adequate systemic blood pressure	Administer pressors, dopamine, epinephrine as needed in addition to volume; hydrocortisone if not responding to pressor support

D. When To Consider ECMO:
1. After maximal therapy has been achieved and the PaO_2, is<50 torr with pre-ductal sats <85 for 2-3 hrs
2. Cerebral saturations (NIRS) <60 for 2-3 hours on maximal therapy
3. Raising lactates combined with marginal oxygenation
4. Worsening $AaDO_2$ or Oxygen Index (OI)
   a. AaDO2's of 610 - 620
      $AaD0_2$ = Barometric Pressure-47-$PaC0_2$-$Pa0_2$, when $Fi0_2$ = 1.0
   b. OI >40
      OI = Mean airway pressure x $FIO_2 \div PaO_2$ x 100

ECMO CRITERIA
1. Weight greater than 2 kg.
2. ≤ 10-14 days of assisted ventilation
3. Reversible lung disease
4. No severe IVH (>grade II)
5. Failure of maximal medical management

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FAMILY CENTERED CARE &
COMMUNICATION WITH PARENTS

I. PARENTING TIME & VISITATION GUIDELINES

A. Parents are encouraged to be at their baby's bedside 24/7 or as they are able and there are no restrictions on visitation for parents in the NICU. Parents are also encouraged to be on morning rounds. If a parent is on rounds, the focus of the discussion should include the parent when appropriate. Parents are also encouraged to stay at their infant's bedside during routine procedures in order to provide support to their child.

B. Parents may bring family members and close friends to visit their infant. Only 3 people will be allowed at the bedside at a time, due to space issues. Parents may assign up to six designated visitors who can visit independent of the parents. Designated visitors cannot bring in other visitors. The charge nurse can show you the location of the book containing information on designated visitors. Obviously only the parents should be given clinical information. Visiting hours for everyone except the parents are the same as the general hospital visiting hours, 10:00 a.m. - 8:00 p.m.

C. Siblings
   1. 3 years old or greater: siblings may visit under adult supervision until 8 pm for up to 30 minutes at the discretion of the nursing staff. They may not be left alone in a patient's room or in the waiting rooms at any time. For the protection of all NICU infants, an Infectious Disease Form must be filled out and a nurse will take a brief medical history (such as temperature, and/or history of recent contact with contagious disease) to determine the safety and eligibility of sibling entrance into the unit.
   2. < 3 years: siblings may be allowed under special circumstances, when prearranged with staff, and for limited periods of time, e.g., 5-10 minutes. Discuss this with the social worker &/or charge nurse if a parent asks for permission to bring in a younger sibling. Siblings visiting must be free of illness and wash their hands appropriately. The NICU has a Child Life Specialist who may be consulted to help families communicate with siblings struggling with a hospitalization or specific diagnosis and/or to help prepare a sibling for a visit.

D. When an infant is dying, exceptions to the above rules appropriate to the circumstances should be made.

E. It is our goal to provide a "family centered" environment, so exceptions to all of the above rules can be made with the agreement of the social worker involved, the attending, and charge nurse.

F. Telephone information: For security reasons, the parents will be told that they must give the last 4 numbers of the medical record number (CH) as an identifier. Do not give information to anyone who cannot give you these numbers.

II. NICU FAMILY CENTERED CARE PROGRAM

A. The Program

The NICU has collaborated with the March of Dimes NICU Family Support program to develop a Family Centered Care program. In addition to the social work support, we have a dedicated NICU Family Support Specialist who will be working with our staff to make the NICU experience for our families as positive as possible. The Program has instituted the following:

1. Parent presence on rounds
2. Expanded sibling visitation and sibling support
3. Bi-Monthly scrap booking for families
4. Expanded bereavement support
5. Weekly Mom's support group with NICU Family Support and Lactation Nurse
6. Monthly support for Dads and Grandfathers from a NICU Graduate Dad
7. A Parent Care Kit with supportive and educational materials is provided to parents of all infants and is specific to the projected length of stay of the baby. There is a bag for a LOS expected to be less than 14 days and one for a LOS greater than 14 days. The bag has information about Children's National Health System resources, the NICU, the staff, and disease states. The book can be updated as the infant's condition changes, so information about certain new diseases may be added during hospitalization, e.g., HMD, NEC, ROP, etc.
8. A keepsake journal, parenting resources, and other educational materials are also provided to all parents.
9. Photography – a NICU Parent volunteer will come in periodically to take pictures of the infant to give to the parents as keepsakes. You may see these on the isolette at certain times.
10. A parent–to-parent support system. Parents whose children have graduated from the NICU and have been specially trained volunteer to talk to parents in the NICU setting to give support, etc. This list is kept as a diagnoses specific list, so parents with an infant with a specific disease state can talk to a parent who has had a child with that disease state.

B. Communication

1. Communication with parents:
   Communication between parents and support of staff members within the NICU is essential. We encourage parents to be on rounds so they can hear our plans, but many cannot make it to rounds because of work schedules. It is your duty to get to know your parents, keep them updated on what is going on with their infant. ***Most parents want to know about acute changes in their infants, even in the middle of the night***. They also need to know if we are considering transfer to another unit or back-transfer to the referring hospital. Key procedures to let them know about are: septic workup, you do not have to get separate permission in the NICU for LP, but parents need to know that the infant is sick enough to have a septic w/u and an LP; intubation; cardiac arrest; and any other event that is life-threatening.

   If you have any difficulty communicating with parents, do not hesitate to call a fellow or attending. When a child has died, it is ultimately the Attendings' responsibility to let a parent know, to obtain autopsy permission and to see that proper plans are made for the infant. However, if you feel comfortable, you may speak with the parents alone, after talking with an attending.

2. Communication with referring physicians and private pediatricians:
   Both referring physicians and private pediatricians want to hear about their infants. It is your responsibility to communicate information to both the parents and the referring or

follow-up physician.

III. SOCIAL WORK ASSESSMENT

All patients and parents will have an initial social work assessment. After this assessment the Social Worker will make a plan for continued assessment and support. Social Worker will remain involved with the family for the duration of your patient's stay.

Families are assessed and handled according to priorities. The cases receiving higher priorities include:

1. Parents of critically ill or dying babies
2. Parents whose baby is significantly ill, physically or neurologically
3. Parents with a history of mental illness or who have complicated social situations
4. Parents who are alleged drug abusers or otherwise require child protection involvement.

Some departments, including cardiology, neurosurgery, etc., have their own social workers and they appreciate being notified if one of their patients' needs to be assessed. In the NICU, our Social Workers further support families by establishing multi-disciplinary meetings between specialists, and also screen mothers for post-partum depression and anxiety disorders.

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METABOLIC BONE DISEASE OF PREMATURITY

I. GENERAL INFORMATION

Also known as osteopenia, metabolic bone disease (MBD) of prematurity, has generally been declining as nutritional support of premature infants has improved. Nonetheless, MBD remains a significant cause of morbidity in premature infants.

II. RISK FACTORS

A. Prematurity, gender (male), gestational age and birthweight

B. Long term need for TPN

C. Vitamin D deficiency

D. Inability to feed

E. Immobility including secondary to sedation

F. Lack of exposure to sunlight

G. Use of medications affecting bone mineralization:
   1. Phenobarbital
   2. Lasix
   3. Steroids
   4. Aluminum containing medications (albumin)

III. ASSESSMENT

Clinical evidence of MBD generally presents between 6 and 12 weeks of age. Clinical signs may include poor weight gain/growth failure, respiratory disease due to poor chest wall compliance, rickets and or fractures.
Diagnosis remains challenging as there is a paucity of sensitive and specific screening tests. Currently, diagnosis is based on primarily on radiologic findings along with serum markers.

A. Serum calcium: may remain normal until very late in disease

B. Serum phosphate: low levels (< 3mg/dL) are highly specific, but not sensitive

C. Low inorganic phosphate (<1.8mmol/L) AND elevated alkaline phosphatase (>900 international units/L) may be more sensitive and specific
   a. Elevations in alkaline phosphatase alone may be seen in additional comorbidities of liver and intenstine, as well as in transient hyperphosphatasia of infancy

D. Vitamin D (1,25 di-hydroxy vitamin D): elevated

IV. MANAGEMENT

A. OT consult for mobilization

B. Ability to feed and discontinue TPN

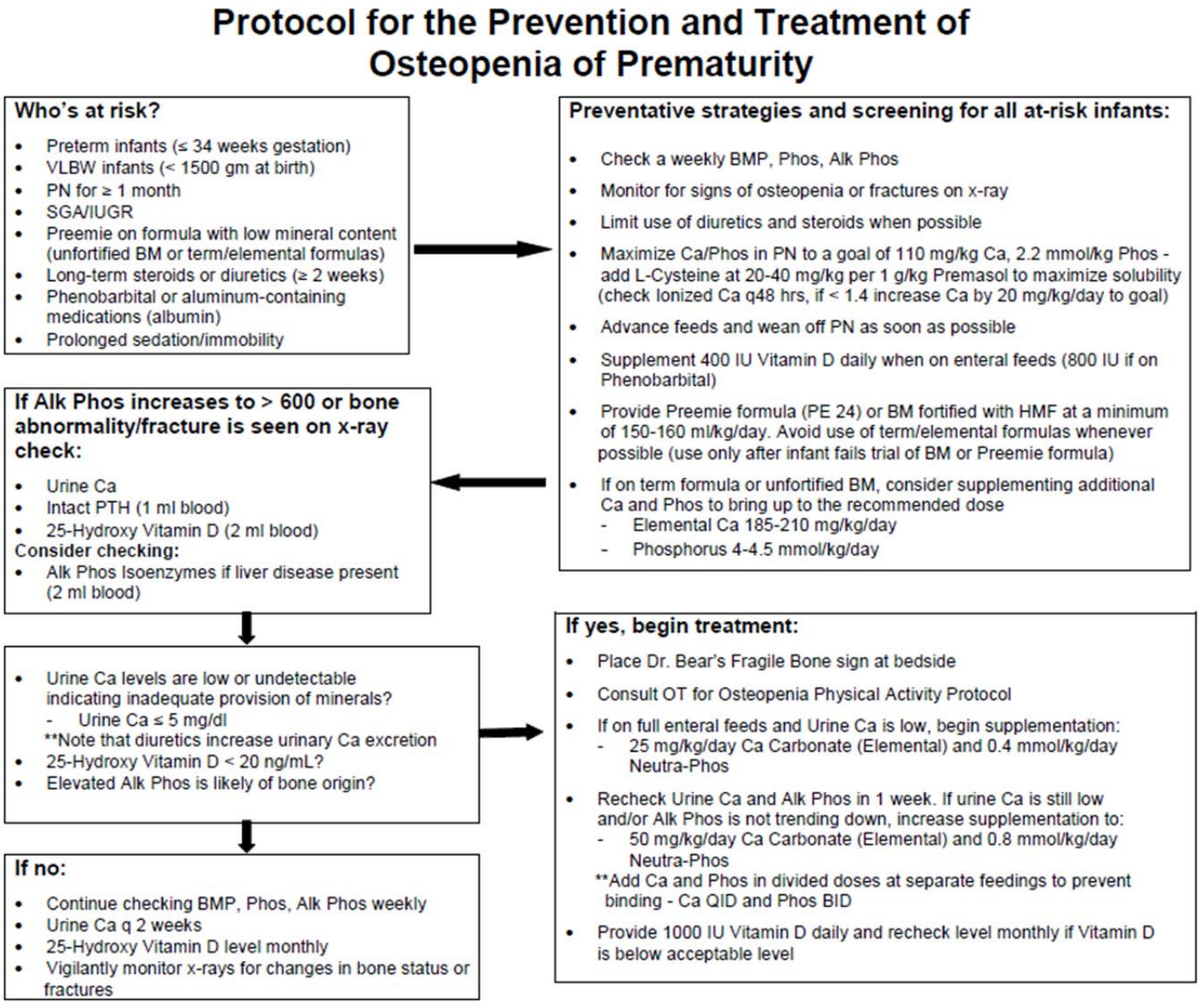
C. Limiting use of medications that affect bone mineralization (Lasix, Phenobarbital, steroids)

D. Checking serum 25-Hydroxy Vitamin D levels to determine need to supplement

E. Check Alk Phos isoenzyme fractionation when > 1000

F. Keep serum Ca 10-11 mg/dl and serum Phos 6-7 mg/dl

G. Maintain appropriate calcium: phosphorus ratio in TPN



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NUTRITION

I. GENERAL INFORMATION

The goals of nutrition are to provide adequate fluid, calories, protein, vitamins, minerals and trace elements to support growth that mimics intrauterine growth rate and preserve the integrity and function of the GI tract. Administration of nutrition should also avoid abnormalities in fluid, electrolyte and nutrition status, and to use parenteral nutrition judiciously while promoting safe, effective and efficient use of enteral nutrition.

II. NUTRITIONAL ASSESSMENT AND MONITORING

Parameter	Measure	Responsibility
Weight	Sunday, Tuesday, Friday	Nursing
Length and head circumference	Sunday night	Nursing
Plotting growth on growth chart	Daily	Dietitian
Estimated intake based on feeding order	Daily	Dietitian
Actual 24-hour Intake	Daily	Resident/LIP
Laboratory values	Monday: Large TPN set Thursday: Small TPN set PRN labs as discussed on rounds	Resident/LIP

Adequacy of the nutrition support regime is best measured by monitoring appropriateness of growth. The medical team evaluates parameters together and makes decisions regarding nutrition support based on the above data. Appropriateness of growth will be discussed on rounds weekly.

A. Expected weight gain

< 2 kg: 15-20 g/kg/day
> 2kg: 20-35 g/day

B. Measured and estimated weights

Birth weight is used for the first 7-10 days or until birth weight is regained. If a patient is edematous, an “estimated dry weight” rather than actual weight should be used. This estimated weight should be discussed on rounds and adjusted at least every Monday for dosing both nutrition support and medications. Estimated dry weight can be modified weekly by finding an estimated weight on the infant’s growth curve. If an infant is too unstable to be expected to grow during a specified week, estimated dry weight will not be adjusted.

C. Estimated calorie & protein needs

Enteral

	Preterm	Term
Kcal	110-130 kcal/kg	100-120 kcal/kg
Protein	3.5-4.5 g/kg	1.5-2.5 g/kg

Parenteral

	Preterm	Term
Kcal	85-95 kcal/kg	80-90 kcal/kg
Protein	3.5-4 g/kg	2.5-3 g/kg

Combined Enteral + Parenteral

	Preterm	Term
Kcal	100-120 kcal/kg	90-110 kcal/kg
Protein	3.5-4.5 g/kg	2-3 g/kg

III. FLUIDS

Fluid needs are affected by gestational age, postnatal age, sources of radiant heat, use of bilirubin lights, ambient humidity, nursing practices and clinical condition of the patient. Writing a fluid prescription requires knowledge of maintenance fluid needs and evaluation of current fluid balance for each patient. While goals of hydration and nutrition are interrelated, they are separate entities and should be evaluated as such. Fluid requirements and provisions should be discussed on rounds with the medical team. (For more information, please refer to FLUID AND ELECTROLYTE MANAGEMENT)

IV. ENTERAL NUTRITION

The provision of enteral nutrition promotes maturation of intestinal motor activity in preterm infants, as well as increases circulating gut peptides and reduces risk of infection (1). Lack of enteral intake leads to reduced enterocyte turnover, decreased bile acid secretion and an impaired intestinal epithelium. Early enteral nutrition does not increase the risk of NEC. However, late initiation of feeding is significantly associated with more cholestatic jaundice, longer duration of parenteral nutrition, greater hospital costs, and greater degree of postnatal growth restriction at discharge (2,3,4). Benefits associated with early feedings include fewer days on parenteral nutrition, decreased risk of sepsis, decreased need for central access, shortened time to full feeds and decreased length of hospitalization. However, rapid advancement of feeds (greater than 40ml/kg/day) and use of hyperosmotic formulas (greater than 450 mOsm/kg H_2O) have been associated with NEC (4,5). Judicious monitoring of clinical status should occur while initiating and advancing feeds.

A. Indications for enteral feeds
   1. If medically stable, initiate feeds within the first 24 hours of life
   2. Feed as soon as it is medically feasible
   3. Evaluation of ability to feed should be discussed daily on rounds
   4. Indications for feeding include: presence of bowel sounds, lack of abdominal distension, stable blood pressure, stable electrolytes (electrolyte abnormalities affect gastric motility), stable respiratory status, functional GI tract, patient medically stable enough to feed

B. Absolute contraindications for feeding
   1. NEC/Ileus/Obstruction
   2. Symptomatic sepsis
   3. Severe/unstable hypotension

4. Use of pressors with unstable blood pressure
5. Significant hypoxemic/asphyxia event/acidosis
6. Presence of symptomatic PDA
7. Significant electrolyte abnormalities
8. Bile- or blood-stained aspirates

C. Potential Contraindications for Feeding*
   1. Use of Indomethacin
   2. Use of pressors with stable blood pressure
   3. Presence of UAC

   *While literature may not support holding feedings in these situations, evaluate clinical status of patient and discuss ability to feed with the medical team before starting feeds. Practice may vary.

D. Feeding Choice
   Mother's breast milk (MBM) is the feeding of choice for all infants. If MBM is not available or medically appropriate to use, pasteurized donor human milk (DBM) can be provided to infants who meet criteria once maternal consent is obtained. Mother's milk and/or donor milk should be fortified for preterm infants and infants with IUGR who were born less than 2-2.5 kg.

E. Donor Breast Milk (DBM)
   1. Usage criteria:
      a. Infants ≤ 1500 grams at birth and/or ≤ 30 weeks gestation
         Continue until 34 weeks CGA or until tolerance of full feeds are established for 1 week
      b. Infants > 1500 grams with a history of NEC, abdominal wall defects, bowel resection/short bowel syndrome, or infants with significant feeding intolerance with formula
         Continue until full feeds are established for 1 week
   2. Written consent for donor milk will be obtained by the LIP, preferably on admission. An information sheet should be provided at time of consent. Consent may be obtained from the <u>mother only</u> and phone consent will be accepted if she is unable to be present. Once consent is obtained, a donor milk diet order can be entered into Cerner. An infant cannot be transferred to another unit or be discharged home on donor milk. At that time, the infant should be weaned from donor milk to an appropriate formula. Any symptoms of illness or changes in the infant's clinical status that may be related to donor milk should be reported to the attending physician and the dietitians.

F. Formula & Fortifiers
   Infants who do not meet the above criteria for DBM and do not have mother's breast milk available should be initiated on feeds with an age-appropriate formula.
   Standard term infant formulas do not meet the nutrient needs of premature infants. In the event that the use of a hydrolyzed protein or free amino acid product is deemed necessary due to protein allergy or malabsorption, consult the dietitian for nutrient evaluation.
   Soy formulas are not to be used in the premature population due to the phytic acid and aluminum content, which decreases the bioavailability of calcium and other minerals,

thereby increasing risk of bone disease. Also, soy formulas do not meet the protein, vitamin, and mineral needs of premature infants. (For more information, please see APPENDIX A: Formulas and Fortifiers)

	Infants born <2200 grams	Infants born > 2200 grams
Breast Milk	Fortify with 1 vial HMF per 50 ml breast milk when feeds reach 80 ml/kg (22 kcal/oz). Fortify with 1 vial HMF per 25 ml breast milk when feeds reach 100 ml/kg (24 calorie/oz)	Fortify with 1 vial HMF per 50 ml breast milk when feeds reach 80 ml/kg (22 kcal/oz) OR Supplement with preterm discharge formula. At discharge, d/c HMF and provide supplemental preterm discharge formula.
Formula	Enfamil Premature High Protein formula (24 kcal/oz)	Preterm discharge formula (22 kcal/oz): Enfamil Enfacare Similac Neosure

*HMF: Human Milk Fortifier

V. INITIATING AND ADVANCING ENTERAL FEEDS

A. Trophic feeding

Also known as minimal enteral nutrition, gut priming or hypocaloric feeding, trophic feeding refers to the provision of small volumes of enteral substrate in an attempt to stimulate gastric motility, function, and maturation. Use of trophic feedings have been shown to reduce number of days to full feeds, reduce days on TPN, decrease cholestasis, improve growth, reduce incidence of sepsis, and allow for earlier discharge than NPO counterparts .

Enteral feedings should begin as soon as an infant is medically stable enough to feed. Most recent literature suggests use of 10-24 ml/kg/d of full strength breast milk or premature infant formula and feeding every three hours (3,6,7).

Optimal duration of trophic feeds varies per infant. See chart below for the standardized feeding initiation and advancement protocol. If an infant is showing signs of feeding intolerance, stop or extend length of time that trophic feeds are used until ready to advance feeds.

B. Indications for use of trophic feeds:
1. Preemies < 1500 grams
2. Babies recovering from NEC
3. Babies who have been NPO for an extended period of time

C. Feeding Advancement

Faster advancements (30-35 ml/kg) of enteral volumes may have a protective effect for low birth weight infants. Benefits include reduced length on parenteral nutrition, earlier establishment of full enteral nutrition by 1-5 days, faster time to regaining birth weight and reduced risk for invasive infection. Feeding advancements of 30-35 ml/kg have no statistically significant differences on NEC rates and all-cause mortality when compared

to slow feeding advancements (15-24 ml/kg/day) in very low birth weight infants (4,8). There is limited information available on the appropriate feeding advancement for extremely preterm infants, extremely low birth weight infants, and growth restricted infants.

CNHS Standardized feeding protocol

Weight	***Trophic feeding***	***Daily advancement***
≤750 grams	10-20 ml/kg/day x 5 days	20 ml/kg/day
751-1000 grams	20 ml/kg/day x 4 days	20 ml/kg/day
1001-1250 grams	20 ml/kg/day x 3 days	20-30 ml/kg/day
1251-1500 grams	20 ml/kg/day x 2 days	20-30 ml/kg/day
1501-2000 grams	20 ml/kg/day x 1 day	20-30 ml/kg/day

1. Feedings should be advanced based on the current weight
2. Infants NPO for ≤48 hours may resume feeds at the volume/strength last tolerated
3. Infants s/p NEC may benefit from trophic feeds for 2-5 days before advancing
4. Adjust volume of feeds and/or caloric density of feeds as needed to promote growth

D. Assessing feeding tolerance

Assessing infants for feeding tolerance involves evaluation of the GI tract in relation to the overall clinical status of the patient. Signs of feeding intolerance include abnormal increase in abdominal circumference, bloody stools, acidosis, bloody or bilious residual volume, vomiting and diarrhea. Feedings should be held if there is adequate clinical evidence that there is a feeding-related issue.

Checking gastric residuals as a sign of feeding intolerance in preterm infants is not supported by evidence (9). Do not check for large volume residuals (10). Gastric residuals up to 2x or more of the hourly feeding volume (or 50% of bolus feed volume) may be normal when receiving full feeds or while feeds are advancing to goal, and may be larger than trophic feeding volume. Ultimately, the goal of checking gastric residuals is to check color, consistency and for blood, not to check volume. Always re-feed if residual is normal in appearance because residuals contain partially digested nutrients, functional enzymes and protective stomach acid. Although not statistically significant, when infants are re-fed residuals compared to all fresh milk feeds, they reach full feeds 1.3 days faster and have reduced risk for spontaneous intestinal perforation, surgical necrotizing enterocolitis, or death (11).

Gastric residuals should not be the only reason feedings are stopped. If gastric residuals are concerning and there is an abnormal GI exam, stop feedings. A clinical assessment must be completed to rule out signs of feeding intolerance and intestinal damage.

Delayed gastric emptying is characteristic in premature infants and is often referred to as “feeding intolerance”. Delayed emptying may manifest as constipation with an increase in abdominal circumference. The buildup of stool in the GI tract creates an environment that favors bacterial overgrowth which is associated with the development of NEC. Appropriateness of stool output should be evaluated daily. Delayed gastric emptying may also be characterized by an increase in gastric residual volume. The presence of small residual volumes is normal and should not lead to automatic discontinuation of feedings.

E. Monitoring for feeding intolerance

Before stopping feeds, refer to the most updated feeding tolerance algorithm and assess entire clinical picture. No infant should be made NPO without an MD, NNP, or PA examining the infant.

1. Assess clinical picture:
   - Abdominal distention or tenderness
   - Bowel sounds
   - Stooling pattern (constipation delays gastric emptying)
   - Abdominal x-ray
   - Gastric residual color and consistency
   - Emesis
   - Temperature instability
   - Hypotension

2. Stop feeds*:*
   - Exam worrisome for NEC
   - Aspiration event
   - Frequent/severe emesis
   - Bile stained gastric residuals or emesis
   - Severe apnea/bradycardia
   - Severe acidosis/thrombocytopenia

VI. METHOD OF FEEDING

A. Oral feeds

Within the first 30 minutes of life, full term infants show signs of oral feeding readiness such as mouthing, sucking, and hand to mouth activities. Early and late preterm infants, on the other hand, have poor coordination between sucking, swallowing and breathing. Thus, enteral feedings are provided via gastric tube until PO skills can mature. Attempt oral feedings when the infant is corrected to a gestational age of 34 weeks and has stable respiratory status (12).

B. Continuous vs. intermittent feeds

It has been shown that continuous feeds of breast milk can lead to a reduction in calorie content of feedings and an increased risk for poor weight gain. Specifically, continuous feeds (because of the extended interaction with tubing) results in an average loss of 40% of fat, 33% of calcium, and 20% of phosphorus (13).

It is recommended to provide intermittent feeds every 3 hours, 8 times per day for infants who can tolerate bolus feeds. According to current research, there is not sufficient evidence to promote feeding every 2 hours rather than every 3 hours. When comparing feeding frequency, more frequent feedings did not increase feeding tolerance or decrease incidence of apnea, NEC, or hypoglycemia. Moreover, nursing satisfaction and quality of care can decrease as time spent on feeding increases (14).

Intermittent feeds are more physiologic than continuous feeds and are not associated with increased risk for NEC or other negative clinical outcomes when compared to other modes of feeding. However, bolus feeds may increase respiratory distress or GERD in some infants. Method of feeding should be evaluated with the medical team in light of current clinical status of each patient (15).

C. Feeding strategy

1. Attempt intermittent feeds first if deemed medically feasible.

2. Avoid discontinuing feeds if intermittent feeds fail; instead, attempt continuous feeds. Continuous feeds may be better tolerated in infants with respiratory distress/malabsorption or significant reflux.
3. If continuous feeds are started, goal would be to eventually transition back to intermittent feeds.
4. Transpyloric feedings must be given via continuous drip. Consider limiting concentration of feeds to 24-26 kcal/oz given risk of dumping and high ostomy output.

VII. ENTERAL VITAMIN AND MINERAL SUPPLEMENTATION

Supplemental vitamins and minerals are recommended throughout the first year of life. In particular, vitamin D deficiency is common, and increases with decreasing GA. Check Vitamin D levels monthly for infants at risk for deficiency. Increase supplementation with D-vi-sol (25-hydroxy-vitamin D) if vitamin D deficient (<20 ng/ml) or insufficient (20-35 ng/ml). If deficient/insufficient, supplement D-vi-sol at 1000 international units per day. Once vitamin D level is sufficient, decrease to 400 international units per day.

Recommended Supplementation

	Premature Infants	**Term Infants**
Breast Milk	<2kg: 200 international units (0.5 ml) of cholecalciferol while on HMF or PE24 >2kg: 400 international units (1ml) cholecalciferol while on HMF or PE24 Mostly unfortified breastmilk or breast milk enriched with powder: 1 ml Poly-vi-sol w/iron	400 international units of cholecalciferol (1 ml D-vi-sol)
PE 24, 27, 30	< 2 kg: 200 international units cholecalciferol > 2 kg: 400 international units cholecalciferol	n/a
Preterm Discharge formula	1 ml Poly-vi-sol *May include iron if indicated by H/H	n/a
Term formula	1 ml Poly-vi-sol *May include iron if indicated by H/H	400 international units of cholecalciferol. Discontinue when formula intake >1L/day
Infants with cholestasis (D Bili >2)	< 2kg = 1 ml AquADEK divided BID > 2kg = 1 ml AquADEK	1 ml AquADEK

VIII. ORAL IMMUNE THERAPY

Emerging evidence has supported the administration of human milk directly onto the oral mucosa with the expectation that cytokines and other immune agents will be absorbed through the buccal cavity and provides protection against infection as well as protection of the GI tract

(16,17). To be eligible to receive oral immune therapy an infant must be:

A. NPO

B. Have *fresh* breast milk available (only 0.2 ml of breast milk is needed)

C. Have an order for "Oral Immune Therapy", ordered for all infants with mouth care

IX. PARENTERAL NUTRITION

The use of parenteral nutrition (PN) allows for early provision of nutrients to premature babies while enteral feedings are being initiated and advanced to goal rates. It takes 7-14 days to reach feeding "goal" with infants who have no feeding tolerance issues. Full parenteral nutrition can be delayed up to 3 days for term infants, but during this time period they require dextrose-containing fluids. It is also important to keep in mind that PN is a medication and is associated with its own risks such as increased risk for infection, fluid and electrolyte abnormalities, blood glucose problems, acidemia, and cholestasis/liver failure. Once feeds are providing 100-120 ml/kg, PN should be discontinued and dextrose-containing IV fluids can be ordered to meet fluid needs until feeds are at goal.

A. Starter PN

All infants <1800 g at birth should receive Starter PN immediately on admission. It is intended to provide protein to infants soon after birth to avoid negative nitrogen balance. Starter PN can also be ordered for older preterm infants transferred to the unit as a bridge until full TPN can be initiated. Starter PN is ordered through Cerner ("Neonatal Starter PN") and Pharmacy keeps a total of 3 bags on hand at all times.

Starter PN is standardized to run at 60 ml/kg/day via a central or peripheral line and should only be ordered at this rate. When ordering, you will need to calculate the rate per hour (ml/hr) based on the patient's weight so that it provides the appropriate volume.

The starter PN bag contains:
- 7.5% Dextrose
- 5% Protein
- 50mg Elemental Ca/100ml

When run at 60ml/kg/day, this provides:
- GIR of 3.1mg/kg/min*
- 3 g/kg Protein
- 30 mg/kg Elemental Ca

*Additional D10% will need to be run at a minimum of 15-20 ml/kg/day to bring the GIR up to the minimum of 4 mg/kg/min. If the baby becomes hyper- or hypoglycemic while receiving Starter PN, please make adjustments to the additional IVF rather than the Starter PN if possible (18).

B. Initiation and Advancement of PN

Preterm

	Initiation	**Advance**	**Goal**
Dextrose	4-6 mg/kg/min	1-2 mg/kg/min	11-15 mg/kg/min
Lipid	0.5-1 g/kg	0.5-1 g/kg	3 g/kg (maximum)
Protein	3-4 g/kg	1 g/kg	3.5-4 g/kg

Term

	Initiation	Advance	Goal
Dextrose	6 mg/kg/min	1-2 mg/kg/min	10 mg/kg/min
Lipid	1-2 g/kg	1 g/kg	3 g/kg (maximum)
Protein	2.5-3 g/kg		2.5-3 g/kg

- Do not provide a GIR <4 mg/kg/min as this is "basal" need for brain function.
- Hyperglycemia (a blood sugar greater than 180 mg/dl) occurs frequently in very low birth weight infants, particularly in the first few days of life. Unexpected hyperglycemia may be a sign of sepsis in the infant on a stable glucose infusion rate. Hyperglycemia can result in hyperosmolality and hyperosmotic diuresis. Do not let blood sugar levels exceed 150-190 mg/dl. Following guidelines for initiation and advancement of glucose infusion rate will assist in the prevention of hyperglycemia
- The use of insulin is recommended to control blood sugars that are consistently > 150 mg/dl over restricting of dextrose provision from PN. Infants require dextrose as a primary energy source. Please refer to the insulin protocol for use of insulin in the NICU.
- Check triglyceride level 24 hours after initiation of lipid and with each advancement.
    - D/C lipids x 24 hours for triglycerides >300 mg/dl
    - Decrease lipid infusion by 0.5-1 g/kg for triglycerides >200 mg/dl but <300 mg/dl
    - Do not withhold lipids completely for >48-72 hours secondary to risk for essential fatty acid deficiency (19). In setting of persistent hypertriglyceridemia, minimum IV lipid intake of 0.5-1 g/kg/day is necessary to prevent essential fatty acid deficiency (20).

Electrolytes

	Initiate	Adjust	Needs
Sodium	0-2 mEq/kg	1-2 mEq/kg	1-6 mEq/kg
Potassium	0-1 mEq/kg	0.5-1 mEq/kg	1-6 mEq/kg
Magnesium	0.1-0.3 mEq/kg (if <1.7)	0.05-0.1 mEq/kg	0.2-0.4 mEq/kg
Chloride:Acetate	As needed to maintain normal acid-base balance		

Calcium:Phosphorus

	Initiate	Adjust	Goal
Calcium	30-50 mg/kg	10-20 mg/kg/d keeping Ionized Calcium <1.4. Ionized Calcium levels should be checked daily while advancing calcium infusion until stable	**Preterm:** 100 mg/kg **Term:** As needed
Phos	0.8-1 mmol/kg	Adjust with calcium to keep in ratio	**Preterm:** 2.5 mmol/kg **Term:** As needed

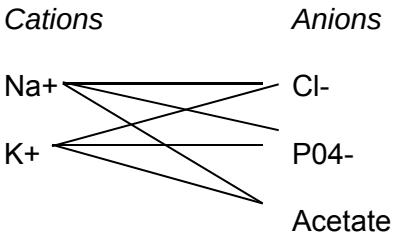
Ratio: needs to be considered daily while on TPN since it affects bone mineralization.

Ca	40	50	60	70	80	90	100
Phos	1	1.25	1.5	1.75	2	2.25	2.5

Ideal Calcium:Phos Ratio
Preterm: 1.6-1.7 calcium to 1 phosphorus
Term: 1 calcium to 1 phosphorus
**May not attain ideal ratio if correcting abnormal calcium or phosphorus levels.*

Calculating Ca:Phos ratio:
Desired Calcium ÷ 30 ÷ desired ratio = amount of phosphorus to prescribe
Desired Phosphorus x 30 x desired ratio = amount of Calcium to prescribe

C. Balancing ions and acid-base balance



Anions and cations must balance in the PN solution.
For every 1 mEq of Sodium you can add 1 mEq of Cl- or Acetate
For every 1 mEq of Potassium you can add 1 mEq of Cl- or Acetate

*Metabolic Acidosis: Add more acetate to PN and less chloride
*Metabolic Alkalosis: Add more chloride to PN and less acetate

Discuss provision of chloride/acetate to PN in the management of metabolic alkalosis/acidosis on rounds. In some cases the treatment of the cause of the metabolic derangement is required to treat the alkalosis/acidosis rather than an adjustment in the PN. These decisions should be made as a team on rounds. Adjustment of chloride/acetate in PN does not help correct respiratory acidosis/alkalosis.

Acetate: Premasol, the amino acid infusion used in neonates, is an acidic compound. Current literature suggests that provision of IV Amino Acid will not cause or worsen acidosis. It is advisable to consider the provision of at least 1 mEq/kg of acetate in the management of metabolic acidosis.

Ammonium Chloride: Ammonium Chloride may be used as a supplement for patients with significant metabolic alkalosis. When ammonium chloride dissociates, it increases acidity by increasing free hydrogen ion concentration which combines with bicarbonate ion to form CO_2 and water. The net result is the replacement of bicarbonate ions by chloride ions.

1. To adjust acid/base in Baxa
   At the top of the PN program there is an “Ions” tab. Your options are:
   - Minimize chloride (this will “maximize acetate”)
   - Minimize acetate (this will “maximize chloride”)
   - Chloride float. Enter amount of acetate you want and the computer will automatically match the remaining cations with chloride

- Acetate float. Enter the amount of chloride that you want and the computer will automatically match the remaining cations with acetate.

If you are providing maintenance amounts of cations, you will be providing maintenance amounts of anion. When there is a need to exceed maintenance amounts of sodium and potassium, keep an eye on the amount of chloride and acetate you are providing as excessive amounts of either can affect acid/base balance.

D. Vitamins (MVI)
< 2.5 kg: 2 ml/kg/day
> 2.5 kg: 5 ml/day

Vitamin Preparation per 5 ml

Vitamin A	2300 USP units
Vitamin D	400 USP units
Vitamin E	7 USP units
Vitamin C	80 mg
Thiamine	1.2 mg
Riboflavin	1.4 mg
Niacinamide	17 mg
Pyridoxine	1 mg
Folate	140 mcg
B12	1 mcg
Pantothenic	5 mg
Biotin	20 mcg
Vitamin K1	200 mcg

E. Trace elements
Special considerations regarding trace elements for patients with hepatobiliary or renal disease.

1. Cholestasis (DBili > 3mg/dl):
   Standard trace elements (MTE-4 or Peditrace) should be discontinued from TPN when a patient has cholestasis (Direct Bili > 2 mg/dl) as manganese is excreted via the hepato-biliary system and may accumulate and become toxic if supplemented (6).
   a. Adjust TPN:
      i. Discontinue MTE-4 and Peditrace
      ii. Copper: add 20 mcg/kg/day for all patients (6,21)
      iii. Selenium: add 2 mcg/kg/day if not already provided
      iv. Zinc: add 400mcg/kg/day if weight < 2.5 kg
          add 250mcg/kg/day if weight >2.5kg
      v. Intralipid: limit to 1 gm/kg/day or consider Omegaven if available
   b. Monitor levels regularly:
      i. Check serum copper monthly
         Normal range: 30-40mcg/dL (preterm) 12-67 mcg/dL (term)
      ii. Check ceruloplasmin levels monthly.
         Normal range for ceruloplasmin is 5-18 mg/dL.
      iii. Adjust TPN as needed
         If low, increase copper in TPN to 30 mcg/kg/day (can increase to 40 mcg/kg/day if persistently low)

If high decrease to 10 mcg/kg/day and/or omit.

2. Renal disease:
   a. When an infant's creatinine is >1 mg/dL, discontinue MTE-4 (and selenium) or Peditrace to limit provision of chromium, molybdenum, and selenium. Add back when renal function improves (or per clinical judgment if renal failure continues >2 weeks) (7).
   b. High-output renal failure may require up to 600 mcg/kg/day zinc parenterally (7).

MTE-4 Ped

	Zinc (mcg/kg/day)	Copper (mcg/kg/day)	Chromium (mcg/kg/day)	Manganese (mcg/kg/day)	Selenium (mcg/kg/day)
Contents in 0.2 ml/kg/day	200	20	200	5	--
Add for patients <2.5 kg	200	--	--	--	2
Add for patients >2.5 kg	50	--	--	--	2

Peditrace

	Zinc (mcg/kg/day)	Copper (mcg/kg/day)	Manganese (mcg/kg/day)	Selenium (mcg/kg/day)	Fluorine (mg/kg/day)	Iodine (mg/kg/day)
Contents in 1 ml/kg/day	250	20	1	2	0.057	1
Add for patients <2.5 kg	150	--	--	--	--	--
Add for patients >2.5 kg	--	--	--	--	--	--

F. Solutions to common errors in TPN Baxa
   1. Maximum MVI peds
      a. The patient's weight increased beyond the 2.5kg cutoff in neonatal templates.
      b. Change "MVI peds" to per day instead of per kg, then change the dose to 5.
      c. Dose should read: MVI-Pediatric 5 mL/day
   2. No common sources for substID and secondaryID Phosphate.
      a. Increase K or Na in the order. Approximately 0.75 mmol Phos can be obtained per every 1 mEq K or Na.
      b. If Na must be limited, go to the Ions tab and uncheck the "Phosphate Source: Prefer Sodium over Potassium" box so that Baxa will use KPhos instead of NaPhos.
   3. Insufficient volume requested.
      a. The TPN order contains too many ingredients to fit in the TPN bag;
      b. Increase total fluid goal or decrease dextrose, protein, and/or calcium.
      c. If infant is advancing on feeds and feeds are 90-100 ml/kg/day, may not need to

write for TPN.

4. Hard Stop for Osmolarity Concentration (peripheral lines only).
    a. Reduce osmolarity by decreasing the amount of certain nutrients. Contributors to increased osmolarity include:
        i. Protein
        ii. Dextrose
        iii. Sodium
        iv. Potassium
        v. Calcium
    b. Increasing fluid goal and/or decreasing non-TPN volume can help reduce osmolarity.
    c. CNMC's maximum osmolarity is **900 mOsm/L**. Osmolarity of the TPN order can be found under "Order Information" on the right-hand side of the Baxa screen.
5. Calculated Ingredient Volume is too small. Sodium Chloride 23.4%.
    a. Increase sodium until error goes away.

G. Monitoring and laboratory assessment
1. Initating and advancing TPN:
    a. Daily glucose, triglycerides and BMP, Mg. Phos until stable values at goal
2. Ongoing TPN administration:
    a. Large TPN set (every Monday): LFT with direct bilirubin, BMP, Mg, Phos, ionized Cal and triglycerided
    b. Small TPN set (every Thursday): BMP, Mg, Phos
3. Additional considerations:
    a. Preterm infants with osteopenia may need regular Alkaline phosphatase levels (see osteopenia protocol)
    b. Unstable patients, patients with renal disease, significant fluid shifts or diuretics may need more frequent labs
    c. Infants with cholestasis may require regular direct bilirubin levels while transitioning to full enteral feeds until cholestasis resolves

X. PARENTERAL VITAMIN SUPPLEMENTATION

A. Vitamin A

Previous evidence has shown that Vitamin A given intramuscularly to the smallest infants will decrease the incidence and severity of BPD (22). CNHS protocol is to administer 5000 IU intramuscularly every Monday, Wednesday and Friday for the first month of life to infants < 1250 grams who require oxygen > 24 hours.

B. Iron

IV iron supplementation will be required for infants who have been TPN dependent for ≥ 4 months and/or are on Erythropoietin. If Erythropoietin is used, supplement Fe+++ 1mg/day (not per kg) for term infants or 0.1 mg/kg/day for preterm infants.

C. Albumin

The use of IV albumin to treat hypoalbuminemia is controversial (23). It is a colloid and is meant to be used as an oncotic agent, not a nutritional supplement. Guidelines for use in the NICU are:

1. < 1000 grams: 1 g/kg albumin x 3 days for level < 2 mg/dl. Discontinue when level > 2.5 mg/dl

2. Use albumin as a medication, not as a means to treat non-symptomatic hypoalbuminemia in infants > 1000 grams
3. When the use of albumin is indicated, it will be given as a separate infusion, not added to TPN solution

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NECROTIZING ENTEROCOLITIS

I. INTRODUCTION

Necrotizing enterocolitis (NEC) is a syndrome of acute intestinal necrosis and one of the most common gastrointestinal emergencies in the newborn infant. The etiology of NEC is unknown; however its pathogenesis is probably complex and multifactorial. The largest predisposing factor is prematurity. In reported clinical series, 62% to 94% of patients are premature.

The incidence is markedly increased in infants at lower gestational ages. Other predisposing factors include low birth weight, fetal distress, premature rupture of membranes, low Apgar scores, umbilical catheterization, and exchange transfusion. Hyperosmolar feeding has also been implicated. Although the incidence varies between 1-2/1000 live births, NEC may occur in 1-5% of all NICU admissions.

The most commonly affected areas of bowel are where the microcirculation is the poorest, the terminal ileum and cecum, which receive little primary blood supply and are fed by collateral circulation from both the superior and inferior mesenteric arteries.

II. RISK FACTORS

The available information supports the notion that the development of NEC involves multiple factors in the setting of a stressed gut with immature protective mechanisms. The primary initiator(s) of the disease remain unknown.

A. Perinatal
   1. Prematurity
   2. Perinatal asphyxia, especially in term infants
   3. Maternal cocaine usage
   4. Umbilical catheterization

B. Congenital
   1. PDA
   2. Cyanotic congenital heart disease, i.e. ductus dependent cardiac lesions on prostaglandin
   3. Congenital GI anomalies

C. Co-morbid disease
   1. Severe dehydration
   2. RDS
   3. Hypothermia
   4. Shock
   5. Hypoxia
   6. Polycythemia
   7. Thrombocytosis
   8. Anemia
   9. Exchange transfusion
   10. Chronic diarrhea

D. Other
   1. Naso-jejunal (NJ) feedings
   2. Hypertonic formula

III. CLINICAL PRESENTATION

Early diagnosis of NEC is the most important factor in determining outcome. This is accomplished by careful clinical observation for nonspecific signs in infants who are at risk to develop NEC. There is a broad spectrum of disease manifestation. The clinical feature of NEC can be divided into systemic and abdominal signs. Most infants have a combination of findings.

A. Systemic signs
   1. Respiratory distress
   2. Apnea and /or bradycardia
   3. Lethargy
   4. Temperature instability
   5. Irritability
   6. Poor feeding / Glucose instability
   7. Hypotension (shock) with and without signs of decreased perfusion
   8. Acidosis (metabolic / respiratory)
   9. Oliguria
   10. Bleeding diathesis / DIC

B. Abdominal and enteric signs
   1. Delayed gastric emptying (feeding residual)
   2. Abdominal distention
   3. Abdominal tenderness
   4. Vomiting (bilious or hematemesis or both)
   5. Ileus (decreased or absent bowel sounds)
   6. Abdominal wall erythema or induration
   7. Persistent localized abdominal mass
   8. Ascites
   9. Occult / Gross blood in stool

C. Laboratory and radiographic features
   1. Thrombocytopenia
   2. Leukocytosis/Leukopenia
   3. Persistent metabolic acidosis
   4. Hyponatremia
   5. Presence of blood and carbohydrate in stools (heme positive & reducing substance positive stools)
   6. On abdominal x-ray: presence of pneumatosis intestinalis, ileus, fixed or thickened loops of bowel, hepatic portal venous gas, ascites, and free intraperitoneal air
   7. On fluoroscopy (upper-GI series) with contrast: presence of gaseous blebs and slow motility
   8. On abdominal ultrasound: detection of micro bubbles of gas within the portal vein); not often done in clinical settings

IV. CLINICAL STAGING

A clinical staging system for NEC was devised by Bell et al:

A. Stage IA - Suspected NEC
   1. Systemic signs: Temperature instability, apnea, bradycardia, lethargy
   2. Intestinal signs: Elevated pre-gavage residuals, mild abdominal distension, emesis,

heme-positive stools
3. Radiologic signs: Normal or intestinal dilatation, mild ileus

B. Stage IB - Suspected NEC
1. Systemic signs: Same as stage IA
2. Intestinal signs: Bright red blood from rectum
3. Radiologic signs: Same as stage IA

C. Stage IIA - Definite NEC (mildly ill):
1. Systemic signs: Same as stage IA
2. Intestinal signs: Same as stage IA, plus absent bowel sounds, +/- abdominal tenderness
3. Radiologic signs: Intestinal dilatation, ileus, pneumatosis intestinalis

D. Stage IIB - Definite NEC (moderately ill)
1. Systemic signs: Same as stage IIA, plus mild metabolic acidosis, mild thrombocytopenia
2. Intestinal signs: Same as stage IIA, plus absent bowel sounds, definite abdominal tenderness, +/- abdominal cellulitis or right lower quadrant mass
3. Radiologic signs: Same as stage IIA plus portal vein gas, +/- ascites

E. Stage IIIA - Advanced NEC (severely ill, bowel intact)
1. Systemic signs: Same as stage IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, neutropenia
2. Intestinal signs: Same as stage IIB, plus signs of generalized peritonitis, marked tenderness, and distension of abdomen
3. Radiographic signs: Same as stage IIB, plus definite ascites

F. Stage IIIB - Advanced NEC (severely ill, bowel perforated)
1. Systemic signs: Same as stage IIIA
2. Intestinal signs: Same as IIIA
3. Radiologic signs: Same as stage IIB, plus pneumoperitoneum

V. DIAGNOSIS

Laboratory evaluation reflects signs of sepsis, including leukocytosis or leukopenia, thrombocytopenia, electrolyte imbalance, acidosis, hypoxia, and hypercarbia. Pneumatosis intestinalis, indicating air within the subserosal bowel wall, is the radiologic hallmark used to confirm the diagnosis of NEC. Pneumoperitoneum is indicative of intestinal perforation; however, the radiographic assessment of intestinal perforation is not always precise. Some infants will not show these specific radiographic findings. A large, distended, immobile, intestinal loop on repeated x-rays suggests a gangrenous loop of bowel. A gasless abdomen may indicate perforation and peritonitis.

VI. CLINICAL MANAGEMENT AND MEDICAL TREATMENT

A. General rules
1. Stop enteral feedings immediately. Support with intravenous fluids and nutrition
2. Initiate gastric drainage (appropriate-sized nasogastric tube should be placed for either free drainage or intermittent suction)
3. Obtain bacterial cultures (may include cultures for anaerobic organisms from the stool, blood, nasogastric aspirate, and cerebrospinal fluid). Lumbar puncture is optional depending in degree of illness and suspicion of meningitis.
4. Examination of stool for rotavirus, especially in seasons when it is common

5. Start broad spectrum antibiotics* (e.g. ampicillin, gentamicin & flagyl)
6. Test all stools for blood and Clinitest
7. Consider enteric isolation precaution in acute phase and during the first few days of antibiotic therapy.

B. Evaluate frequently (every 6-8 hours initially)
   1. Physical examination including abdominal girth to be done with cares
   2. Abdominal radiographs, including cross table or left lateral decubitus views if pneumatosis is present
   3. Serum electrolytes
   4. Arterial blood gases
   5. Complete blood count and platelets

C. Consider
   1. Clotting studies if bleeding develops
   2. Mechanical ventilation as required
   3. Cardiovascular support with volume expansion and low dose dopamine (3-5 μg/kg/min.) to optimize the effect on splanchnic and renal blood flow
   4. Umbilical artery catheter should be promptly removed
   5. Paracentesis if deterioration or abdominal erythema develops

D. Guidelines for use of antibiotics

***** Antibiotic therapy can be adjusted based on culture results but only 40% of blood cultures will be positive, necessitating continued broad spectrum coverage in most cases. Treatment is maintained for 7-14 days depending on the severity at the initial presentation. If an organism is cultured, decrease antibiotic coverage to be specific for the bacteria found. If no organism is found and the diagnosis of NEC is questionable, antibiotics may be stopped after three days. There is no evidence to suggest that enteral antibiotics play a role in the treatment of NEC except for clostridium species where oral vancomycin is recommended.

If Staphylococcus species are suspected, combination of vancomycin, gentamicin and flagyl should be chosen.

<u>Additional guidelines recently developed at CNHS for NEC</u>

1. Abdominal concerns as part of R/O sepsis
   Antibiotics/NPO for 48-72 hours pending culture results and clinical state.
2. Abdominal concerns as R/O NEC (X-rays no pneumatosis but signs of bowel wall thickening, feeding intolerance, etc.):
   Antibiotics/NPO 3 days pending cultures and clinical state.
3. NEC (pneumatosis on X-ray, +/- thrombocytopenia, no bloody stools, hemodynamically stable) with symptoms that clear quickly
   Antibiotics/NPO 5-7 days after first X-ray without pneumatosis and no further clinical signs of NEC.
4. NEC (pneumatosis, thrombocytopenia, +/- bloody stools, hypotension requiring therapy):
   Antibiotics/NPO for ~10 days. Continue antibiotics/NPO until pneumatosis and thrombocytopenia resolve. Treat 3-5 days beyond resolution.
5. Surgical NEC/bowel perforation with bowel resection (if remaining bowel is healthy):
   Antibiotics/NPO 7 days
6. Surgical NEC with residual unhealthy bowel:
   Antibiotics 10 days and reevaluate.
7. Drain placement for isolated bowel perforation:

Antibiotics while drain is in place plus 24 hours after removal.

VII. SURGICAL TRATMENT

Indications for surgery are commonly accepted to be as follows:

A. Highly specific indications
   1. Pneumoperitoneum
   2. Positive paracentesis
   3. Erythema on the abdominal wall
   4. Abdominal mass

B. Nonspecific supportive findings
   1. Abdominal tenderness
   2. Portal venous gas
   3. Persistent thrombocytopenia
   4. Progressive neutropenia
   5. Clinical deterioration
   6. Severe GI bleeding

Surgery consists of excision of affected loops of bowel with creation of proximal diversion and distal mucus fistula. Patients with extensive involvement of bowel may require a second look operation usually within 24-72 hours.

Use of peritoneal drainage under local anesthesia in selected infants with severe NEC to allow stabilization and later surgical intervention when required has been suggested. This seems to be beneficial only in infants <1000 grams under carefully selected instances and cannot be universally applied. Progressive sepsis after local drainage mandates laparotomy.

VIII. REFEEDING

A. General guidelines
   1. Completion of seven-ten days of antibiotic therapy
   2. Ensure normal abdominal x-ray
   3. Absence of acute clinical signs & symptoms of NEC

B. Schedule
   1. Maternal breast milk, donor breast milk or regular preterm formula can be used. A more elemental formula is not usually necessary.
   2. Volume and strength should not be increased simultaneously. Advance feeds over 10-14 days at a rate of 15 to 30 mL/Kg/day.
   3. Infants with ileostomy may have difficulty tolerating total feeds (watch ostomy output carefully when increasing enteral feedings).
   4. If ostomy output remains significant, electrolyte supplementation such as Na+, Ca++ and HCO3- may be required as their losses are usually significant with large outputs.

IX. PROGNOSIS

NEC is the most common cause of death in premature neonates undergoing abdominal surgery. The average mortality is 30% to 40%. Stricture formation occurs in 10% to 35% of survivors after either medical or surgical therapy. This can present as failure to thrive, feeding abnormalities, diarrhea, or moore classical bowel obstruction.

A. Late complications of NEC
   1. Stricture, adhesions.
   2. Fistula
   3. Abscess
   4. Recurrent NEC
   5. Short-gut syndrome
   6. Malabsorption
   7. Cholestasis
   8. Complications of TPN / central venous lines.

B. Long-term follow-up of infants with NEC

At discharge, many infants who have survived acute NEC remain at significant risk for under-nutrition, poor growth, recurrent illnesses, gastrointestinal complications, frequent re-hospitalizations, and questionable developmental outcome. The continuing morbidity highlights the importance of meticulous follow-up in infants surviving NEC.

Before an infant who survived NEC is discharged home, all current and anticipated medical and developmental concerns must be identified and communicated to the infant's parents or caregivers. For the infant with ongoing problems, the parents should have a working knowledge of the infant's problems and be comfortable and proficient in continuing all aspects of infant's care before discharge. Appropriate developmental intervention should be initiated while the infant is in the hospital.

Strictures are the most common long-term gastrointestinal complication of NEC, occurring in 10% to 35% of all survivors. Most arise in the distal defunctionalized bowel, typically in the large intestine, and result from healing and subsequent cicatrical scarring of an ischemic area of bowel that did not perforate. Although most become symptomatic during the initial hospitalization, some strictures may not become obvious for as long as 6 months after the acute incident, long after most NEC survivors are discharged. All strictures do not cause symptoms. There are many non-obstructing, "silent" strictures that are only identified during follow-up with contrast enema examinations. They are a common cause of persistent gastrointestinal bleeding after NEC. Survivors of NEC who have hematochezia or persistent melena should have a barium enema. Some strictures become obvious during follow-up with signs of lower bowel obstruction, which include crampy pain, distension, vomiting (not always bilious), and constipation. Bowel obstruction may occur suddenly and be associated with life-threatening sepsis or perforation.

If the infant had surgery for NEC, there is an additional risk for developing bowel obstruction secondary to adhesions. Bowel obstruction develops in at least 9% of patients who have had abdominal surgery for NEC. The risk for bowel obstruction owing to adhesions increases with more complicated surgical procedures. Parents of NEC survivors must be instructed about the signs of bowel obstruction.

Short-bowel syndrome is the most serious long-term gastrointestinal complication associated with NEC. The syndrome refers to malabsorption and under-nutrition after extensive bowel resection resulting from decreased absorptive surface area, enzyme depletion, and gut hypermotility. An important determinant of future gastrointestinal function is the absence or presence of the ileocecal valve, regardless of the length of the intestine resected. More than 50% of the small bowel generally must be removed before substantial malabsorption occurs. The jejunum is the primary site for carbohydrate digestion and absorption. However, resection

of the jejunum is well tolerated because of the remarkable ability of the ileum to adapt and compensate for jejunal function. Ileal resection is more poorly tolerated, because the ileum contains most active of the transport sites for nutrient absorption, particularly for fat, intrinsic-factor bound vitamin B12, and conjugated bile salts. With ileal resection, rapid bowel transit occurs, especially if the ileocecal valve has been removed. The ileocecal valve is normally a physiologic barrier that prolongs the intestinal transit time. The colon provides a major absorptive surface for water and in neonates serves as a salvage pathway to rescue carbohydrates. The severity of diarrhea is affected by the amount of colon that remains.

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NEONATAL JAUNDICE

I. GENERAL INFORMATION

Neonatal jaundice designates all situations in the newborn in which the total serum bilirubin (TSB) is sufficiently elevated to cause visible yellowing of the skin, ocular sclera, or both (usually with serum bilirubin > 5mg/dl). Hyperbilirubinemia in healthy term newborns is defined as TSB ≥ 12 mg/dl at 25 t0 48 hours of age, TSB ≥ 15 mg/dl at 49-72 hours of age or TSB ≥ 17 at 72+ hours of age. Severe hyperbilirubinemia is defined as TSB ≥ 20 mg/dl in the first 30 days of life. Neonatal jaundice is estimated to occur in 60% of term newborns in the first week of life, and approximately 2% reach TSB ≥ 20 mg/dl. The TSB normally rises over the first 3 to 5 days and then declines. Physiologic jaundice occurs as a result of reduced red cell life span, altered transport and metabolism of bilirubin in the liver, and increased enterohepatic circulation of bilirubin. The "classic" pattern of physiologic jaundice is described by a regular rise in bilirubin from 1.5mg/dl in cord serum to 5-6mg/dl on the third day of life, followed by a decline to normal levels by the 10-12th day of life (this pattern is usually exaggerated in Asian infants). The severity and pattern of physiologic jaundice can be further altered by breast-feeding, with two different phenomena being recognized: breast-feeding jaundice and breast-milk jaundice.

Breast-feeding jaundice can occur in the first week of life, resulting primarily from dehydration and nutritional inadequacy (relative starvation). Breast-milk jaundice (late-onset) begins in the fifth or sixth day of life, peaks in the 2nd or 3rd week, and may persist at moderately high levels for 3-4 weeks before declining slowly. It is a diagnosis of exclusion. In an otherwise well infant, it is considered a benign condition. If feeding with breast-milk is stopped, the serum bilirubin usually falls, however this is rarely indicated, as the potential harms of stopping breast feeding often outweigh any risks of a mild to moderate hyperbilirubinemia. The etiology of breast-milk jaundice is unknown, but there is some support for both a hormonal factor in the milk acting on the infant's hepatic metabolism, and an enzyme (lipase) facilitating intestinal absorption of bilirubin.

II. PATTERNS OF NEONATAL JAUNDICE

Disease or pathology that can increase bilirubin production or alter the transport/metabolism of bilirubin, causing increasing jaundice includes maternal race, gestational age, and exclusive or partial breastfeeding. The onset of clinical jaundice with TSB > 8 mg/dl within the first 24 hours of life and/or an hourly rate of rise in serum bilirubin of > 0.5mg/dl strongly suggests the possibility of increased bilirubin production (i.e., hemolytic disease). Although serum bilirubin levels of 20-26mg/dl can be explained by physiologic jaundice, pathologic disorders must be ruled out before drawing this conclusion. Conjugated bilirubin (direct fraction >10% of total serum bilirubin) suggests that hepatobiliary disease or a metabolic disorder must be ruled out. In this era of early discharge from the hospital it is helpful to note that a bilirubin level ≥ 5mg/dl within the first 24 hours or ≥ 10mg/dl within the first 48 hours of life is highly predictive of bilirubin >17 mg/dl by the 4th or 6th day of life. (Figure 1)

Figure 1:

Preterm birth increases the duration and intensity of physiologic jaundice. Peak bilirubin concentrations may not be reached until the 4th or 5th day of life, with mean peak bilirubin concentrations being approximately twice those of healthy, mature infants. Preterm infants are at increased risk for bilirubin toxicity because of the greater frequency with which they suffer from sepsis, shock, hypoxia, respiratory acidosis and intracranial hemorrhage, all of which are believed to facilitate entry of bilirubin into the central nervous system.

III. BILIRUBIN TOXICITY: ENCEPHALOPATHY AND KERNICTERUS

Encephalopathy or kernicterus describes the clinical neuropathologic observations resulting from bilirubin toxicity to the central nervous system. Brain pathology is characterized by neuronal death and pigment deposition in the brain, particularly in the regions of the basal ganglia and cerebellum. Bilirubin encephalopathy can range from early, mild disease (lethargy, altered muscle tone, poor feeding) to severe disease (opisthotonos, seizures, and death). Late and permanent manifestations of neonatal bilirubin toxicity can range from mild motor dysfunction to choreoathetoid cerebral palsy, hearing loss, dental dysplasia and paralysis of upward gaze.

A. Factors influencing risk of kernicterus:
    1. Reduced albumin - binding capacity
        a. prematurity
        b. asphyxia
        c. acidosis
        d. hypoalbuminemia
        e. infection

    2. Competition for binding sites
        a. hemolysis
        b. NEFA
        c. cold stress
        d. starvation
        e. hypoglycemia
        f. drugs, i.e. sulfonamides, salicylates, diazepam

    3. Increased cell susceptibility to bilirubin toxicity
        a. asphyxia
        b. hypoglycemia

The approach to determining the toxic level of bilirubin is based on the assumption that albumin-bound bilirubin cannot enter the brain, blocked by the blood-brain barrier. Free bilirubin, presumed to be lipid soluble, would have free access to the brain and be considered the toxic fraction.

IV. EVALUATION & TREATMENT OF INDIRECT HYPERBILIRUBINEMIA

A. Evaluation and special considerations

Although recent approaches to the management of neonatal jaundice have become relatively liberal, jaundice in the newborn continues to be a problem that needs to be taken seriously, particularly if there is evidence of hemolytic disease (remember that hemolysis may not be clinically detectable in G-6PD and other red cell enzyme deficiency states) or genetic risk factors. No jaundice should be dismissed as physiologic without a review of the maternal and infant history and thorough examination of the infant. For example, unexplained hyperbilirubinemia may be the only manifestation of sepsis urinary tract infection in an otherwise healthy-appearing newborn.

Initial work-up should include determination of the infant's blood group, a Coombs test, together with a complete blood count (including a smear for morphology), reticulocyte count, and a fractionated (direct and indirect) bilirubin level.

Inherited defects of erythrocyte metabolism, membrane function, and hemoglobin synthesis may all manifest in the newborn period. Baseline screening for glucose 6-phosphate dehydrogenase (G-6PD) deficiency is imperative if there is evidence of unexplained hyperbilirubinemia in an infant of a high-risk population. The erythrocyte has a metabolic system that can prevent oxidative metabolism; absence of G-6PD is inherited as a sex-linked recessive disorder, with Asian, Middle Eastern, Mediterranean, African American infants being particularly at risk. However, with the increased incidence of interracial marriages ethnic risk factors may be more difficult to determine. Newborns have a diminished ability to deal with oxidative stress; as a result, newborns with G-6PD deficiency are at increased risk for the development of hemolytic anemia, however, *in most cases, hemoglobin and reticulocyte counts are normal* and there is new data to indicate that an associated deficiency of bilirubin conjugation by the liver may be a more important factor producing hyperbilirubinemia in those infants. G-6PD deficiency is most severe and frequent in the male infant, although female infants may also be affected.

B. Treatment

1. Phototherapy

   Phototherapy is considered effective in reducing serum bilirubin concentrations when used optimally. Total bilirubin levels are used for all recommendations, and direct-reacting bilirubin fractions are not subtracted from the total. Recommendations for use of phototherapy vary depending upon the infant's clinical status, and whether there is concurrent illness i.e., sepsis (Table 1). Indications for use of phototherapy will also be increased in the infant with Rh or ABO incompatibility, particularly if there is a rapid rate of rise in total serum bilirubin. Any infant with bilirubin level of >25 mg/dL within the first week of life should be considered a candidate for exchange transfusion if unresponsive to intense phototherapy. (Figure 2)

   a. Guidelines for phototherapy

      i. Basic work-up should include: smear, H/H, type and coombs, fractionated bilirubin
      ii. Check bilirubin every 6-8 hours until it levels off.
      iii. Recheck bilirubin every 12-24 hours after phototherapy is discontinued until bilirubin is showing steady downward trend.

iv. Between 10 and 20 percent additional fluid to the usual requirements should be given to compensate for the increased insensible water loss. Oral feeding is preferable when possible to increase stooling and prevent the reabsorption of bilirubin from the bowel.

b. Side effects of phototherapy
   i. Increased insensible water loss
   ii. GI effects: watery diarrhea and increased fecal water loss
   iii. Decrease in serum calcium levels in preterm infants have been described
   iv. Retinal damage has been described in animals exposed to phototherapy. The eyes should be shielded with eye patches during phototherapy.
   v. Skin: Tanning of the skin, erythema and increased skin blood flow, and "bronze baby" syndrome in infants with direct hyperbilirubinemia.
   vi. Cell damage: Effects in tissue culture cells exposed to phototherapy have been seen. These include mutations and DNA strand breaks. It may be wise to shield the scrotum during phototherapy
   vii. Tryptophan, methionine, histidine, vitamin A and riboflavin are reduced in HAL solutions when exposed to phototherapy therefore the solution should be shielded from phototherapy by using brown bags.
   viii. Effect of phototherapy on growth and head circumference has been described in some studies but not in others.
   ix. Phototherapy may upset maternal-infant interaction and should be used with adequate thought and explanation.
   x. No significant long-term developmental differences have been found in infants treated with phototherapy as compared with controls.

Table 1:
Figure 2:

2. Fluids
   More frequent feedings, either breast or formula, may be appropriate initial management for the healthy jaundiced infant, provided that pathologic jaundice has been ruled out. Intravenous fluid supplement may also become necessary in the infant with jaundice *and* dehydration (extra fluid will not help a non-dehydrated infant and may reduce caloric intake inappropriately). Supportive, knowledgeable personnel should be available to counsel the breast-feeding mother. In the case of the healthy infant with breast-feeding or breast-milk jaundice, in whom other underlying causes have been excluded, treatment options should not be considered until the serum bilirubin level approaches 17 mg/dl, unless the infant is significantly dehydrated.

3. Management Options for Jaundiced Breastfed Infants

a. Continue observation
b. Continue breastfeeding; administer phototherapy
c. Supplement breastfeeding with formula, with or without phototherapy
d. Interrupt breastfeeding temporarily; substitute formula
e. Interrupt breastfeeding temporarily; substitute formula; administer phototherapy

4. Phototherapy Guidelines in Low Birth Weight Infants
   Treatment thresholds are lower in low birth weight infants (Table 3).

Table 3:

The AAP has provided guidelines for prevention and management of hyperbilirubinemia in newborns of ≥35 weeks' gestation. There are currently no guidelines for treating hyperbilirubinemia in patients <35 weeks' gestation by AAP but they have been developed by other international health care systems. As a result of a recent QI project by Drs. Massa and Alsofrom a new guideline has been established which recommends at Children's National Neonatal Intensive Care Unit to initiate phototherapy at 5 ml/dl/kg (5 x birth weight) in infants < 35 weeks. To reduce the variation in treatment of hyperbilirubinemia in our ELBW and VLBW infants we recommend the following:

a. Guidelines for patients < 1500 grams or <35 weeks GA:
   i. Obtain a bilirubin level upon admission if the patient is under 1 week of life and there is ABO/Rh incompatibility, and/or extensive bruising
   ii. Obtain a bilirubin level by 12 hours of life if patient is <12 hours old at admission
   iii. Initiate phototherapy if bilirubin level is greater than 5 ml/dl/kg or if the patient has bruising on physical exam or ABO/Rh incompatibility.

5. Summary
   In summary, phototherapy is primarily used in preterm infants or term newborns that are ill or at risk for having hemolysis with the primary goal being to prevent exchange transfusion. Light causes bilirubin to be photoisomerized into four isomers of bilirubin, which are non-toxic; they diffuse into the blood and are excreted into bile. Begin when indirect bilirubin is approximately half of exchange index. "Prophylactic" use of bili lights in premature infants is discouraged because of increased insensible water loss while under lights, although the bili blanket is not associated with this risk.

V. EXCHANGE TRANSFUSIONS

Any infant should be considered a candidate for exchange transfusion regardless of clinical status, time of onset of jaundice or bilirubin level if clinical signs suggest bilirubin encephalopathy (poor feeding, increased lethargy, apnea, etc). Remember that impending bilirubin encephalopathy constitutes an emergency. Use of uncrossmatched blood may be considered (see below). Early

onset of clinical jaundice and a rapid rise in serum bilirubin concentration should raise concern regarding the existence of possible hemolytic disease, which could increase the risk for bilirubin encephalopathy (see indications below). Any infant who has had hyperbilirubinemia severe enough to warrant an exchange transfusion should be screened early for possible hearing loss (BAER), preferably prior to discharge.

A. Indications for early exchange transfusion
    1. Presence of hydrops in a known sensitized infant

    2. Hemolytic disease with:
        a. Cord bilirubin > 4.5 mg/dl and Hg < 11 mg/dl
        b. Bilirubin increasing > 1 mg/dl/hr despite phototherapy
        c. Hg 11-13 mg/dl and bilirubin rising > 0.5 mg/dl despite phototherapy

    3. If none of the other indications pertain exchange level must be individualized after considering factors such as state of health, gestation, and other risk factors for bilirubin encephalopathy after discussion with the attending/fellow.

    4. Infants < 1 week of age with bilirubin level > 25 mg/dL should be considered and prepared for exchange transfusion if fail to respond to intensive phototherapy and hydration.

B. Orders and procedure
    1. Type of blood-depends on indication for exchange transfusion
        a. Washed packed RBC's in FFP (Hct 50-60)
        b. Packed whole blood (Hct 50-60)
        c. For non-sensitized infant: use specific type and Rh; may use uncrossmatched O negative blood in acute emergencies
        d. For Rh sensitized infant use type specific Rh negative blood; May use low (A,B) titer O-negative blood or O-negative cells and AB negative plasma
        e. For ABO sensitized infant use O Rh specific cells and AB plasma or low (A,B) titer O Rh specific whole blood

    2. Preparation of blood
        a. Warm blood using a coil and an approved blood warmer; Do not warm blood under warmer or in sink or pan of warm water.
        b. Mix blood in bag frequently during exchange.

    3. Amount
        a. Attempt 2 volume exchange.
        b. Wt. in kg x 80 cc/kg x 2 = 2 volume exchange
        c. Exchange in 5-10-20 cc increments depending on infant size.

d. Increment should be less than 5% of total blood volume of infant. Watch for end of donor blood so infant is not left in negative balance.

4. Time
   a. Exchange should take place in no less than 60 minutes to optimize decrease in bilirubin level and avoid rapid changes in cardiovascular status
   b. Flow should always be easy and continuous
   c. Pressure should not be exerted while either removing or injecting blood.

5. Route
   a. Use UA catheter if already in place.
   b. Otherwise, in large infant, place a UV catheter, preferably across ductus venosus in the IVC.
   c. The catheter is placed under sterile conditions with gloves and gowns and hair restrained.
   d. In VLBW infants both UA or peripheral arterial line and UV catheter or large venous cutdown line for simultaneous exchange of blood may be used to avoid massive volume and pressure shifts.
   e. Blood is withdrawn through the arterial line and replaced through the venous line.
   f. If two line access cannot be achieved, exchange blood in smaller aliquots.

6. General care
   a. Place the infant on warmer with monitor.
   b. Many babies will vomit during exchange. If possible keep NPO prior to exchange. Aspirate stomach prior to exchange and leave NG tube in place. May feed after exchange as soon as stable, usually 1-2 hours.
   c. Oxygen dependent babies may need an increased FiO_2 during exchange.
   d. If sick baby, be sure glucose, electrolytes, Ca, and blood gases are normal before starting the exchange transfusion.
   e. Giving calcium during exchange is no longer indicated routinely.
   f. Post exchange -- type and cross in case of need for additional exchange, check H/H, bilirubin, Ca, Na and K, follow blood glucose every half hour for 3 hours.
   g. Check for bilirubin rebound in 4-6 hours.
   h. Antibiotics are not given for exchange alone. (Remember that exchange may alter blood levels of vital drugs and make appropriate therapeutic adjustments).
   i. Be aware that in a sick and unstable infant, an exchange transfusion can be a very stressful procedure, causing bradycardia, tachycardia, hypotension and metabolic acidosis.

C. Potential complications

1. Vascular - embolization hemorrhagic infarction
2. Metabolic - K, and Ca, and Mg, and glucose, Mg, acidosis
3. Cardiac - arrhythmias,cardiac arrest, volume overload
4. Clotting defects - thrombocytopenia
5. Infection - bacteremia, hepatitis
6. GI - NEC
7. Misc - blood incompatibility, hypothermia
8. Mortality: 1%

D. Additional treatments to abort rising bilirubin
   1. Be sure baby is stooling.
   2. Feed as soon as possible.
   3. Keep well hydrated: watch rising specific gravities; should be low if infant is well hydrated.

E. Additional considerations

   In the presence of persistent unexplained hyperbilirubinemia with the continuing need for exchange transfusion, consider the diagnosis of intraventricular hemorrhage or other location for sequestered hemorrhage.

VI. DIRECT HYPERBILIRUBINEMIA

A. Causes
   1. Obstructive cholestasis
      a. Biliary atresia
      b. Congenital bile duct anomalies (choledochal cysts)
      c. Cholelithiasis
      d. Alagille syndrome

   2. Hepatocellular cholestasis
      a. Hepatitis (hepatitis A, hepatitis B, hepatitis C)
      b. Alpha1-antitrypsin deficiency
      c. Inborn errors of bile acid synthesis
      d. Drug-induced cholestasis
      e. Total parenteral nutrition (TPN)–associated cholestasis

B. Treatment
   1. Directed towards correcting underlying cause of jaundice.

   2. Cholestasis often does not respond to medical therapy of any sort.

   3. Some reports indicate success in children with chronic cholestatic diseases with the use of ursodeoxycholic acid, which acts to increase bile formation and antagonizes the effect of hydrophobic bile acids on biological membranes.

4. Phenobarbital may also be useful in some children with chronic cholestasis.

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WELCOME TO THE NEWBORN INTENSIVE CARE UNIT

We want your time with us to be an educational experience, so we encourage open communication and welcome constructive comments about the rotation.

The enclosed NICU policies, procedures and protocols are guidelines, since therapy may change faster than revisions are revised. Please do not hesitate to ask questions of the fellows, Attendings, staff, NNPs/PAs, clinical coordinators, primary nurses and respiratory therapists.

I. PARENTING TIME & VISITATION GUIDELINES

A. *Parents are encouraged to be at their baby's bedside 24/7 or as they are able and there are no restrictions on visitation for parents in the NICU.* Parents are also encouraged to be on morning rounds. If a parent is on rounds, the focus of the discussion should include the parent when appropriate. Parents are also encouraged to stay at their infant's bedside during routine procedures in order to provide support to their child.

B. Parents may bring family members and close friends to visit their infant. Only 3 people will be allowed at the bedside at a time, due to space. Parents may assign up to 6 designated visitors who can visit independent of the parents. Designated visitors cannot bring in other visitors. The charge nurse can show you the location of the book containing information on designated visitors. Obviously only the parents should be given clinical information, unless a written authorization signed by the parents is in the medical record. Visiting hours for everyone except the parents are the same as the general hospital visiting hours, 10:00 a.m. - 8:00 p.m.

   Telephone information: For security reasons, the parents will be told that they must give the last 4 numbers of the medical record number (CH) as an identifier. Do not give information to anyone who cannot give you these numbers

C. Siblings of the patient, who are at least 3 years old, may visit under adult supervision until 8 pm for up to 30 minutes at the discretion of the nursing staff. They may not be left alone in a patient's room or in the waiting rooms at any time. For the protection of all NICU infants, an Infectious Disease Form must be filled out and a nurse will take a brief medical history (such as temperature, and/or history of recent contact with contagious disease) to determine the safety and eligibility of sibling entrance into the unit.

   Siblings younger than 3 years may be allowed under special circumstances, when prearranged with staff, and for limited periods of time, e.g., 5-10 minutes. Discuss this with the social worker &/or charge nurse if a parent asks for permission to bring in a younger sibling. Siblings visiting must be free of illness and wash their hands appropriately. The NICU has a Child Life Specialist who may be consulted to help families communicate with siblings struggling with a hospitalization or specific diagnosis and/or to help prepare a sibling for a visit.

D. When an infant is dying, exceptions to the above rules appropriate to the circumstances should be made.

E. It is our goal to provide a "family centered" environment, so exceptions to all of the above rules can be made with the agreement of the social worker involved, the Attending, and charge nurse.

II. NICU FAMILY CENTERED CARE PROGRAM

The NICU has collaborated with the March of Dimes NICU Family Support program to develop a Family Centered Care program. In addition to the social work support, we have a dedicated NICU Family Support Specialist who will be working with our staff to make the NICU experience for our families as positive as possible. The Program has instituted the following:

- Parent presence on rounds
- Expanded sibling visitation and sibling support
- A Parent Care Kit with supportive and educational materials for parents of all infants and is specific to the projected length of stay of the baby. There is a bag for a LOS expected to be less than 14 days and one for a LOS greater than 14 days. The bag has information about Children's National Health System resources, the NICU, the staff, and disease states. The book can be updated as the infant's condition changes, so information about certain new diseases may be added during hospitalization, e.g., HMD, NEC, ROP, etc.
- A keepsake journal, parenting resources, and other educational
- Photography – a NICU Parent volunteer will come in periodically to take pictures of the infant to give to the parents as keepsakes. You may see these on the isolette at certain times.
- A parent–to-parent support system. Parents whose children have graduated from the NICU and have been specially trained volunteer to talk to parents in the NICU setting to give support, etc. This list is kept as a diagnosis specific list, so parents with an infant with a specific disease state can talk to a parent who has had a child with that disease state.
- Bi-Monthly scrap booking for families
- Expanded bereavement support
- Weekly Mom's support group with NICU Family Support and Lactation Nurse
- Monthly support for Dads and Grandfathers from a NICU Graduate Dad

III. COMMUNICATION WITH PARENTS

Communication with parents and support of staff members within the NICU is essential. Both referring physicians, including obstetricians and maternal-fetal medicine specialists, and private pediatricians want to hear about their infants. It is your responsibility to communicate information to both the parents and the referring or follow-up physician.

We encourage parents to be on rounds so they can hear our plans, but many cannot make it to rounds because of work schedules. It is your duty to get to know your parents, keep them updated on what is going on with their infant*. Most parents want to know about acute changes in their infants, even in the middle of the night.* They also need to know if we are considering transfer to another unit or back-transfer to the referring hospital. Key procedures to let them know about are: septic evaluation (you do not have to get separate permission in the NICU for lumbar puncture but parents need to know that the infant is sick enough to have a septic evaluation and a lumbar puncture), intubation; cardiac arrest; and any other event that is life-threatening.

If you have any difficulty communicating with parents, do not hesitate to call a fellow or Attending.

When a child has died, it is ultimately the Attendings' responsibility to let a parent know, to obtain autopsy permission and to see that proper plans are made for the infant. However, if you feel comfortable, you may speak with the parents alone, after talking with an Attending.

IV. CONSENT FOR NICU PROCEDURES

So you do not have to get permission for every procedure done to the baby, e.g., lumbar punctures, intubation, central lines, etc. the NICU has a global consent form for procedures routinely done in an intensive care setting. This form describes that their baby may need to be evaluated for sepsis, including lumbar puncture, that when placing IV, sometimes the head is used, and that the hair may need to be shaved (this is a crisis for some parents), etc. A separate consent for blood products is also included with each admission. *These consents must be obtained within 72 hours of admission.* If blood products are required before then, these consents must be obtained prior to administration. It is your job to go over this consent with your parent(s). Please ask your fellow/Attending if you have any questions regarding the procedures included in the consent forms. Blood cannot be ordered unless this consent is signed. A blood product information sheet is attached to the consent, so give the parents a copy of the consent with this information after they sign it.

V. SOCIAL WORK ASSESSMENT

All patients will have an initial social work assessment. After this assessment the Social Worker will make a plan for continued assessment and support. Social Worker will remain involved with the family for the duration of your patient's stay.

Families are assessed and handled according to priorities. The cases receiving higher priorities include:

1. Parents of critically ill or dying babies
2. Parents whose baby has a grave prognosis
3. Parents with a history of mental illness or who have complicated social situations
4. Parents who are alleged drug abusers or otherwise require child protection involvement.

Some departments, including cardiology, neurosurgery, etc., have their own social workers and they appreciate being notified if one of their patients' needs to be assessed. Often, the NICU social workers can provide these updates as needed.

VI. TRANSPORT

Transport calls are directed to the Fellow's Ascom phone. If the Fellow is tied up in a procedure, the transport RN should be called to take the call. In some instances that person is also out on a transport, so if the resident takes the call, remember the following:

A. We accept all referrals, so take key information, name of patient, name and contact number of referring physician, referring hospital, reason for transfer, and tell them someone will call them back shortly but that we will accept the infant. Notify the charge RN & Transport RN. The Attending is the only one who can make the decision to not take a patient. This decision has to be taken to the medical administrator on-call by the NICU Attending prior to a denial occurring. After the contact information has been collected by the resident, the fellow will call back to get all information and give an estimated time of arrival.
B. Non emergent transfers require preauthorization. During business hours, it is important to alert the case manager so that preauthorization for the admission can be obtained before the baby arrives.

C. Rapid Transport: for high risk deliveries, the transport team *may* be dispatched prior the birth of the infant, in order to collect necessary signatures and consents prior to delivery, and minimize transfers (from L&D to OSH NICU to transporter). The majority of rapid transports are identified by the Fetal Medicine team and designated a level 2R or level 3 delivery. Under select circumstances, the transport team may be dispatched in a similar manner for an extremely pre-term delivery at a hospital without neonatology support (e.g., 23 week infant being born at a level 1 nursery). Other than the known Fetal Level 2R deliveries, additional rapid transports can only be authorized by the Attending, in conjunction with the transport team.

INHALED NITRIC OXIDE (iNO)

I. GENERAL INFORMATION

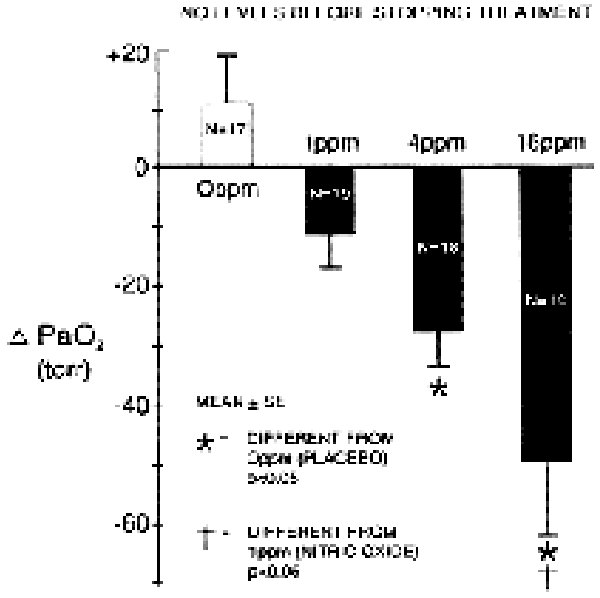
Nitric Oxide is a potent vasodilator that plays a major role in maintenance of vascular tone in all blood vessels. Because it is a highly active molecule (has an extra electron, like an oxygen radical), it has other functions in the body, such as its role as a bactericidal agent in white cells and has a very acute effect on platelet adhesion. Because of its vasodilating properties, it is used therapeutically for pulmonary hypertension. Nitric oxide is a gas, and therefore can be placed into the ventilator circuit (inhaled nitric oxide, iNO) to be delivered into the lungs. In the lungs it causes the pulmonary vessels to dilate. It is then deactivated by the red cells in the blood, so it is unusual to see any systemic side effects. This binding to RBCs causes the formation of methemoglobin, which can be toxic. One should follow the trend changes, but if the methemoglobin level exceeds 5%, then iNO needs to be decreased or stopped. Another byproduct formed when using iNO is nitrogen dioxide (NO_2), which is very toxic. Levels of iNO and NO_2 are measured continuously using the NO monitoring devise. Any level of NO_2 >5 ppm can be lethal. Most levels are <1ppm while on iNO.

II. USE

Studies in term/near term newborns have shown that about 25-30% of infants with PPHN can be kept off ECMO with iNO therapy. In both the NINOS and the Clarke Trial *(NEJM, 342(7): 469-474, 2000),* iNO was started when the oxygen index (OI) was 25. Only the Clark study showed long-term improvement with iNO, e.g., lower incidence of CLD. Patients in the two studies were on <u>iNO for an average of 5 days</u>.

III. ADVERSE EFFECTS

With long-term use, there are concerns for cellular injury to the lungs. This agent is a potential carcinogen, and has been implicated as a causative agent in lung cancer (cigarette produce 200-300ppm at the end of the cigarette). Nitric oxide also alters platelets activity and will prolong bleeding times in patients on iNO. Therefore if a patient has a major bleeding disorder, one should take this factor into the decision to start iNO.



IV. TOLERANCE

Of concern, is the tolerance that develops with the use of iNO. Even patients who do not respond to iNO develop marked tolerance to the drug *(Davidson, et al, Pediatrics, 104:231-236, 1999)*. Acute withdrawal can result in marked pulmonary vasoconstriction and hypoxia. Patients on iNO at the referring hospital who did not respond to the iNO therapy should be left on iNO during transport. Weaning should occur over 24-48hr period.

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NITRIC OXIDE USE FOR PPHN: GUIDELINES

I. PATIENT POPULATION

A. Patients >34 week gestation in respiratory distress (Only approved for use in infants >34 weeks gestation
B. Documented PPHN, either clinically by pre-post ductal PaO_2, "flip-flop" phenomenon, or ideally, cardiac echo evidence of PH
C. No major bleeding complication

II. STARTING CRITERIA

A. Requiring ventilation
B. Oxygen Index (OI) $\geq$25 *Note:* OI = MAP x FIO_2 x 100 ÷ PaO_2

III. MONITORING

A. Continuous monitoring of iNO and NO_2 concentrations
B. Methemoglobin levels q 4 hrs until stable, then daily.
    1. MetHgb levels that are rising indicate the need for decrease or discontinuation of iNO
    2. Levels $\geq$ 5 indicate immediate reduction in iNO concentration
    3. If you cannot keep the level <5, then iNO should be discontinued.

IV. DOSING

A. Start at 20ppm
    1. No response
        a. Try 40ppm (most patients who do not respond to 20ppm, do not respond to higher doses of iNO)
        b. ** Note: never use >80 ppm of NO; severe toxicity can occur with pulmonary edema/ death**
        c. If no response, do not stop the iNO.
            i. Wean by 5 ppm q hrs 4-8 hrs until you are on 5ppm
            ii. At 5ppm, wean by 1ppm q 4-8 hrs until you are at 1 ppm
            iii. Wean off iNO after 4-8 hrs of 1 ppm.
    2. Positive response to 20 or 40 ppm
        a. Leave at that level for 24hrs, then start to wean when FIO_2 <70%.
        b. Wean by 5ppm every 4-8hrs until 5ppm is reached
        c. At 5ppm, wean by 1 ppm q 4-8 hrs as tolerated until 1 ppm is reached.
        d. After 4-8 hrs of 1ppm, d/c iNO
    3. Note: If rebound occurs, increase FIO_2 or iNO until stable.
B. iNO on ECMO.
    1. iNO can be weaned faster on ECMO; since iNO reduces platelet function, you can increase the risk of bleeding while on heparin.
    2. VA ECMO: wean off immediately or within the first few hours.
    3. VV ECMO: wean every hourly as tolerated

V. TRANSPORT

A. If a patient is on iNO at the referring hospital, leave the patient on that concentration of iNO during transport. *Do Not Try To Wean iNO during transport*
B. iNO should be taken on transport for use on any infant with PPHN. Start at 20 ppm. Met hemoglobin levels can be obtained after return to CNMC.

VI. TOXIC SIDE EFFECTS

A. If methemoglobin increases >5% decrease iNO concentration until <5%; stop iNO if level continues to be >5%
B. If NO_2 >5ppm, decrease iNO until NO_2 is less than 5ppm. Stop iNO if level continues to be >5ppm
C. Abnormal bleeding develops thought to be related to iNO therapy, start to wean iNO and come off as quickly as possible

General Surgery Infantile Hemangioma Propranolol Initiation Plan

2015

Criteria Requiring Inpatient Admission

1. Infant < 8 weeks corrected age with symptomatic infantile hemangioma.
2. Infant of any age with inadequate social support.
3. Infant of any age with comorbid conditions affecting the cardiovascular system, the respiratory system including symptomatic airway hemangioma or blood glucose maintenance problems (or disorders).

Contraindications to Propranolol Administration

1. Premature infants with corrected age < 5 weeks
2. Infants weighing ≤ 2 kg.
3. Known hypersensitivity to propranolol.
4. Asthma or history of bronchospasm.
5. Bradycardia (<80 beats per minute), >1st degree heart block, decompensated heart failure.
6. Blood pressure < 50/30 mmHg
7. Family history of Pheochromocytoma
8. Active Hypoglycemia

Relative cardiac contraindications require EKG and Cardiology evaluation

1. Arrhythmia
2. PHACES also requires ECHO, Neurology and MRI evaluation prior to initiation
3. Family history of congenital heart conditions or arrhythmias
   eg. Heart block, long QT syndrome, sudden death

Where to Admit:

1. Clinic provider determines if Cardiology evaluation is required.
   EKG and Cardiology evaluation is indicated if:
   a. Infants (1-12 months old), HR < 80 beats per minute
   b. Children (>12 months old), HR < 70 beats per minute
   c. Family history of congenital heart conditions or arrhythmias (eg heart block, long QT syndrome, sudden death).
   d. History of an arrhythmia or an arrhythmia is auscultated during examination.
2. If Cardiology evaluation is needed patient will be admitted under Cardiology and go to HKU.
3. If Cardiology evaluation is **NOT** needed patient will be admitted under Surgery and go the surgical unit unless they meet criteria for NICU.

Pre-Admission Procedure

1. Patient is seen in Vascular Anomalies (VAC) or Dermatology Clinic with symptomatic hemangioma and meets inpatient admission criteria.
2. Ordering provider discusses potential admission dates with family.
3. Provider emails Felicita Simpson (ENT scheduler) at fsimpson@childrensnational.org and provides patient name, MR #, parent name and contact information along with proposed date of admission. She will obtain insurance approval for admission which can take anywhere for 48 hours to 14 days depending on insurance.
4. Provider contacts either Cardiology, Surgery or NICU to arrange admission. Email appropriate individuals to notify of patient information anticipated admission date.
5. Provider discusses urine collection study with parents and consent family. If consent is obtained cotton balls are provided to them in clinic to place in diaper prior to coming to

hospital the morning of admission. VAC NP to notify admitting floor via email if consent was obtained prior to admission

6. **Cardiology Admission: cc the following staff:**
   - Admitting to HKU- Notify the following staff via email.
   - Medical Director of HKU
   - Lisa Williams RN (Nurse Manager, HKU)
   - Sarah Gallagher and Kelly Murphy-Forbes (Clinical Supervisors, HKU)
   - Cardiologist on HKU service (name obtained from CNMC operator or online intranet schedule)
   - Following individuals should be cc'd on email to be aware of admission:
   - Dr. Nancy Bauman- Otolaryngology
   - Dr. Phil Guzzetta- Surgery
   - Gina Krakovsky Nurse Practitioner, Vascular Anomalies Clinic
   - Felicita Simpson (ENT surgery scheduler- obtains Prior Authorization)

7. **Surgical Admission: cc the following staff:**
   - Admit to Surgical Care unit- 5 East- Notify the following staff via email.
   - Ginger Winder, Nurse Manager Surgery Floor
   - Katie Worst, NP Surgery
   - Dr. Ivan Gutierrez, Surgical Chief Resident (name obtained from CNMC operator or online)
   - Dr. Jarod McAteer, Surgical Chief Resident
   - The following individual's should be cc'd on email-
   - Dr. Nancy Bauman -Otolaryngology
   - Dr. Phil Guzzetta - Surgery
   - Gina Krakovsky Nurse Practitioner Vascular Anomalies Clinic
   - Felicita Simpson (ENT Surgery scheduler- obtains Prior Authorization)

8. **NICU Admission:**

   Consider NICU for the following conditions:
   - **Ex – premie < 44 weeks corrected age and/or < 3 kg**
   - **Comorbidities- A's/B's etc.**

   Notify the following staff:
   - Dr. Lamia Soghier, NICU Medical Director
   - Dr. Billie Short- NICU Attending
   - Dr. Nickie Niforatos- Andescavge NICU Attending
   - Maureen Maurano, RN manager

   CC following staff:
   - Dr. Nancy Bauman- Otolaryngology
   - Dr. Phil Guzzetta- Pediatric Surgery
   - Gina Krakovsky Nurse Practitioner Vascular Anomalies Clinic
   - Felicita Simpson (ENT surgery coordinator- obtains prior authorization)

Day of Admission

1. Parent calls admitting on the anticipated day of admission prior to coming to the hospital to verify a bed is available (202) 476-4068.
2. Patient goes to admitting upon arrival to CNMC

Admission Protocol

GENERIC PROPRANOLOL 20mg/5 ml (4mg/ml)
Target dose is 2mg/kg/day BID

1. Obtain baseline Vital Signs. Confirm normal cardio-respiratory exam. **EKG's are needed before medication is started and prior to discharge (if patient is admitted to HKU).** If patient does not require admission to HKU no EKG is needed.
    a. If baseline VS are abnormal or arrhythmia is noted patient will need to be under Cardiology service and closely monitored per protocol.

2. If urine consent has been obtained please see guidelines for urine collection. VAC NP is to notify floor if consent has been obtained. Upon arrival to floor check diaper for saturated cotton balls. If cotton balls not placed at home by parents place them upon arrival to floor. Urine is to be collected prior to giving first dose of Propranolol. Do not hold dose if urine is unavailable. (See attached guidelines)

3. Start medication
   Propranolol (20mg/5ml) target dose 1mg/kg/dose = 2mg/kg/day divided PO **BID**
    a. Doses must be given at least 9 hours apart with feeding.
    b. Hold doses for illness, wheezing, vomiting or decrease PO.

4. Feeding
    a. Babies up to 6 weeks of age should be fed at least every 4 hours.
    b. Babies between 6 weeks and 4 months of age should be fed at least every 5 hours.
    c. Babies older than 4 months of age should be fed at least every 6 hours.

5. Monitor BP and HR 1 and 2 hours after each dose given.
   Decrease subsequent dose to 75% target dose if either HR or BP drops below the following:
    - Newborns < 1 month old HR < 70 BP ≤50/30
    - Infants 1-12 months HR <80 BP ≤ 80/55
    - Children > 12 months HR < 70 BP ≤90/55
      (Kent A.L. et. al 2007)

   If after decreased 2nd dose, HR and BP are stable may increase to target dose for 3rd dose.
    a. If 1 and 2 hours after 3rd dose HR and BP stable may discharge home.
    b. If after decreased 2nd dose HR or BP is low decrease to 50% target dose.
    c. If persist to be low discontinue medication.

If after 3rd dose glucose, HR and BP are stable may discharge home

6. Complete accucheck blood sugar every hour x 2 after first dose- Record in power chart. Hold next Propranolol dose if blood sugar is less than 70 gm/dl. Decrease subsequent dose to 75% target dose.
   a. Recheck glucose every hour x 2 after decreased dose. If within normal limits may increase to target dose.
   b. Recheck glucose every hour x 2 after target dose. If within normal limits do not need to check glucose after additional doses. If remains low decrease to 50% target dose.
   c. If continues to be low discontinue medication.

7. Patient may be discharged if glucose, HR and BP are WNL and tolerating medication.

Follow-up Instructions

1. Patient is to be scheduled a follow up appointment in 2-4 weeks at one of the following clinics:
   a. VAC (4th Tuesday of the each month- all team members) in DC.
   b. Dr. Guzzetta Surgery clinic Tuesday mornings in DC.
   c. Shady Grove VAC (1st Thursday of each month) ENT and Surgery only.

2. Email Rose-Mary Edimo @ RMEdimo@childrensnational.org to request follow appointment to be scheduled. cc: VAC @ vclinic@childrensnational.org . If questions arise, contact Gina Krakovsky gkrakovs@childrensnational.org or Dr. Nancy Bauman nbauman@childrensnational.org, or contact Yvette Dill at (202) 476-2151.

3. Provide parents with Beta Blocker Parent Information sheet. Indicate correct medication, dosage, frequency and review with parent.

Admission/Discharge Checklist for Propranolol patients.

1. Baseline VS HR & BP
2. Baseline Glucose
3. EKG if on HKU
4. Urine collection (if notified by VAC NP that consent was previously obtained)
5. First dose medication- Do Not Hold dose waiting for patient to void.
6. Monitor VS every hour x 2 after three doses. BP and HR
7. Monitor BS 1 hour after first dose and subsequent doses if low.
8. If stable after 3 doses may be discharged.
9. Provide Beta Blocker Parent Information Sheet
10. Schedule follow up appointment.

Patients admitted to HKU:

1. Print off hard copy of abnormal rhythm strips and apply sticker to store in patient's chart.
2. Repeat EKG prior to discharge.
3. Discharge patient if tolerating medication, HR, BP and EKG are normal.

INBORN ERRORS OF METABOLISM IN INFANCY

I. GENERAL INFORMATION

Inborn errors of metabolism (IEMs) may present any time from birth to adulthood. IEMs as a group represent significant treatable causes of morbidity and mortality and should be on differential list of any critically ill newborn. In general, inborn errors of metabolism lead to early concerns for the following reasons:

A. Brain Edema
   Formation of a compound that lead to brain edema and subsequent encephalopathy (i.e. ammonia in urea cycle disorders, organic acidemias; leucine in maple syrup urine disease)
B. Hypoglycemia
   Disorders that lead to low glucose levels secondary to abnormal metabolic demand (fatty acid oxidation defects, mitochondrial disorders, glycogen storage disorders, organic acidemias)
C. Bleeding/Clotting Disorders
   Disorders with increased risk of blotting or bleeding (cobalamin deficiencies, MTHFR, homocystinuria)
D. Systemic/ Organ Failure
   In the neonatal period, examples include cardiomyopathy in fatty acid oxidation defects, galactosemia and liver dysfunction, and non-immune hypdrop fetalis in storage disorders.

II. HISTORY

Consider metabolic disorders in any critically ill newborn. Upon admission, be sure to inquire about:

A. Early death of a previous sibling or multiple maternal miscarriages; prepare a pedigree analysis.
B. Complications of pregnancy: Acute fatty liver of pregnancy (AFLP), HELLP syndrome, and hyperemesis have been linked to the presence of disordered fatty acid metabolism in the fetus.
C. Consanguinity: homozygosity for defective genes.
D. History of recurrent clinical disease episodes: for example recurrent vomiting may represent phenylketonuria, often mistaken for pyloric stenosis.
E. Sepsis-like picture: Galactosemia may be associated with *E. coli* septicemia or metabolic disorder causing neutropenia and secondary immune deficiency.
F. Time of presentation of illness: Asymptomatic infants who become progressively sicker or overwhelming abnormal neurologic exam at birth is worrisome for IEM.

III. CLINICAL PRESENTATION

Clinical signs of inborn errors of metabolism are <u>non-specific</u>. It is important to include IEMs in the differential diagnosis of <u>ALL</u> acute neonatal illness.

A. Clinical signs in newborns with <u>acute metabolic decompensation</u> due to inborn errors of metabolism may include: ALTE, poor feeding, emesis, lethargy, seizures, tone abnormalities (hyper/hypotonia), coma, abnormal smell (odor of urine or cerumen), hyperventilation or respiratory failure, hepato-splenomegaly, acidosis, apnea.

B. Encephalopathy is a common sign for many IEM
   1. With metabolic acidosis: Consider organic acidemias (ketosis), fatty acid oxidation defects, HMG CoAlyase deficiency, lactic acidosis secondary to pyruvate dehydrogenase or carboxylase deficiencies and/or mitochondrial respiratory chain disorders
   2. Without metabolic acidosis: Consider urea cycle disorder, MSUD, peroxisomal disorders

3. Seizures without abnormal metabolites: Consider nonketotic hyperglycinemia, pyridoxine and folinic responsive seizures, GABA transaminase deficiency, GLUT-1 deficiency.

IV. EVALUATION

A. Blood Tests
   1. CBC with differential as bone marrow suppression is common with organic acidemias
   2. Blood gas (arterial) to assess for metabolic acidosis (Figure 2)
   3. Chemistries: Glucose, BMP,LFT, PT
   4. Lactate and pyruvate (drawn concurrently) as the ratio may be informative for disorders of pyruvate metabolism
   5. Serum ammonia (free-flowing sample, placed on ice)
   6. Plasma amino acids, quantitative:
      a. Alanine- High suggests lactic acidosis. Low characteristic of MSUD
      b. Glycine- Massive elevation in propionic academia, milder elevation typical in methylmalonic academia and non-ketotic hyperglycinemia
      c. Citrulline- Low suggests proximal urea cycle defect (NAGS, CPS, OTC), High suggests distal urea cycle defect (citrullinemia, ASL)
      d. Arginine- Low suggests urea cycle defect (NAGS, CPS, OTC, citrullinemia, ASL) or renal dysfunction, High suggests arginase deficiency.
      e. Branched chain amino acids (isoleucine, leucine, valine;in characteristic 1:2:3 ratio), elevation with perturbed ratio suggests MSUD, elevation with preserved ratio likely dietary source, low BCAAs suggests inadequate protein intake and catabolic stress.
      f. Phenylalanine - massive elevation in PKU.
      g. Tyrosine - elevated in tyrosinemias, but also in general hepatic insufficiency
   7. Acylcarnitine profile
      a. Abnormal acylcarnitine with even number fatty acid (6-10 MCAD, 12-18 V/LCAD)
      b. Abnormal acylcarnitine with odd-number fatty acid (3 or 5 organic academia)
   8. Uric acid - If glycogen storage diseases or diseases of purine metabolism are suspected
   9. If exam concerning for diagnosis, 7-dehydrocholesterol: disorders of cholesterol metabolism (SLO)

B. Urine tests
   1. Urine organic acids for suspected organic acidemias, orotic acid in distal urea cycle disorders
   2. Urine ketones for suspected organic acidemias or glycogen storage disease (type I)
   3. Less useful: Urine reducing substances (very non-specific) for galactosemia, hereditary fructose intolerance, tyrosinemia

C. CSF Studies
   1. Specific neurotransmitted testing can be collected and coordinated for send-out testing with neurology
   2. Amino acids: must be drawn concurrent with plasma AAs – abnormal CSF:Plasma ratio of glycine is diagnostic for non-ketotic hypoglycinemia

D. Newborn Screening
   1. Expanded NBS includes tandem mass-spectroscopy assessment of specific amino acids and acyl-carnitine compounds; may vary from state to state
      a. Good for: distal urea cycle defects, specific amino acidopathies, fatty acid oxidation defects, most organic acidemias

b. Not good for: proximal urea cycle defects (OTC, CPS,NAGS), disorders of carbohydrate metabolism, large-molecule diseases
2. Results unfortunately often come later than initial presentation.

E. Neuroimaging
1. MRI with MR Spectroscopy for metabolic disorders (discuss timing with team).

V. MANAGEMENT OF SUSPECTED LIFE-THREATENING METABOLIC DISEASE

A. Immediate empiric management:
1. Cardio-respiratory support: lower metabolic demand, counter respiratory/myocardial depression, maintain adequate systemic perfusion
2. Fluid resuscitation: Start 1.5-2 x maintenance fluids with D10 NS or ½ NS based on electrolytes and glucose. Avoid Lactate (LR) and hypotonic fluids
3. Metabolic acidosis: Fluid resuscitation, address hemodynamics. Cautious administration of sodium bicarbonate (0.5-1 meq/kg IV) or acetate for severe acidosis – pH < 7.0 anion gap organic acidemias as not beneficial and can be harmful in hyperammonemia and worsen cerebral edema and acidosis.
4. Hypoglycemia: treat aggressively and promote anabolism: send critical metabolic labs and initiate D10 fluids with GIR (8-15 mg/kg/min) for goal glucose 80-150 mg/dL to acheive anabolic state; may need central line if need > D12.5; likely will need insulin if secondary hypergyemia due to cellular uptake of glucose being abnormal (0.2-0.3 IU/kg).
5. NPO until metabolic labs obtained and provisional diagnosis to not exceed 24 hours. Then, use protein and fats judiciously with consult with metabolism.
6. Obtain STAT metabolic-genetic consults (preferably before treatment if readily drawn).
7. Correct coagulopathy with FFP
8. Empiric antibiotics is presenting with septic like picture while awaiting culture results
9. Hemofiltration/peritoneal dialysis: as indicated for severe hyperammonemia, acidosis, cerebral edema (coma), hyperkalemia, hyperleucemia.
10. Consider Co-factors:
a. Cobalamin B12: metabolic acidosis in organic acidemias (MMA)
b. Pyridoxine (100 mg IV), Folinic acid: intractable seizures
c. Biotin: intractable seizures in multiple carboxylase deficiency.
d. Carnitine (50 mg/kg IV f/b daily) : in fatty acid oxidation disorders, carnitine deficiency.

B. Hyperammonemia: Must be treated aggressively in addition to above, please page genetics for any of these interventions.
1. Establish arterial and central venous access.
2. Initiate IV-based ammonia scavenger (i.e. Sodium benzoate and Sodium phenyl acetate (Ammunol)). May not be able to tolerate bolus if volume or sodium load will be an issue, can begin continuous infusion
3. Arginine may become essential amino acid and supplemented separately

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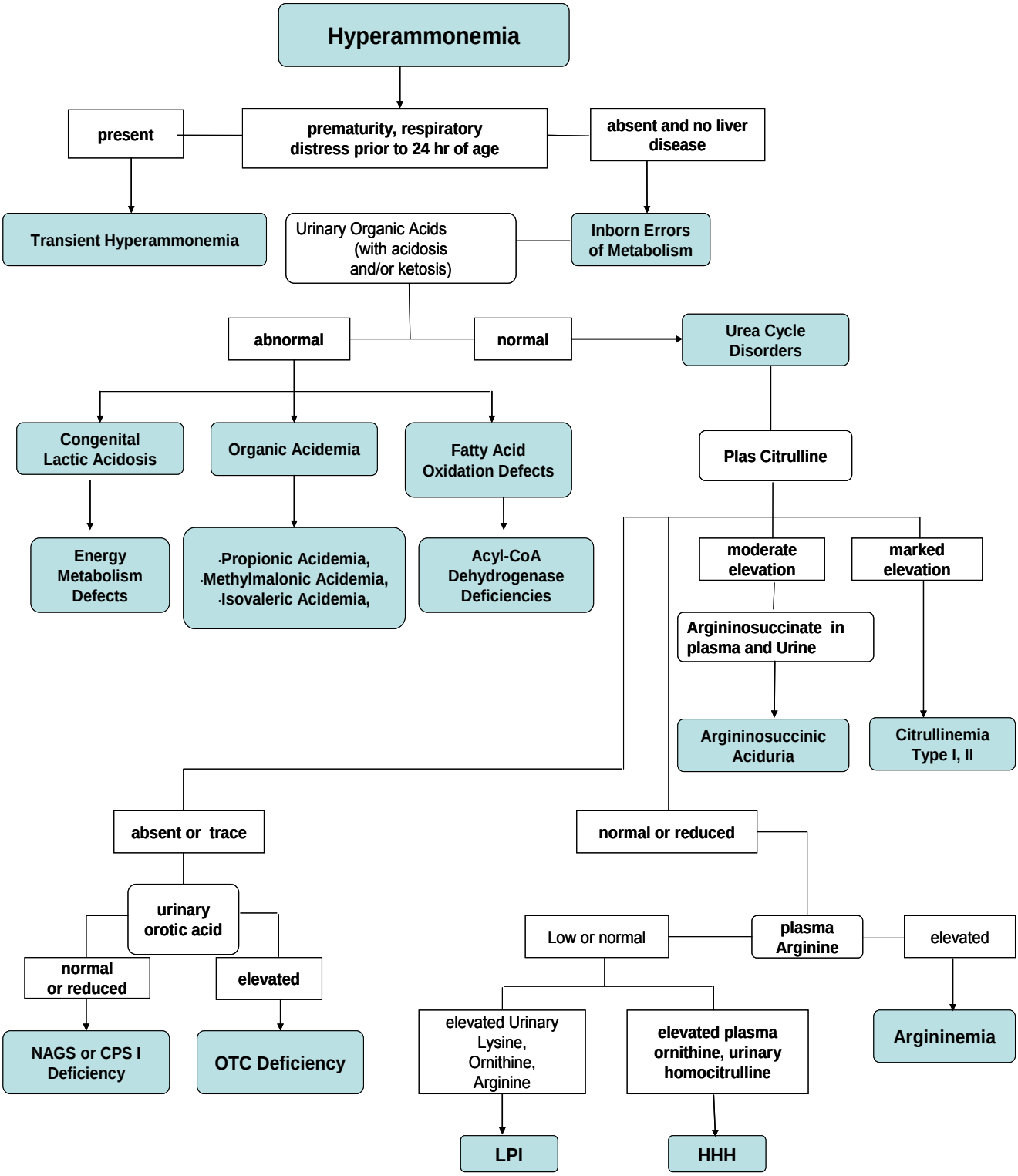
Table 1: Important Inborn Errors of Metabolism with Presentation in the Neonatal Period			
IEM DISORDER*	**Presentation**	**Laboratory Test**	**Treatment and Remarks**
AMINO ACID METABOLISM Defect in amino acid (AA) breakdown with accumulation of intact amino acids and by-products	No acidosis or hyperammonemia	NMS Plasma AA	Acute: early use of fluids, avoid catabolism, limit protein, dialysis Chronic: Diet restriction of specific amino acid, monitor plasma AA
Maple syrup urine disease AR Branched-chain 3-keto acid dehydrogenase	Acute encephalopathy, vomiting, urine and cerumen maple syrup odor (leucine)	Urine ketones (+) Plasma AA and urine organic acids	Avoid hypotonic fluids; avoid leucine (neurotoxic; Ile/Val to compete) Diet restriction of branched-chain AA, especially leucine
CARBOHYDRATE METABOLISM Defect in carbohydrate breakdown or synthesis	Hypoglycemia with ketosis; hepatomegaly	Hypoglycemia w/ ketosis Elevated lactate	Acute: early use of fluids, avoid catabolism Chronic: Diet modification/restriction
Galactosemia AR, Galactose 1-phosphate uridyltransferase (MC); galactokinase; epimerase	Liver failure, cataracts, associated w/ E.coli sepsis	Galactose and galactose 1-phosphate assay, molecular assay	Lactose-free diet for life
Glycogen storage disease Type Ia (von Gierke's disease); AR, Glucose-6-phosphatase	Hypoglycemia with ketosis; increased lactate, uric acid, triglycerides, hepatomegaly	Liver biopsy enzyme assay	Corn starch and overnight feeds
FATTY ACID OXIDATION Defect in β-oxidation of fatty acids.	Acute nonketotic hypoglycemia, acidosis	Plasma acylcarnitines, ketones during hypoglycemia	Cardiac dysfunction can result from emergency deficiency due to lipid usage.
Medium-chain acyl-CoA dehydrogenase deficiency AR V/Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (V/LCAD) AR	Acute encephalopathy, SIDS, multi-organ failure, rhabdomyolysis, retinal degeneration	Urine organic acids, Plasma acylcarnitines (C6-10 in MCAD and C12-18 in VLCAD), gene test	Acute: Treat hypoglycemia (D10 or higher) and acidosis Chronic: Low fat diet, Avoid fasts, Night feeds, Carnitine supplement, medium chain fat supplement, Treat Rhabdomyolysis
ORGANIC ACIDEMIAS Defect in amino acid breakdown, accumulation of organic acid byproducts	Metabolic acidosis with anion gap; hyperammonemia	NMS Urine organic acids	Acute: Early use of fluids, avoid catabolism, no protein, dialysis Chronic: Low protein diet, carnitine supplement, liver transplant
Methylmalonicaciduria AR Methylmalonyl-CoA mutase, Cobalamin metabolism Propionic aciduria AR Propionyl-CoA carboxylase	Acute encephalopathy, newborn with coma/ALTE/SIDS, bone marrow suppression, cardiomyopathy	Acylcarnitine (C3,5) profile, urine organic acids	Correct acidosis with sodium bicarbonate, carnitine, vitamin B_{12}, supplementation, buphenyl or ammunol, carbiglu, dialysis
UREA CYCLE DEFECTS Ornithine transcarbamylase deficiency X-linked (Differential diagnosis of hyperammonemia in Fig 1)	Hyperammonemia without acidosis, acute encephalopathy/coma, ALTE/SIDS, respiratory alkalosis	Ammonia, plasma AA, rrine orotic acid, Liver biopsy, enzyme concentration	Acute: Fluids, avoid catabolism, no protein, sodium benzoate, arginine, dialysis Chronic: Low-protein diet, Phenylbutyrate; Arginine/Citrulline supplement, Liver transplant

Table 1 cont'd: Important IEM Presenting in the Neonatal Period			
Miscellaneous			
IEM DISORDER*	**Presentation**	**Laboratory Test**	**Treatment and Remarks**
LYSOSOMAL STORAGE DISORDERS Gaucher's disease AR, β-glucocerebrosidase	Coarse facial features, hepatosplenomegaly, bone lesions, neuropathy (Type II)	Leukocyte β-glucocere-brosidase assay	Enzyme therapy, bone marrow transplant
PEROXISOMAL DISORDERS Zellweger syndrome AR, Peroxisome membrane protein	Dysmorphic face, large fontanel, brain abnormalities, hypotonia, seizures, liver dysfunction, mental retardation, early death	Plasma very-long-chain fatty acids	No specific treatment available
CHOLESTEROL METABOLISM DISORDER Smith-Lemli-Opitz disease (SLO), AR, 7-dehydrocholesterol reductase	Dysmorphic feature, multiple congenital abnormalities, neurodevelopmental delays	Very low serum cholesterol(LDL), elevated 7DHC, gene test	Cholesterol supplement

* Name, Inheritance (AR=Autosomal Recessive), Enzyme defect

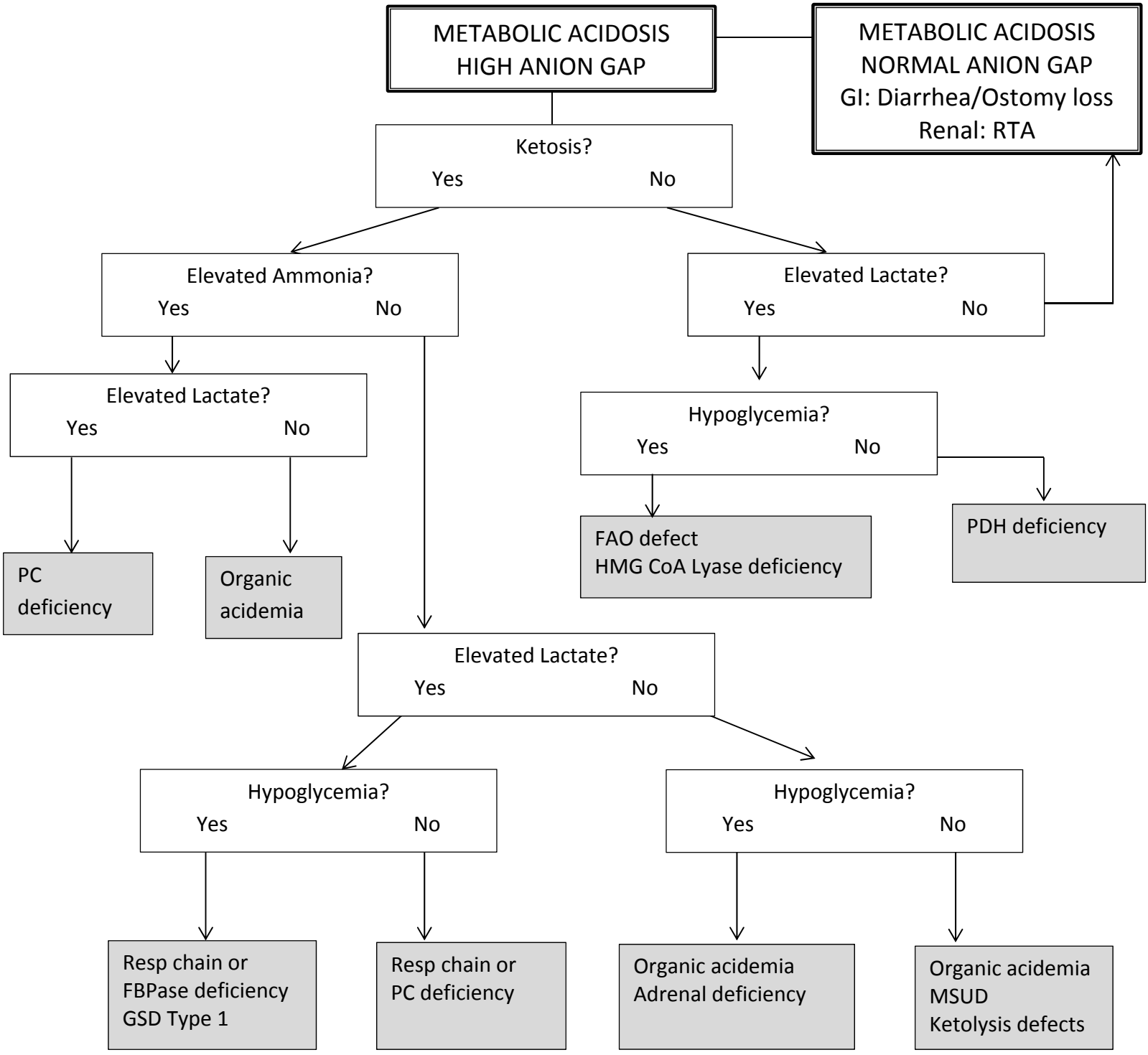
Table 2: Common Clinical Findings associated with IEM	
Findings	**Possible diagnosis**
Brittle Hair	Urea Cycle Defects, Menkes Syndrome
Cardiomyopathy	LCHAD, VLCAD, glutaric aciduria II, Carnitine deficiency, Pompe Disease, mitochondrial disorders, I-cell disease
Coma/encephalopathy	MSUD, Urea Cycle Defects, peroxisomal diseases, non-ketotic Hyperglycinemia, organic acidemias, FA oxidation defects, Mitochondrial disorders, pyruvate carboxylase deficiency
Ketosis	Organic acidemias, MSUD, Glycogen storage disease Gluconeogenesis defects
Hypoglycemia (hypo-ketotic)	Fatty acid ß oxidation defect, Ketone production defect Carnitine deficiency
Metabolic acidosis (with high anion gap)	Organic acidemias
Hyperammonemia with acidosis	Organic acidemias (propionic, methylmalonic, or isovaleric)
Hyperammonemia with alkalosis	Urea cycle enzyme defects
Presence of vacuoles in lymphocytes	Lysosomal storage diseases (such as mucopolysaccharidosis)
Elevated serum triglycerides	Hyperlipidemias, glycogen storage disease
Low serum phosphorus	Disorders with Fanconi syndrome (Tyrosinemia, galactosemia, fructose intolerance
Thromboembolism	Homocystinuria
Non-immune Hydrops Fetalis	G6PD def, Pyruvate kinase def, Lysosomal Storage diseases
Hepatomegaly	Storage diseases, peroxisomal diseases

Figure 1: Differential Diagnosis of Hyperammonemia



Algorithm for differential diagnosis of hyperammonemia. Plasma amino acids, lactate and urinary excretion of orotic acid and organic acids are measured. LPI, lysinuric protein intolerance; HHH, the hyperammonemia hyperornithinemia homocitrullinuria syndrome; ASA, argininosuccinic acid.

Figure 2: Differential Diagnosis of Metabolic Acidosis



Algorithm for differential diagnosis of IEM metabolic acidosis (high anion gap). GSD: Glycogen storage ds, PC: Pyruvate carboxylase, FBPase: Fructose 1,6 bisphosphatase, MSUD: Maple syrup urine disease, PDH: Pyruvate dehydrogenase.

HYPOPHOSPHATEMIA

I. DEFINITION

A. Serum phosphorus level less than 4 mg/dL

B. Severe hypophosphatemia is less than 1 mg/dL

II. CAUSES

A. Inadequate maternal intake.

B. Phosphorus levels often decline rapidly over the first week of life in the premature infant who is not being fed enterally, as calcium but no phosphorus is often given over the first few days.

C. Inadequate oral phosphorus intake may result when feeding breast milk without fortifier or formulas low in phosphorus to premature infants. Prolonged hypophosphatemia accompanied by inadequate calcium intake will result in rickets.

D. Hypophosphatemia is commonly seen in the sick infant with complex pathologies and/or multiple nutrient deficiencies.

E. Congenital hyperparathyroidism (low phosphorus associated with high calcium may be seen).

F. Some medications may also deplete phosphorus.

III. TREATMENT

A. Replace with sodium phosphate (3mM PO4/ml + 4 mEq Na/ml) or potassium phosphate (3mM PO4/ml + 4.4 mEq K/ml)

B. Phosphate should be ordered in mM, not mEq.

C. Usual replacement dose is <u>0.5 to 1.0 mM/Kg/dose over 4 to 6 hours.</u>

D. Maximum IV infusion rate is <u>0.2 mM/Kg/hr</u> of phosphate. If potassium phosphate is used, rate may be limited by maximum potassium infusion rate. All the precautions of potassium infusions apply when potassium phosphate is given.

E. Phosphate replacements should not be added to IV fluids containing calcium (such as TPN) as there is potential for precipitation.

F. Phosphate may also be replaced orally, as long as <u>severe</u> hypophosphatemia is not present.

G. Watch for stooling or vomiting with oral supplements. Can cause abdominal pain.

H. Other side effects: Tetany, hyperphosphatemia, hyperkalemia, hypocalcemia, hypotension.

References

1. Taeusch, Ballard and Avery: Diseases of the Newborn, Sixth Edition, W.B. Saunders Company, 1991, page 931.

2. Siberry and Iannone: The Harriet Lane Handbook, Fifteenth Edition, Mosby year Book, 2000.

3. Tsang and Nichols: Nutrition during infancy, The C.V. Mosby Company, 1988, pages 184-185.

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HYPONATREMIA

I. DEFINITION

Serum Sodium level less than 130 mEq/L.

II. CAUSES

A. Over-hydration as a result of maternal or neonatal administration of electrolyte free fluid.

B. Renal losses, seen with diuretic therapy and secondary to renal immaturity in premature infants.

C. Gastrointestinal losses from vomiting, diarrhea, naso-gastric or ostomy drainage

D. SIADH where clinical manifestations include low NA+, increased urine specific gravity, urine osmolarity > serum osmolarity, urine sodium loss, normal renal function.

E. Fluid overload secondary to cardiac or renal failure

III. TREATMENT

A. Over hydration: Add maintenance sodium (2-4 mEq/Kg/day) to IV fluids. Replace Na+ using formula below if Na is <120 mEq/L. In some contexts decreasing the free water load is the best approach, especially if total fluid exceeds 150cc/k/d.

B. Renal losses: Replace over 24 hours using formula below. After the first week of life, a VLBW infant may require up to 10-12 mEq/Kg/day maintenance. Document renal loss, rule out over-hydration.

C. G.I. losses: replace NG drainage 1cc per cc or 0.5 cc per cc (1:2) with D5 ½ NS (may also need K+). Replace sodium as per renal losses if still hyponatremic.

D. SIADH: restrict fluids to insensible losses + 1/3 to 1/2 urine output. Do not replace sodium unless 120 mEq/L or less, or if infant is symptomatic.

E. Fluid overload: Restrict fluids. Do not replace Na unless 120mEq/L or less, or if infant is symptomatic.

IV. REPLACEMENT

A. Formula:

Na (in mEq) desired - Na (in mEq) present x wt (in Kg) x 0.6 = total replacement.

B. Replace ½ over at least 6 hours (8 is preferable). It is easiest to replace in maintenance IV fluid without changing the IV rate.

C. Check Na level after first replacement to make sure values are going in right direction and are not overshooting. If additional replacement is needed, replace the second ½ over 16 hours.

D. Maximum concentration =
    1. For a central line 500 mEq/1000cc
    2. For a peripheral line 154 mEq/1000 cc (= NSS)

References

1. Fallon, M. Inappropriate antidiuretic hormone, Neonatal Network, June 1983.

2. Siberry and Iannone: The Harriet Lane Handbook, Fifteenth Edition, Mosby Year Book, 2000.

3. Merenstein and Gardner: Handbook of Intensive care, Second Edition, The C.V. Mosby Company, 1989, page 217.

4. Vestal and McKenzie: High risk perinatal nursing, W.B. Saunders Company, 1983, pages 465-466.

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HYPOMAGNESEMIA

I. DEFINITION

A. Magnesium level less than 1.5 mg/dL

B. This is often associated with hypocalcemia

II. PREDISPOSING FACTORS

A. Maternal diabetes (associated with neonatal hypocalcemia and decreased parathyroid function)

B. Prematurity or SGA

C. Infants undergoing exchange transfusions

III. CAUSES

A. Inadequate intake.

B. Unreplaced losses from gastrointestinal or biliary fistulas.

C. Chronic diarrhea and/or intestinal malabsorption.

D. Magnesium losing nephropathies.

E. Transient hypoparathyroidism (usually occurs the first day of life).

F. Increased phosphate intake.

III. TREATMENT

A. IV or IM replacement = 0.2- 0.4 mEq/Kg elemental Mg q4-6h for 3-4 doses.

B. May be given by constant infusion, not to exceed a total of 1.2 mEq/minute.

C. Precipitation may occur if added to a solution containing calcium.

D. ANTIDOTE: Calcium gluconate

E. Maintenance = .2 to .5 mEq/Kg/day elemental Mg. (Note: 125mg of Magnesium Sulfate = 1mEq Magnesium)

F. Monitor levels q12h during acute therapy, and monitor for hypocalcemia.

G. Have resuscitation and ventilatory support available, as apnea is a complication of hypermagnesemia.

References

1. Taeusch, Ballard and Avery: Diseases of the Newborn, Sixth Edition, W.B. Saunders Company, 1991, page 931.

2. Siberry and Iannone: The Harriet Lane Handbook, Fifteenth Edition, Mosby year Book, 2000.

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5. Pawlak and Herfert: Drug administration in the NICU; A handbook for nurses, Neonatal Network, 1988, pages 128-129.

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HYPOKALEMIA

I. DEFINITION

Serum potassium level less than 3.5 mEq/L.

II. CAUSES

A. Renal losses, often secondary to diuretic therapy. May also be seen in renovascular disease.

B. Increased gastrointestinal losses from vomiting or diarrhea, as well as N.G. or ostomy losses.

C. Metabolic or respiratory alkalosis.

D. Iatrogenesis.

E. In the absence of severe alkalosis, hypokalemia implies *significant intracellular depletion*, and potassium needs to be supplemented.

III. TREATMENT

A. Treat the underlying cause.

B. 1 mEq/Kg KCl should raise serum K+ 1 mEq/L.

C. 1 mEq/Kg of KCl may be given, preferably over a **minimum** of 4 hours.

D. For emergency replacement of symptomatic hypokalemia (muscle weakness, cardiac arrhythmias), 0.5-1 mEq/Kg may be given over one hour. (MAXIMUM infusion rate = 1 mEq/Kg/hr.)

E. Do **not** give potassium to an infant who is not voiding.

F. MAXIMUM concentration =
   1. For a central line, 200 mEq K+/1000ml.
   2. For an umbilical line, 120 mEq K+/1000ml.
   3. For a peripheral line, 40 mEq K+/1000ml.

G. Exceptions
   1. Post-op cardiac bypass in the first 24 hours or ECMO infants during first 12 hours.
      a. KCl replacements may be given over 1 hour at a maximum rate of 1 mEq/Kg/hr., maximum concentration 1 mEq/mL.
      b. Very hyperosmolar, discuss with Fellow and/or CT surgery staff.

References

1. Siberry and Iannone: The Harriet Lane Handbook, Fifteenth Edition, Mosby Year Book, 2000.

2. Merenstein and Gardner: Handbook of Intensive care, Second Edition, The C.V. Mosby Company, 1989, page 217.

3. Vestal and McKenzie: High risk perinatal nursing, W.B. Saunders Company, 1983, pages 465-466.

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HYPOCALCEMIA

I. DEFINITION

A. Serum calcium level less than 7 mg/dL (optimal range = 8.5 to 10.5 mg/dl).

B. Ionized calcium < 4 mg/dl (optimal range = 4.4 to 5.4 mg/dl) OR

C. Ionized calcium (SI) < 1.00 mmol/L (optimal range = 1.00 to 1.18 mmol/L); note our ISTAT system uses SI units

II. PREDISPOSING FACTORS

A. Maternal factors (diabetes, eclampsia or hyperparathyroidism)

B. Prematurity

C. Neonatal asphyxia or hypoxia

D. Sepsis

E. Shock

III. CAUSES

A. Maternal calcium deficiency.

B. High maternal intake of vitamin D.

C. Inadequate calcium administration to infant.

D. High phosphate intake.

E. Hypomagnesemia.

F. Hypoparathyroidism.

G. Intestinal malabsorption of calcium and magnesium.

H. Metabolic acidosis treated with NaHCO3.

I. Renal tubular disease preventing calcium reabsorption.

J. Furosemide therapy, which, when prolonged, may lead to bone demineralization through calciurias.

K. Hypoalbunemia may result in low total calcium (although the ionized calcium may be normal), and result should be corrected for the low albumin.

III. TREATMENT

A. Early (before 72 hours of age) hypocalcemia may be prevented by including 20-30 mg/Kg/day elemental Ca in the admission IV fluids. Watch phosphorus levels carefully to avoid hypophosphatemia.

B. Maintenance requirements for the premature infant may reach 70-80 mg/Kg/day elemental Ca or more when on full IV caloric intake. Because of the damage caused by Ca in IV sloughs, maintenance Ca should be given as IV slow infusions with total divided q.i.d.

C. Correction is more effective if given via continuous infusion or repeated slow infusions (10 to 20 mg/Kg elemental Ca over 4 to 6 hours).

D. If infant is symptomatic (i.e. seizures), 10-20 mg/Kg elemental Ca may be given in IV fluids over 30 minutes. MONITOR FOR BRADYCARDIA OR ARRHYTHMIAS AND DISCONTINUE INFUSION FOR HEART RATE LESS THAN 100 BEATS/MINUTE. Calcium given over a short period of time may cause bradycardia in any infant, and asystole in infants with underlying cardiac disease. INFANTS WHO ARE ON DIGOXIN SHOULD RECEIVE CALCIUM BY CONSTANT INFUSION ONLY!

E. If infant remains hypocalcemic despite repeated replacements, evaluate for hypomagnesemia or hyperphosphatemia. If normal evaluate for DiGeorge's Syndrome.

F. Extra calcium replacements should **not** go into fluids which contain bicarb or phosphorus as precipitation may occur.

IV. PREPARATIONS

A. Calcium chloride 10%:
Provides 100mg CaCl/ml or 27.3mg/ml elemental calcium or 1.4 mEqCa++/ml.

B. Calcium Gluconate: Comes 9% for elemental calcium.
Provides 9mg/ml elemental calcium.

References

1. Taeusch, Ballard and Avery: Diseases of the Newborn, Sixth Edition, W.B. Saunders Company, 1991, page 931.

2. Merenstein and Gardner: Handbook of Intensive care, Second Edition, The C.V. Mosby Company, 1989, page 217.

3. Vestal and McKenzie: High risk perinatal nursing, W.B. Saunders Company, 1983, pages 465-466.

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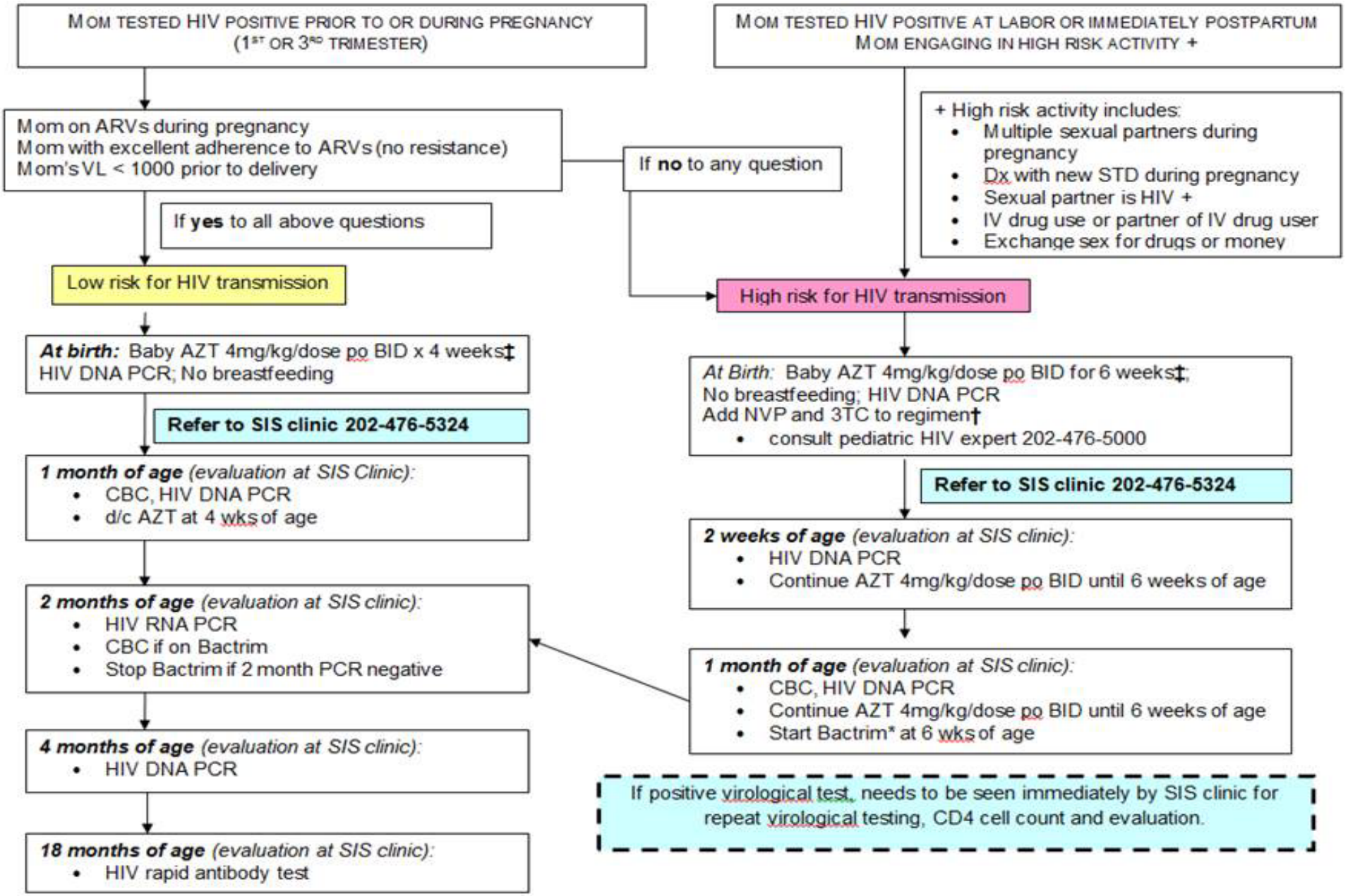
NEONATAL HIV ALGORITHM



‡ This dosing applies to infants ≥ 35 weeks gestation. 1st dose of AZT should be given as soon as possible after birth

† NVP dose: BW 1.5 – 2kg: 8mg/dose po / BW > 2kg: 12mg/dose po

- 1st dose within 48 hrs of birth, 2nd dose 48 hrs after 1st, 3rd dose 96 hrs after 2nd
- Please note BAND dosing for NVP dose, **NOT** per kg dosing

† 3TC (lamivudine) dose: 2mg/kg/dose po BID x 2 weeks

***** Bactrim dose: 5mg/kg/dose or 75mg/m2/dose po bid on M T W

Additional Resources:

- SIS consult: call hospital operator 202-476-5000
- SIS clinic coordinator: 202-476-5324 or 202-476-4705 (confidential voicemail)
- National Perinatal HIV Hotline: 1-888-448-8765

Adapted from: Special Immunology PMTCT Algorithm 12/5/2016

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NEONATAL ENCEPHALOPATHY & THERAPEUTIC HYPOTHERMIA

I. INTRODUCTION

Therapeutic hypothermia is standard of care for treating near term/term neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE).(1-4) Cerebral cooling with either *moderate* whole body cooling (to 33.5°C core temperature)(5), or selective head cooling (to 10°C with a CoolCap® device, maintaining a core temperature of 34-35°C)(2) has been demonstrated to reduce the risk for death or moderate to severe neurological sequealae from >60% to ~40%. At CNHS, we provide whole-body hypothermia according to the NICHD Neonatal Research Network protocol as described in this chapter.(1)

II. DEFINITIONS

Gunn & Gunn have suggested the following classification for degrees of hypothermia:(6)

A. Mild: 36-34^{o}C (1-3^{o}C below normal)

B. Moderate: 33-31^{o}C (4-6^{o}C below normal)

C. Severe: 30-27^{o}C (8-10^{o}C below normal)

D. Profound or deep: 26-15^{o}C ($\geq$15-20^{o}C below normal)
Sometimes performed with deep hypothermic circulatory arrest during surgical repair of complex congenital heart disease.)

III. ELIGIBILITY CRITERIA

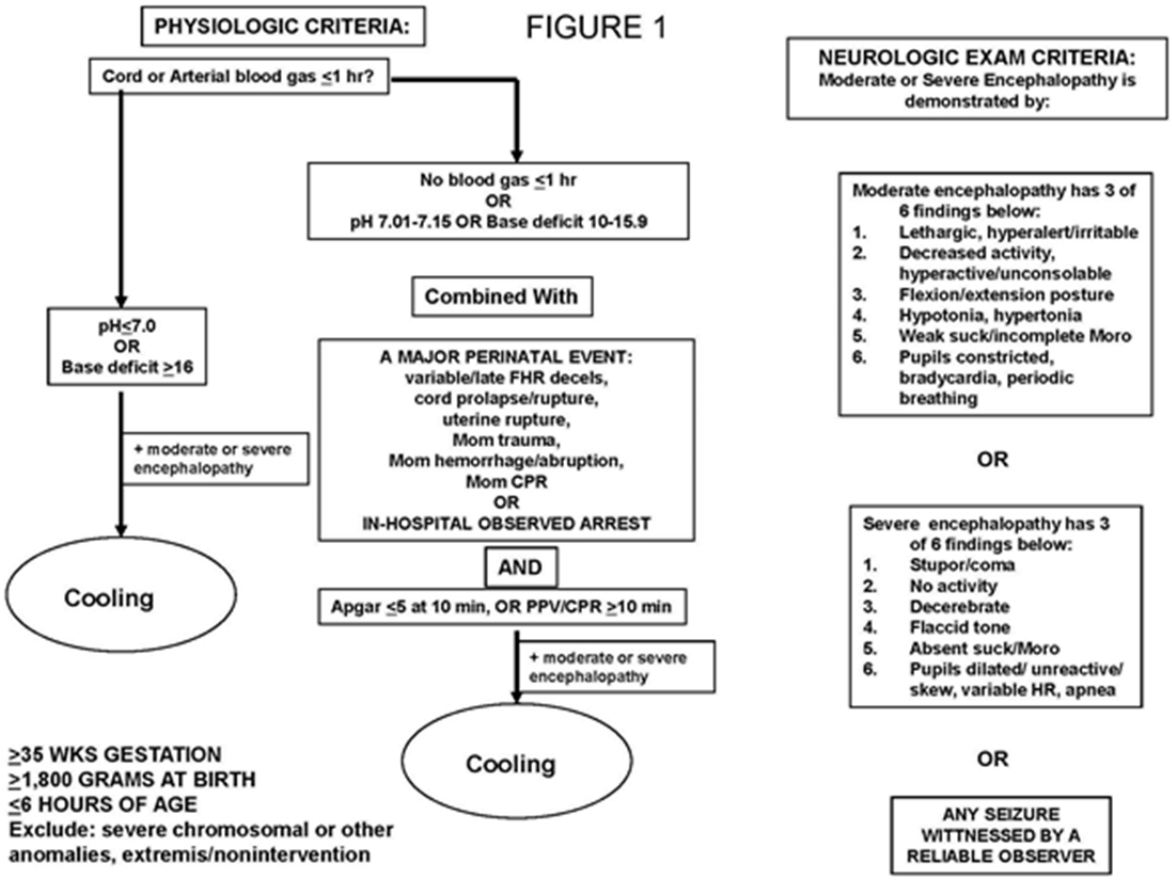
A. Inclusion
1. 35 weeks completed gestation, AGA >1800g at birth
2. Must initiate cooling within six hours of birth
3. Demonstrated evidence of perinatal depression followed by manifestation of neonatal encephalopathy (NE) (figure 1 and section C below)

B. Exclusion:
1. Moribund infants not receiving resuscitation and life support
2. Premature neonates younger than 35 weeks are currently excluded since hypothermia in this population is associated with increased mortality,(7) although ongoing trials are investigating safety and efficacy of cooling in the late preterm (34-36wk GA) infant

C. Evidence of NE includes
1. Requirement for resuscitation at delivery (in particular an Apgar score $\leq$5 requiring positive pressure ventilation at 10 minutes of life)
2. Arterial/venous/or mixed umbilical vessel blood pH of $\leq$7.00, or having a significant base deficit of at least -16 mEq/L. Also qualifying for therapy are blood gas disturbances within the first hour of life with pH 7.01-7.15 and/or a base deficit between -10 to -15.9 mEq/L, along with an ominous perinatal history (fetal heart rate decelerations, umbilical cord prolapse or rupture, uterine rupture, severe maternal trauma preceding birth, and abruption of the placenta, or the expectant mother experienced any life-threatening event requiring CPR).

3. Clinical signs of a moderate to severe encephalopathy must also be present (an infant who is lethargic, or completely stuporous, has diminished or completely absent activity and muscle tone, having weak or absent sucking and Moro reflexes, with fixed-constricted or unresponsive dilated pupils, having fixed flexion or extension posturing of extremities, or a seizure observed by an experienced clinician). Infants with such symptoms persisting for several days have about a 60 percent risk for death before hospital discharge or moderate to severe life-long neuro-developmental disabilities (cerebral palsy, deafness, blindness, mental retardation, and/or recurrent seizure disorder).(1, 8)
4. Verification of eligibility criteria can be performed using the "Therapeutic Hypothermia Clinical Presentation Checklist" (Appendix 1)

FIGURE 1



IV. PERFORMING HYPOTHERMIA

A. Eligibility criteria MUST be documented in the history and physical including :
   1. Time of birth
   2. Apgar scores
   3. Cord/ 1st hour blood gas
   4. Perinatal sentinel event (if present
   5. Qualifying clinical exam

B. Additional documentation

1. Babies should have clear documentation of these eligibility criteria, or conversely if decision is made not to cool, examination features justifying this decision should be clearly documented.
2. Head circumference (including percentile) is important to document on admission.

C. Passive cooling
If referring physician confirms criteria are met, initiation of passive cooling should be advised (i.e. turn off radiant warmer, monitor temperature every 15 minutes. Active cooling can be initiated on transport, and on admission, infants should be examined by the neonatology fellow/ attending to document presence and severity of clinical encephalopathy (noting that this exam may have evolved from initial presentation). Admission neuro exam should be documented under *"Hypothermia Exam" in the Neuro section of the Neonatal H&P in Cerner*.

D. Active cooling
Infants meeting criteria are placed before 6 hours of age supine (wearing only a diaper) onto a water-filled cooling blanket (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero Inc.). A warmed, flexible esophageal temperature probe is then positioned in the distal third of the esophagus (measured nares-to-auditory meatus-to-xiphoid process and minus 2 cm), and the water mattress cooling unit's thermostatic-controller is then immediately set to 33.5°C. Blanket water temperature rapidly cools the baby (30-40 minutes), then water temperature increases to about 31-34^{o}C (88-93^{o}F) to maintain the esophageal probe at 33.5^{o}C.[1] A second, larger pediatric-size blanket is also attached parallel into the cooling system. Water circulates through both blankets with the larger blanket hung on an IV rack at bedside serving as a capacitor to diminish fluctuations in the esophageal temperature (to less than ±1.0 C).(9) Although we use a warmer bed platform as a convenient crib, the over-head warmer is usually turned off during the cooling period. Abdominal-wall skin temperature is also monitored with a surface probe from the warmer bed (in monitor mode, warmer off).

E. Re-warming
After 72 hours, at the set point of 33.5^{o}C the automatic controller on the cooling system is increased by 0.5°C per hour, and blanket re-warming occurs. After six hours, the esophageal probe and cooling blankets are removed, and the anterior abdominal wall skin temperature is then regulated using the radiant warmer's servomechanism set at 36.5^{o}C (warmer on). Body temperature is monitored at a separate site (usually axillary) as a safety precaution to prevent hyperthermia >37.5^{o}C. The purpose for re-warming slowly is to avoid rapid shifts in critical electrolytes (calcium and potassium). Cardiac arrhythmias (ventricular tachycardia has been reported) fever, and seizures were observed more commonly with rewarming during the Network study[1], and in particular re-warming overshoot (fever >37.5^{o}C) is to be avoided by reducing the warming device servo-control in 0.5^{o}C increments.(10)

V. MONITORING AND MANAGEMENT DURING HYPOTHERMIA

A. Temperature
Esophageal, abdominal skin and axillary temperatures are monitored and recorded every 15 minutes for the first 4 hours of cooling, every hour for the next 72 hours of hypothermia. Most of the infants overshoot 33.5 and the blankets may warm up a bit to regulate the infant's temperature. Above all, hyperthermia >37.5^{o}C axillary temperature is to be avoided, since fever in this setting contributes to brain injury.(10)

B. Vital Signs

Infants otherwise receive routine clinical care, including the continuous monitoring of vital signs. Mild sinus bradycardia 80-90 beats-per-minute, and a small decrease in blood pressure usually <10 mm Hg are commonly observed. These are responsive to intervention with vasopressor therapy. Pulse-oximetry is usually normal unless there are other comorbid disease processes (e.g. PPHN).

C. Laboratory

Frequent surveillance laboratory studies are performed at baseline and daily after initiating hypothermia and during re-warming (use ***Hypothermia Order Set*** on admission). IStat electrolytes and blood gases are monitored every 6 hours in the first 24 hrs. Values may be altered during moderate hypothermia and/or as a result of the initial asphyxiating event. Special attention should be paid to:

1. Sodium- maintaining normal to high sodium (>140) is important with the potential for cerebral edema. Evaluation for SIADH should be considered in the face of hyponatremia and fluid restriction may be used if confirmed. (Keep in mind that infants may have urinary retention during hypothermia so bladder catheterization should be considered to confirm low urine output). If electrolytes and fluid status are unstable requiring titration/ alteration of IVF volume/ concentration, TPN initiation may be deferred until after rewarming.
2. Glucose: Avoiding hypo- or hyper-glycemia is critical for the injured brain. Initiating and maintaining a minimal physiologic GIR of 4 mg/kg/min is recommended. Restricting GIR to 4 and/or insulin can be considered for hyperglycemia (BG>150).
3. Coagulopathy: PT/PTT, platelets and fibrinogen are routinely monitored. Targets include maintaining INR<2, Fibrinogen >150 and Platelets >100K. FFP, platelet, or cryoprecipitate transfusions may be administered as needed. Keep in mind that the hypothermia order set includes daily surveillance laboratories- more frequent monitoring may be needed if the baby is receiving transfusion therapy for significant coagulopathy.
4. Signs of major organ dysfunction: The liver and kidney can be injured acutely or even manifest signs of compromise in delayed multisystem organ failure after asphyxia. Thus, AST/ALT and BUN/Cr are monitored routinely.
5. Blood gas determinations are included to monitor and treat in particular pH, ventilatory, and acid-base disturbances. Blood gas data should be adjusted for temperature at 33.5^{o}C and during re-warming.

D. EEG

We provide continuous EEG neuro-monitoring as part of our hypothermia protocol, although the EEG is not included in our clinical criteria for initiating hypothermia.[1] A full montage video-EEG (modified International 10-20 system for newborns) is recorded for about 96 hours to include cooling and rewarming periods. Amplitude-integrated EEG (aEEG) is also reviewed for characterization of background pattern and detection of seizures. Seizure detection is confirmed on raw EEG data and therapy provided (e.g., Phenobarbital). Neurology is consulted and involved with all patients referred for hypothermia.

VI. POST COOLING CONSIDERATIONS

A. Feeding

Asphyxiated infants are at risk for necrotizing enterocolitis resulting from transient intestinal ischemia. Additionally, it is presumed that hypothermia may also affect feeding tolerance. Infants generally remain NPO throughout cooling and rewarming for these reasons.

Feedings *may* be initiated as soon as 2 hours after rewarming if there are no other contraindications to feeding. Oral feeding should be trialed in infants assessed to have adequate suck and gag. In more severely affected infants, NG feeding may be required. Most infants recover oromotor function by the time of discharge. However, the most severely brain injured infants who exhibit no recovery of suck or gag may require gastrostomy placement.

B. Neuroimaging

All infants treated with hypothermia should receive a head ultrasound with Doppler on day one of life (evaluating for cerebral edema, hemorrhage and/or low cerebral blood flow velocity resistive indices [RIs<0.5]). This should be performed during daytime hours so that displaced EEG leads can be replaced by the EEG technicians after the study is completed. If abnormal, HUS can be repeated daily as indicated. Additionally, neuroimaging with MRI and MR spectroscopy (order in Cerner: MRI of brain without contrast, with clinical history written in comments) should be performed as soon as possible after rewarming (day 3-5 of life) and again at day 10-12 of life. Stable, feeding infants should be immobilized and imaged without use of sedation when feasible. Family meetings with neurology are routinely provided once results of MRI are available for parental counseling and prognosis.

C. Follow-up

All infants are followed both by neurology and development following discharge. The initial appointment should be made in the combined neuro-developmental clinic (“cooling clinic”) at 2 months of life. Infants who exhibit early signs of spasticity may also be referred to PM&R (“perinatal brain injury clinic”).

Appendix1

Therapeutic Hypothermia Clinical Presentation Checklist

Patient Name:_____

Date & Time of Birth: _____/_____/_____ _____:_____AM/PM

Clinical Information	Criteria	Instructions
Gestation: _____weeks	1. ≥ 35 weeks □ Yes □ No	Proceed to #2 **STOP**, patient ineligible
Birth Weight: _____grams	2. ≥ 1,800 grams □ Yes □ No	Proceed to #3 **STOP**, patient ineligible
1st blood gas: ____ Umbilical cord blood gas ____ 1st baby blood gas (≤ 1 hour of life): ___ ___:___ ___ (fill in time) pH ___.___ ___ BE ___ ___.___	3a. pH<7.0 or BD≥16 □ Yes □ No 3b. No gas or pH 7.01-7.15 or BD 10-15.9 □ Yes □ No	Proceed to exam** Proceed to #3b Proceed to #4 **STOP**, patient ineligible
Major perinatal events (check all): ___ Variable/late fetal HR decelerations ___ Prolapsed, ruptured, or tight nuchal cord ___ Uterine rupture ___ Maternal hemorrhage/abruption ___ Maternal trauma (*eg* MVA) ___ Mom received CPR	4. History of major perinatal event? □ Yes □ No	Proceed to #5 **STOP**, patient ineligible
Apgar scores: At 1 minute: ____ At 5 minutes: ____ At 10 minutes: ____	5. Apgar <5 at 10 min □ Yes □ No	Proceed to exam** Proceed to #6
Resuscitation after delivery: ___ PPV/intubated at 10 minutes ___ CPR ___ Epinephrine administered	6. PPV/ET at 10 min □ Yes □ No	Proceed to exam** **STOP**, patient ineligible

**Note: If patient meets above criteria and has a witnessed seizure, the patient is eligible for hypothermia regardless of exam findings Seizure: □ Yes □ No

NEUROLOGICAL EXAMINATION:

Circle findings for each domain. Patient is eligible for hypothermia if 3 or more domains with findings in columns 2 or 3.

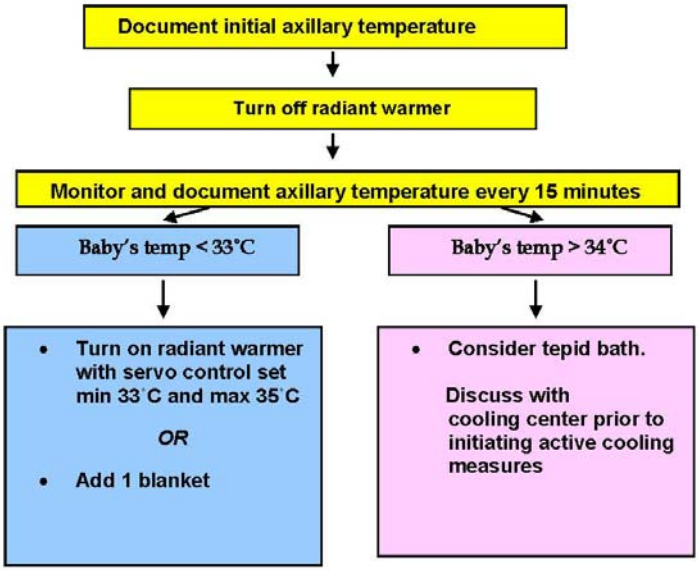
Domain	1	2	3
Level of consciousness	Normal Hyperalert	Lethargic (decreased activity in an infant who is aroused and responsive—can be irritable- to external stimuli, *i.e.* touch)	Stuporous/comatose (not able to arouse and unresponsive to external stimuli)
Spontaneous activity when awake or aroused	Infant is active, vigorous, doesn't stay in one position	Less than active, not vigorous	No activity whatsoever
Posture	Moving around and does not maintain only one position	Distal flexion, complete extension, or "frog-legged" position	Decerebrate with or without stimulation (all extremities extended)
Tone	Normal, resists passive motion Hypertonic, jittery	Hypotonic or floppy either focal or general	Completely flaccid like rag doll
Primitive reflexes	*Suck:* vigorously sucks finger or ET tube *Moro:* normal – extension of limbs followed by flexion with stimulus	*Suck:* weak *Moro:* incomplete	*Suck:* completely absent *Moro:* completely absent
Autonomic System	*Pupils:* Normal size (~1/3 iris diameter), react to light *Heart Rate:* Normal (>100 bpm) *Respirations:* Regular spontaneous breathing	*Pupils:* Constricted (< 3 mm est'd), but react to light *Heart Rate:* Bradycardia (<100 bpm, variable up to 120 bpm) *Respirations:* Periodic, irregular breathing effort	*Pupils:* Skew gaze, fixed dilated, not reactive to light *Heart Rate:* Variable, inconsistent rate, irregular HR *Respirations:* Completely apneac, requiring PPV and/or ET intubation

EXAMINER NAME: _____

DATE: ____/____/_____ TIME: _____:_____ (24:00)

Steps for Initiating Therapeutic Hypothermia:

1. Call your referral center **immediately** if patient meets criteria based on clinical presentation checklist and neurological exam
2. After consultation with cooling center, initiate targeted temperature management
3. Initiate targeted temperature management:



4. Prepare patient for transfer
5. Request placental pathology (or send placenta with baby upon transfer)

Transfers & Consultations:

Children's National Neonatal Intensive Care Unit 202-476-5040

Questions about neuroprotection?

Dr. Taeun Chang	202-476-2120	tchang@childrensnational.org
Dr. An Massaro	202-476-5448	anguyenm@.childrensnational.org

Appendix 2

Therapeutic Hypothermia for Cerebral Protection Information Sheet

Why does my child need cerebral protection?

Your baby has a serious illness called neonatal encephalopathy. This means that his/her brain has become critically sick, which results in loss of normal movement, reduced response to normal stimulation and perhaps even loss of consciousness and the ability to breathe. With routine neonatal intensive care, a mechanical ventilator can support your baby's respirations and perhaps ensure his/her survival. Cerebral protection through the use of therapeutic hypothermia is needed to help prevent neurological damage.

What is therapeutic hypothermia?

Two recent medical studies demonstrated fewer deaths or neurological disabilities occurring in encephalopathic children whose brains were cooled to about 92^{o}F (normal body temperature is 98.6^{o}F). Children's offers this therapeutic hypothermia, or whole-body cooling, where neonates are placed on a water-filled cooling mattress to reduce body temperature to 92^{o}F for 3 days (72 hours). This time period is long enough to interrupt injury. After the three days, the baby recovers to its normal body temperature and is observed in the NICU. This cooling program meets the National Institute of Health's Neonatal Network protocol, which demonstrated a reduction in death or serious disability from about two-thirds to about one-half of infants who had developed serious neonatal encephalopathy within 6 hours of birth.

What happens after therapeutic hypothermia process is finished?

Children's program provides continuous monitoring of electrical brain activity (EEG) to help assess your baby's need for medication (particularly sedatives to prevent seizures) and to assess the brain's health during recovery. After recovery and discharge from the hospital, Children's offers developmental follow-up evaluations by our pediatric/neonatal neurologist and developmental psychologist, who are closely attuned to each baby's needs and eventually school performance.

How can I learn more about this program?

Your baby's doctor will describe our cooling program to you in more detail and answer any questions about this new therapy, its potential benefit and possible risks or unknowns.

Other resources

Intranet:
http://intranet.childrensnational.org/healthcare-professionals/physicians/Documents/pdf/setting-up-therapeutic-hypothermia.pdf

http://intranet.childrensnational.org/healthcare-professionals/nurses/Documents/pdf/guidelines/C11-NPG-therapeutic-hypothermia.pdf

http://intranet.childrensnational.org/healthcare-professionals/order-set-oversight-committee/Documents/Therapeutic Hypothermia Orders for the Neonate.pdf

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Revised: June 2016
An Massaro, M.D.

General Surgery Beta-blocker
Parent Instruction Sheet for Hemangioma Treatment

Your child requires a medicine for his hemangioma. She may be on Hemangeol (Brand) or Propranolol (Generic). The possible side effects are the same for both medicines.

Dosage

(Provider will prescribe medicine and dosing)

1. Give Hemangeol _____ ml **2 times a day** by mouth for 1 week.
   a. Give doses at least 9 hours a part with feedings.
   b. After 1 week increase dose of Hemangeol to _____ ml **2 times a day** with feedings.

2. Give Propranolol _____ml **2 times a day** by mouth for 1 week.
   a. Give doses at least 9 hours apart with feedings.

3. Give Propranolol _____ ml **3 times a day** by mouth
   a. Give doses at least 6 hours apart with feedings.

When to Hold Medicine

1. Hold doses if your child is ill, has a cold, is vomiting, very sleepy, sweating or not eating well. Continue to hold doses until your child is completely well. Call your provider if your child has any of these symptoms

2. Holding doses will not hurt your child.

3. **Restart medicine when child is well.**

Possible Side Effects

(Hold medication if your baby has any of these symptoms)

- **Low blood sugar-** this can cause a child to be sweating, jittery, pale, fussy or sleepy. Sometimes there are no symptoms at all. If the blood sugar is very low, this can cause a child to have a seizure.
- **Decrease in blood pressure or heart rate**
- **Bronchospasm (wheezing).** If your baby has a cold and/or is having breathing problems do not give the medicine until he is completely better.
- ***Sleep Problems***
- ***Diarrhea***

To keep the blood sugar from going low, you should **feed your baby** using these rules:

- Babies **up to 6 weeks of age should be fed at least every 4 hours.**
- Babies **between 6 weeks and 4 months of age should be fed at least every 5 hours.**
- Babies **older than 4 months of age should be fed at least every 6 hours.**

Follow-up Appointments

1. Your child needs to be seen about 2 weeks after the medicine is started and every 1-2 months during treatment.

2. Your child will need the medicine typically for about 4-6 months.

3. To schedule an appointment call 202-476-2150.

4. Contact our nurse practitioner Gina Krakovsky at (202)476-4837 or email at gkrakovs@childrensnational.org if you are unable to get an appointment in the requested time frame.

GASTROESOPHAGEAL REFLUX

I. GENERAL INFORMATION

Gastroesophageal reflux (GER) is a common problem in premature infants secondary to poor gastric motility and lower esophageal sphincter relaxation. Medications such as theophylline and caffeine may contribute to the incidence of GER as they promote relaxation of smooth muscle, increase gastric secretions, and decrease lower esophageal sphincter pressure. Steroids, such as betamethasone and dexamethasone may disrupt development of the esophageal body and sphincter, increasing the risk for development of GER. Physiologic GER is characterized by frequent spitting up, is not associated with complications, and typically resolves spontaneously. Pathologic GER is more problematic and is associated with inadequate weight gain, crying and fussiness during and after feedings, respiratory problems such as aspiration and pneumonia, and anemia. The North American Society of Pediatric Gastroenterology and Nutrition has developed a comprehensive evidence-based approach to treatment management of *pathologic* GER.

II. MANAGEMENT

A. Stage I: Non-Pharmacologic therapies

1. Provide smaller, more frequent feedings.

2. A small subset of infants with GER may be allergic to cow's milk protein. Use of a hydrolyzed protein formula may alleviate symptoms of GER; however, these formulas do not meet the vitamin and mineral needs of premature infants so their use should be carefully evaluated.

3. Use of rice cereal to thicken feeds in the management of GER is not supported by literature and is not currently practiced in the NICU. In premature infants, this practice dilutes out important vitamins and minerals provided in premature infant formulas. A trial use of commercially available pre-thickened formula may be appropriate in term infants. Breast milk cannot be thickened due to the enzymes it contains.

B. Stage II: Pharmacologic Management

Pharmacologic management should be considered if non-pharmacologic therapies prove ineffective.

Class	Drug	Action	Potential side effects
Histamine antagonists	Ranitidine (Zantac)	Decreases secretion of gastric acid from parietal cells by reversibly and competitively inhibiting H2 receptors	Increasing gastric pH in preemies may cause bacterial overgrowth and/or bacteremia. Is associated with higher incidence of NEC in VLBW infants.

Proton pump inhibitors	Omeprazole (Prilosec) Lansoprazole (Prevacid)	Increases gastric pH by blocking hydrogen ion production	Increasing gastric pH in preemies may cause bacterial overgrowth and/or bacteremia
Prokinetic agents	Erythromycin	Promotes gastric emptying by improving gut motility	Diarrhea, cardiac arrhythmias, hypertrophic pyloric stenosis, late onset infections

C. Stage III: Surgical Management

Surgical intervention may be considered when medical management fails to control GER. Potential indications for surgical intervention include severe failure to thrive, reflux induced aspirations and pneumonia, esophagitis, and acute life threatening events. A common surgical procedure for the treatment of GERD is the Nissen fundoplication. In this procedure, the fundus of the stomach is wrapped around the distal esophagus. Complications associated with the fundoplication procedure include recurrences of symptoms necessitating repeat operations, herniation of the wrap through the diaphragmatic hiatus, dysphagia, and dumping syndrome.

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Revised: April 2016
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Mary Revenis, MD

FLUIDS AND ELECTROLYTES

I. GENERAL INFORMATION

A. The newborn infant is in a state of sodium (Na) and water excess at birth. Therefore, a 5 to 15% loss in weight over the first three days of life is appropriate and expected. More weight loss (15 to 20% of birth weight) may occur in very [<1,500 grams at birth] and extremely low birth weight [<1,000grams] premature babies and still be appropriate provided that serum chemistries (serum sodium, potassium, BUN/Cr) are normal, reflecting appropriate fluid balance.

B. Aim to maintain zero balance for water and electrolytes within 3-4 days after birth in term infants and by 5-7 days in preterm infants.

C. At the end of the first week of life begin to provide slightly positive water, sodium and potassium balance necessary for meeting the needs for new tissue growth (matching intrauterine growth rate between 10-15 gms/kg/day).

D. Initiate total parenteral nutrition (TPN) as early as possible to maintain fluid, electrolyte and nitrogen balance. This is critically important because early protein containing TPN can help attenuate the premature newborn's catabolic state. The pharmacy stocks a generic TPN solution of 5% dextrose (D5) with 2 grams of amino acids per 100 mL to start on all premature infants on the day of admission – please see additional details in nutrition chapters.

II. SOURCES OF WATER LOSS

A. Physiologic: expected weight loss over the first few days of life
   1. Represents an initial decrease in total body water (TBW) and change in its distribution between intracellular (ICF) and extra cellular (ECF) fluid spaces
   2. These changes effected largely by the neonatal kidney[5]. During this phase of neonatal transition from placental balance, urine volume formation may normally exceed 80% of parenteral or enteral fluid volume administration.
   3. Weight loss should not exceed 10-15% of birth weight (BW) for full term infants, though it may be as much as 20% for ELBW < 1,000 gms.

B. Sweat: contributes minimal water loss in the neonatal period.
   1. <30 weeks EGA: no sweating occurs.
   2. ≤36 weeks EGA: limited response in sweating.
   3. Term infants: typically do not sweat when in neutral thermal environment.

C. Fecal: losses are negligible in the first day.
   1. Full term infants may have stool water loss of 5-7 mL/kg/d.
   2. Phototherapy increases stool water loss up to 19 mL/kg/d[9].
   3. Phototherapy may decrease gut transit time in jaundiced infants[11].

D. Urine: losses include water required for renal excretion of solute, particularly urea and metabolic acids (sulfuric, phosphoric).

1. Renal water requirements depend upon functional characteristics of the newborn kidney, the renal solute load of the diet (protein turnover that generates urea), and metabolism necessary for growth.
2. Term infant's kidneys can concentrate to 600-700 mOsM/kg usually compared to the adult concentrating capacity 1200-1400 mOsM/kg. Some infants do, however, concentrate to specific gravities 1.020-1.024 with urine osmolality 900-1200.
3. Term infants can dilute urine to 30-50 mOsM/kg, which is more dilute than possible for older children or adults.
4. Fluid administration to maintain 50-100 mL/kg/day of urine or 2-4 mL/kg/hr of urine will maintain urine osmolality, which does not overly stress renal concentrating, or dilution mechanisms.

E. Drainage: losses must be added to the total of daily fluid losses for calculating volume replacement.
   1. Volume of loss plus electrolytes present in drainage must be estimated or measured.
   2. Usual electrolyte content of common gastrointestinal fluids follows:

Note: For Na^+,K^+,Cl^- = 1mM = 1 mEq

Fluid	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Gastric	20-80	5-20	100-150
Small bowel	100-140	5-15	90-120
Bile	120-140	5-15	90-120
Ileostomy	45-135	3-15	20-120
Diarrhea	10-90	10-80	10-110

F. Insensible water loss (IWL): occurs by passive water evaporation from the pulmonary tree (approximately 30% of IWL in term infant) during respiration and as transepidermal evaporative water loss (TEWL) from the skin.
   1. Environmental factors greatly affect IWL[16].
      a. Ambient water vapor density (humidity)--particularly during the first week of life.
      b. Ambient temperature--of the air, and of the incubator or NICU room walls
      c. Air speed--around the infant or warmer.
      d. Thermal blanket use (e.g. Saran plastic or bubble wrap) decreases transepidermal water loss.
   2. IWL is inversely proportional to gestational age. Preemies have increased IWL due to
      a. Increased permeability of the skin to water (low keratin content)
      b. Greater surface area per unit of body weight
      c. Relative increase in vascularity of the skin or greater skin blood flow relative to metabolic rate
   3. Normal values for IWL are:
      a. Term infant IWL = 0.7-1.6 mL/kg/hr (17-38 mL/kg/d)
      b. Very low birth weight (VLBW) preterm infant IWL = 1.8-2.5 mL/kg/hr (40-60mL/kg/day)
      c. Extremely low birth weight (ELBW) premature infant (1,000 gms) as high as 7mL/kg/hr, i.e. 168mL/kg/day!
   4. Factors increasing IWL are:
      a. Gestational age (prematurity increases IWL)
      b. Tachypnea or respiratory distress with increased minute ventilation

c. Increased ambient temperature--increases IWL 3-4 fold when incubator air temperature is above 35° C[4] and without humidification
d. Activity--increases IWL up to 1.7 fold[4]
e. Prolonged crying--increases IWL up to 2 fold
f. Radiant warmer--increases IWL usually by 50% and up to 5 cc/kg/h in VLBW and ELBW infants due to increased peripheral skin blood flow and increased evaporative losses due to exposure to convective air currents[12,13,15]
g. Phototherapy--increases IWL by 2.4 cc/kg/hr max or by 20-50 cc/kg/d[9,13]
h. Skin defects

5. Factors decreasing IWL are:
   a. High relative humidity in the ambient air may decrease IWL by at least 30-50%[4] particularly for VLBW infants in their first few days of life.
   b. Double-walled incubators are most effective in reducing IWL when used with incubator humidification (e.g. the Ohmeda "Giraffe™")
   c. Skin barriers/heat shields (e.g., saran plastic (PVC) blanket) are necessary if ELBW patients must be kept on open warmer beds.
   d. Warming and humidifying the inspired air in a ventilator eliminates IWL from the respiratory tract.
   e. Covering skin defects
   f. Mature skin/gestation age
   g. Topical skin agents (Paraffin, aquaphor, etc); such agents must be used with caution. Prior meta-analysis in high income countries noted an increased risk of infection with use but the most recent Cochrane Review could not demonstrate a benefit or risk with use compared to non-use[20].

III. FLUIDS AND HYDRATION

A. Initiation of fluids:
See table below for suggested rates of and initial type of fluid to be administered[7,10] in first 24 hrs of life. These are starting guidelines only, empirical evaluation is necessary to insure they are appropriate for a given individual. This is especially true in the VLBW and ELBW newborn. For the ≤ 750g neonate with immature skin on an open warmer as much as 200-250 mL/k/d of dextrose and water (not less than D5%) may be required because of high insensible losses (primarily TEWL). There is no substitute for frequent assessment of free water balance during the first days of life in this group of newborns.

	Fluid Rate (mL/Kg/d)				
DOL	**<750 gm**	**750-1000gm**	**1000-1500gm**	**1500-2500gm**	**> 2500 gm**
0-1	110-140	90-110	80-100	70-90	60-80
1-2	120-150	100-130	110-120	90-100	80-100
2-3	130-160	130-150	120-140	110-140	100-120
	Note: Goal initiation GIR for premature infants is 4-6 mg/kg/min and 5-7 mg/kg/min for term infants				

B. Assessing hydration:
1. When possible weigh daily, especially for ELBW babies <1,000 gm
2. Look for evidence of dehydration or over hydration by careful clinical examination for skin turgor, edema, eye turgor, sunken fontanel, etc.
3. Accurately monitor urine output (volume).

a. Aim to achieve 50-100 mL/kg/d or 2-4 mL/kg/hr.
b. Evaluate any infant not voiding after six hours, or producing urine< 1mL/kg/hr over 12 hours (oliguria).

4. Assess plasma osmolality and serum sodium.
   a. Serum sodium: in practice serum sodium is the most useful parameter to follow in VLBW newborns during the first few days of life. Within the first few hours, serum Na reflects mother's value.
      1.<1000g: an early Na can provide a good baseline. In the first 24-48 hours of life major changes in serum Na are due to free water balance, a rising serum Na indicating excessive free water loss from the skin (TEWL).
      2.<750g: Na should be checked every 6 hours and fluid intake adjusted accordingly.
      3.750-1000g infant every 8 hours is usually enough.
      4.Once free water needs are established, less frequent checks are okay.
   b. Plasma osmolality: normal range is <u>280-310 mOsM/kg.</u>
      i. Measure directly or calculate from the following equation

$$1.86 \times Na\ (mEq/L) + \frac{BUN\ (mg\%)}{2.8} + \frac{glucose\ (mg\%)}{18} + 5$$

      ii. Unfortunately, the plasma osmolality bears <u>no fixed</u> relationship to plasma sodium in the first week of life[2].
      iii. *Hyperglycemia* may significantly contribute to increased plasma osmolality. A glucose concentration of 400 mg/dL contributes 20 mOsM/kg to plasma osmolality (about 1mOsM per 20mg).
      iv. *Urea* (A high BUN) may contribute significantly to increase plasma osmolality. A BUN of 100 mg/dL, contribute 35.7mOsM/kg to plasma osmolality (about 3mOsm/kg for each mg/d 10 mg/dL change in BUN). Remember BUN may be increased with dehydration but is also influenced by protein intake, (PO and I.V.) as well as renal function.
      v. *Other* vehicles for certain medications or multivitamins may contribute to hyperosmolality. Propylene glycol in MVI concentrate, phenobarbital IV, digoxin IV, Bactrim IV, etc. have caused hyperosmolality in VLBW premies.
5. Monitor ongoing losses carefully.
   a. Weigh diapers prior to placing on the infant, particularly if diarrhea is a problem.
   b. Measure drainage losses accurately, e.g. NG, ostomy, intraventricular drains or reservoirs, etc.
   c. Monitor for glycosuria. Recognize that hyperosmolar dehydration may occur with hyperglycemia.

C. Special considerations:
1. <u>Congestive heart failure</u>: patients usually require *fluid restriction*. Symptomatic PDA has been associated with fluid provision >150 cc/kg/d in premature infants.
2. <u>Hyaline Membrane Disease</u>: HMD or other forms of respiratory distress have increased insensible water loss but are also exacerbated by excess fluid intake; a careful balance must be maintained.
3. <u>Cerebral edema:</u> requires conservative fluid administration to avoid exacerbating edema.
4. <u>SIADH (Inappropriate ADH syndrome)</u>: requires fluid restriction.
5. <u>Meningitis:</u> conservative fluid administration.
6. <u>Anuric or oliguric renal failure</u>: once the patient has failed to respond to a trial volume and Lasix with increased urine output, requires limitation of fluids to insensible loss plus

urine output (on the order of 30 mL/kg/day) while in oliguric phase. Avoid K+ administration when oliguric or anuric.

7. Hyponatremia: is usually the result of too much solute free water intake, therefore, water volume restriction is recommended. Try to avoid hypertonic (3%) sodium bolus administration. Rate of correction of hyponatremia should not exceed +10 mEq/dL/day to avoid CNS damage.

IV. ELECTROLYTE ADMINISTRATION

A. Sodium

Newborns have an excess of total body sodium (Na) that resolves during transition as normal postnatal weight loss occurs.

1. VLBW/ELBW infants:
   a. Tend to develop hypernatremia in the first 3 days of life due to excessive insensible free water loss (TEWL).
   b. Avoid adding Na+ until serum Na+ is <135 mEq/L during the 1st 72 hours of life.
   c. Monitor serum Na+ frequently in 1st 72 hours of life
   d. Hyponatremia can be seen in VLBW infants after the first few days of life if excess free water OR inadequate sodium is given.
   e. Check serum electrolytes and assess fluid balance prior to adding NaCl to fluids.
   f. Anticipate other sodium sources such as antibiotics (sodium ampicillin, sodium heparin, sodium bicarbonate, sodium acetate), etc. in calculating net Na to be administered.
   g. Small preemies have difficulty conserving sodium and may require (usually after the first 3 days of life) considerably more maintenance sodium. Urinary losses of sodium can be estimated by checking spot urine sodium and the total daily urine output.
   h. Note that excess sodium has been linked to an increase in the occurrence and severity of BPD/CLD[17,18]. **Be sure low serum Na values reflect Na loss and not free water excess.**
   i. Certain drugs given to premature infants (e.g. Theophylline, caffeine, etc) may cause salt loss in urine.
      i. Infants on chronic diuretics (e.g. Lasix) may develop hypochloremia, which may require supplementation with NH_4Cl in addition to NaCl and/or KCl as hypochloremia in infancy inhibits growth.

B. Potassium

1. Always ensure that the infant can void before giving KCl.
2. Start KCl as soon as the infant has voided especially if serum K+ is less than 4.0 mEq/dl.

C. Magnesium and Calcium

See Premature Care Protocol and Intravenous Nutrition Protocol.

D. Monitoring

1. Term infants: measure serum electrolytes on admission to and then daily until stable. Once TPN is stable, QOD – twice weekly serum electrolytes should be adequate except in unusual circumstances.
2. Neonates <750gm: Check electrolytes Q 6-8 hours during first 48-72 hours of life to assess of fluid status.
3. Neonates 750-1000gm: Check electrolytes Q 8-12 hours during first 48-72hours of life.

V. FLUID AND ELECTROLYTE ADMINISTRATION

A. Suggested routes of fluid administration
   1. Intra-arterial lines placed centrally through the umbilicus should not be used solely for fluid administration because of potential catheter complications.
   2. Intravenous umbilical lines can be used solely for fluid administration.
   3. Peripheral IV's (PIVs) require careful monitoring since they may be a source of significant morbidity from skin sloughs, particularly with calcium-containing fluids. To prevent skin sloughs: never completely cover an IV site, recognize that blood return may be present in an infiltrated IV and remove any questionable IV; do not wait until slough occurs.
   4. Gavage/Gastrostomy/Intrajejunal routes of fluid administration also require careful calculation of fluids, however fluid losses are greater through these routes and therefore allow for more leeway in volumes.

B. Suggested type of fluid administered on DOL 0-1
   1. Term infant, NPO: $D_{10}W$ is fluid of choice with addition of appropriate electrolytes.
   2. Preterm infants <1,000 gm: GIR > 6-6.5 mg/kg/min glucose infusion may not be tolerated and hyperglycemia may ensue with attendant diuresis.
      a. Always calculate rate and mg/kg/min of glucose infusion carefully.
      b. Monitor urine for glucose. If urine glucose is greater than 2+ then measure serum glucose and consider adjustment in glucose infusion or insulin administration. Our goal is usually to maintain 50 mg/dL<serum glucose<180 mg/dL.
      c. Glucose infusion of <4mg/kg/min should not be provided
   3. Start parenteral nutrition on as soon as feasible (see Nutrition protocols).
   4. Recognize that older infants (term and preterm) require minimum of maintenance electrolytes if admitted beyond the first few days of life

C. Fluids and electrolytes for the ELBW (<1000gm) neonate[1,78,10,15]
   1. Minimize insensible water losses (see section II above).
      a. Use double walled incubator at neutral thermal environment when possible (skin temperature servo controlled ~36.5^{o}C).
      b. Use heat shield within incubator.
      c. Move the infant's incubator away from cold areas (such as windows).
      d. Provide high humidity (heated to neutral thermal environment temperature) in the incubator. No more than 60-80% saturation is recommended. This is to prevent rain-out (any visible water or mist promotes bacterial and yeast growth).
      e. Avoid placement under overhead warmer with radiant heat source, if possible. Insensible losses of water may be higher in this environment.
      f. Ensure inspired air from the ventilator, if used, is heated and humidified properly.
      g. While historically phototherapy increased fluid losses, more current LED forms of phototherapy do not result in increased losses.
   2. Calculating Fluids
      a. Total fluid goal: use 80-120 cc/kg/d D_5W-$D_{10}W$ on the first day to start fluid therapy based on gestational age/BW.
         i. Adjust rate as needed by monitoring urine output, specific gravity, etc.
         ii. Weigh daily if possible. If greater than 10-15% of body weight is lost in first week suspect dehydration.
         iii. Remember to tally all losses when determining fluid provisions.
      b. Sodium: remember that hypernatremia is often a problem in the first 72 hours of life. After the first 24 hours of life, if serum Na is less than 135 add 2-3 mEq/kg/d Na. After 72 hours of life Na losses may be increased (rarely is up to 12 mEq/kg/d Na

replenishment may be required). Urinary losses should be documented and diuretics adjusted before resorting to such heavy sodium loads.

c. Glucose: begin glucose infusion at no less than 4mg/kg/min; be prepared to treat for hyperglycemia if >6mg/kg/min is provided. Monitor and calculate glucose infusion rate closely

D. Worksheet for Calculation of volume of Fluid to be administered[7]

	mL/kg/d
Basic fluid provision based on age and weight (see the suggested rates for fluid administration)	
Phototherapy (can skip if newer LED lights are used)	**+ 20**
Renal concentrating defect	**- 60 (+ urine out)**
Mechanical ventilation	**- 10**
Acute renal failure	**- 40 (+ urine out)**
Congestive heart failure	**- 30**

TOTAL: cc x kg BW =mL/d

VI. SUMMARY SUGGESTIONS FOR FLUID MANAGEMENT IN PREMATURE NEONATES

A. Anticipate and prevent

1. Trans-epidermal water loss will be high
   - Take active steps to reduce trans-epidermal losses

2. Glucose requirements will be variable
   - Use a volume independent, variable glucose delivery system

3. Parenteral sodium intake is unnecessary until the physiological postnatal isotonic loss of extracellular fluid is underway by 2-5 days after birth
   - Defer maintenance sodium administration until there has been weight loss of the order of 6% of body weight

4. A fluid prescription is a matter of best clinical judgment and is vulnerable to changing clinical circumstances
   - Monitor carefully and continuously

5. The goals of hydration and nutrition are intertwined but distinct
   - Distinguish these goals clearly

6. Initiate starter protein-containing (DAY 0) TPN as early as possible to attenuate early catabolism.

REMEMBER: When prescribing fluids and electrolytes you are substituting for the normal mechanism of thirst (intracellular water volume, circulating blood volume and CNS osmolality). Trust the neonatal kidney to assist maintaining balance.

B. Do's and don'ts

1. **Do not** give furosemide routinely with transfusion of packed red cells
   - Transfusion of packed red cells at 3 mL/kg/h does not lead to intravascular volume overload even in extremely preterm infants

2. **Do not** use repeated doses of furosemide in the oliguric baby; in the non-oliguric infant doses should be administered at no more than 24 hour intervals
   - Furosemide clearance is low and plasma half-life exceeds 24 hours in infants <31 weeks post-conceptual age. Repeated doses will lead to rapid accumulation and increase the risks of ototoxicity, interstitial nephritis, and ductal patency

3. **Do** restrict fluid intake when signs of a patent ductus arteriosus present
   - Restrict judiciously when there is evidence of volume overload; routine fluid restriction will compromise nutrition

4. **Do** ask yourself if your goal is hydration or nutrition whenever considering a change in fluid provision.
   - If hydration is satisfactory, stepwise increments in fluid intake after birth are unnecessary unless accompanied by a clinically relevant increase in nutrition

C. Monitoring fluid balance in the immediate postnatal period

1. Daily changes in body weight
2. No postnatal weight loss or immediate weight gain is indicative of fluid excess:
   - First most usual cause is impaired sodium and/or water excretion
   - Second most usual cause is inappropriate daily maintenance fluid calculations
3. Serum sodium
   - Hyponatremia suggests water excess
   - Hypernatremia suggests water deficit.
4. Urine volume
   - <1 mL/kg/h warrants investigation
   - 2–4 mL/kg/h suggests normal hydration
   - >6–7 mL/kg/h suggests impaired concentrating ability or excess fluid administration or recovery from acute illness with mobilization of capillary-endothelial leak fluid (body edema).

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Children's National™

Recommended Enteral Nutrition Needs

	Preterm	Term
Fluid	140-160 ml/kg	150-160 ml/kg
Kcal	110-130 kcal/kg	100-120 kcal/kg
Protein	3.5-4.5 g/kg	1.5-2.5 g/kg

If fortification is needed, fortify feeds to :

⇒ 22 kcal/oz at 80-100 mL/kg/day

⇒ 24 kcal/oz at 100-120 mL/kg/day.

Children's National Feeding protocol

Weight	Trophic feeding	Daily advancement
≤750 grams	10-20 ml/kg/day x 5 days	20 ml/kg/day
751-1000 grams	20 ml/kg/day x 4 days	20 ml/kg/day
1001-1250 grams	20 ml/kg/day x 3 days	20-30 ml/kg/day
1251-1500 grams	20 ml/kg/day x 2 days	20-30 ml/kg/day
1501-2000 grams	20 ml/kg/day x 1 day	20-30 ml/kg/day

The ranges below show the feeding advancement rate for a 20-30 mL/kg/day increase for a q 6 hour increase, q 12 hour increase and q day increase.

Weight (Kg)	Trophic Feeding Rate	Actual Volume/kg provided by trophic feed rate (mL/kg/day)	mL to advance q 6 hours		mL to advance q 12 hours		mL to advance q day	
0.5	**1.25 mL q 3**	**20**	n/a	n/a	0.5	n/a	1.25	n/a
0.6	1.5 mL q 3	20	n/a	n/a	1	n/a	1.5	n/a
0.7	1.75 m Lq 3	20	n/a	n/a	1	n/a	1.75	n/a
0.8	2 mL q 3	20	n/a	n/a	1	n/a	2	n/a
0.9	2.25 mL q 3	20	n/a	n/a	1	n/a	2.25	n/a
1	**3 mL q 3**	**24.0**	0.71	1.1	1.5	2.1	2.5	3.8
1.1	3 mL q 3	21.8	0.79	1.2	1.5	2.2	2.8	4.1
1.2	3 mL q 3	20.0	0.86	1.2	1.5	2.3	3.0	4.5
1.3	3 mL q 3	18.5	0.93	1.4	1.5	2.3	3.3	4.9
1.4	4 mL q 3	22.9	1.0	1.5	2	2.9	3.5	5.3
1.5	**4 mL q 3**	**21.3**	1.1	1.6	2	2.9	3.8	5.6
1.6	4 mL q 3	20.0	1.1	1.7	2	3.0	4.0	6.0
1.7	4 mL q 3	18.8	1.2	1.8	2	3.1	4.3	6.4
1.8	5 mL q 3	22.2	1.3	1.9	2.5	3.6	4.5	6.8
1.9	5 mL q 3	21.0	1.4	2.0	2.5	3.7	4.8	7.1
2	**5 mL q 3**	**20.0**	1.4	2.1	2.5	3.8	5.0	7.5
2.1	5 mL q 3	19.0	1.5	2.3	2.5	3.8	5.3	7.9
2.2	6 mL q 3	21.8	1.6	2.4	3	4.4	5.5	8.3
2.3	6 mL q 3	20.9	1.6	2.5	3	4.4	5.8	8.6
2.4	6 mL q 3	20.0	1.7	2.6	3	4.5	6.0	9.0
2.5	**6 mL q 3**	**19.2**	1.8	2.7	3	4.6	6.3	9.4
2.6	7 mL q 3	21.5	1.9	2.8	3.5	5.1	6.5	9.8
2.7	7 mL q 3	20.7	1.9	2.9	3.5	5.2	6.8	10.1
2.8	7 mL q 3	20.0	2.0	3.0	3.5	5.3	7.0	10.5
2.9	7 mL q 3	19.3	2.1	3.1	3.5	5.3	7.3	10.9
3	**8 mL q 3**	**21.3**	2.1	3.2	4	5.9	7.5	11.3

END OF LIFE CARE

Unfortunately, the NICU at CNHS admits a number of patients who have a prognosis that warrants asking whether life support measures should be held or withdrawn. Our goals of family centered care extend to end of life decision making in the NICU. Redirecting goals of care and withdrawing life support are not just foregoing specific procedures and treatment, but also requires the transition to ongoing symptom management and comfort care.

What are a few of the many things that go into such a decision?

- Prognosis of the patient with regard to survival.
- Quality of life. To some of us, the concept of interactional potential is important; will the patient relate to, have recognition of, or show some sort of responses to others.
- The amount of suffering expected to be endured in the short and long term
- The family and the likely effect of different options on them.

Some things to be considered either not at all or with very great caution.

- Social and economic status of parents.
- Level of responsibility or interest shown by mother/father

Recognize that the issues are usually murky, ambiguous and complex with room for varied opinions. The responsible parties are the parents/legal guardians, the Neonatology attending and attendings from other clinical services which have expertise in the disease process (Genetics, Cardiology, Neurology etc.). Attendings welcome the important input of all health care workers, including the medical team, nursing staff and other clinical support staffs.

These are difficult and heart wrenching decisions for the family. <u>Unnecessary confusion must be avoided.</u> The Neonatology attending will act as the spokesperson for the medical team to maintain continuity of communication. This will facilitate shared decision-making with the support and participation of the entire team while maintaining open and clear communication with the family. Conflicts within the team should be addressed early, much preferably before their expression to parents or family members, so that necessary supports can be made both to the family and team members.

The Ethics Committee can be enormously helpful in framing issues and providing guidance as to acceptability of certain choices. Anyone involved with or aware of the patient can request an Ethics consult, but whenever possible, it should be funneled through the Neonatology attending. The Palliative Care Team is also available, and members of this team are trained and experienced in dealing with end of life issues. In addition, the palliative care team can provide support for severe, debilitating or chronic illnesses, even if the family wishes to continue intesive medical support. Anyone involved with or aware of the patient can request a Palliative Care consult, including a NICU specific approach to palliative care, but it too should be funneled through the Neonatology attending. In addition to a family's personal religious and spiritual support, the hospital chaplain can be consulted as well. The ultimate goal is that parents feel supported, *regardless of the decision that is made.*

The hospital has a specific and well thought out set of Policies and Procedures that speak to these issues, we must comply with them. The text of these Policies and Procedures will not be detailed here because they can be found easily on the CNMC intranet as follows:

- Go to CNMC Intranet and click on the "Policies and Procedures" tab.

- From the list of choices Scroll down to Heading “Section: Patient Care”
- Open that section by left clicking the little box with + sign
- In section 5 (Death/Dying/Organ Donation) are the relevant PDFs, select CHPC:D:04 (Allowing a natural death) and CHPC:D:04P (Allowing a natural death Procedure).

Specific considerations for high risk newborns

- Compassionate care must be continued for all infants, including those foregoing intensive care (1-4).
- Decisions about treatment should consider the infant’s physiologic maturity as well as the infant’s medical condition (2).
- Management of pain should also include minimizing painful procedures and stressful disruptions as much as possible, including bedside care procedures. Discussion with the family and team members should include timing and frequency of physical examinations, nursing evaluations, environmental stimuli, in addition to more invasive procedures (3)
- Even in the setting of grave illnesses, certain procedures, including surgical procedures, may be needed to improve the quality of life and/or facilitate the transition to home hospice (4).
- Withholding medically provided nutrition or hydration can be considered if it does not provide net benefit, as in cases of severe neurologic injury and persistent vegetative states, severe gastrointestinal malformation or intestinal failure, severe congenital heart disease, renal agenesis or severe chronic illness in the final stages of life. In these circumstances, the provision of medically provided nutrition/hydration may be extending the dying process and worsen symptoms of fluid overload, abdominal distension, edema and skin breakdown (5).
- Withholding medically provided nutrition is not the same as starvation, and allows for natural death, often considered peaceful by surviving family (5).
- Infants capable of safely eating who demonstrate signs of hunger should be provided food (5). Premature infants who have not developed the suck/swallow reflex should be provided nutrition unless there are significant co-morbidities that would preclude the ability to independently suck and swallow that is expected to occur with normal maturation.
- For some family members of children with profound neurologic impairment, continued survival may be considered a benefit to the family, and medically provided nutrition and hydration can be continued to honor the family’s ethical, religious or cultural beliefs (5).

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DRUG MONITORING

I. AMINOGLYCOSIDES: Gentamicin, Tobramycin and Amikacin

A. When to draw levels:
   1. Peak after second dose (see timing below)
   2. Trough after second dose (just before third dose)
   3. Levels are unnecessary if patient is on antibiotics for 48 - 72 rule out sepsis protocol

B. Timing of levels:
   1. Peak: 30 min after end of 30 min infusion
   2. Trough: 0-30 min before next scheduled dose

C. Goal levels
   1. Gentamicin/tobramycin:
      a. Peak concentrations
         i. Gram-positive (MRSA or GBS synergy): 3-5 mcg/mL
         ii. Gram-negative coverage: 6-10 mcg/mL
         iii. Severe gram-negative infection or NEC/GI perforation: 8-12 mcg/mL
      b. Gentamicin/tobramycin trough: <1 mcg/mL
   2. Amikacin
      a. Peak: 20-25 mcg/mL
      b. Trough: <5 mcg/mL

D. Special considerations: gentamicin during therapeutic hypothermia
   1. When to draw levels:
      a. First levels done as described above
      b. Repeat peak and trough levels after rewarming
         i. Peak to be drawn <u>after fourth dose</u>
         ii. Trough <u>before fourth dose</u>
      c. Levels are unnecessary if patient is on antibiotics for 48-72 hour rule out sepsis protocol

II. VANCOMYCIN

A. Troughs only *except* with:
   1. CNS infections
   2. Osteomyelitis
   3. Infective abscess

B. When to draw levels:
   1. Trough before third dose
   2. Peak (when necessary) after third dose

C. Timing of levels
   1. Peak: 60 min after end of 60 min infusion
   2. Trough: 0-30 min before next dose

D. Goal levels:
   1. Trough: 5-15 mcg/mL

2. Trough: 10-15 mcg/mL for serious infections or site has difficult penetration
3. Peak: 25-40 mcg/mL

III. DIGOXIN

A. When to draw levels:
   1. No routine monitoring necessary for management of heart failure or arrhythmia
   2. May take levels if suspected toxicity or at high risk for toxicity (abnormal magnesium, potassium and heart rate)
   3. Steady-state achieved within 1 week

B. Timing of levels:
   1. Trough before steady-state dos

C. Goal levels
   1. 0.8-1 ng/mL

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Revised: June, 2016
Katherine Pham, Pharm.D.

MEDICAL RECORD DOCUMENTATION

I. GENERAL INFORMATION

The written record is all that remains after an infant's hospital experience. In the event of a chart review (e.g. any recall of the case, study or evaluation of medical proficiency), or in the event of a malpractice case, the record is all we have. Therefore it must be complete, it must be accurate and it must not be judgmental**.** ***Only use the Neonatal H&P, Neonatal Progress Notes and Neonatal Discharge Notes in Cerner.***

II. PHYSICIAN NOTES

A. Admission:
Only use the Neonatal H&P. The transport nurse will fill out the transport perinatal history sheets. Data from these sheets and/or from discussion with the parents or referring hospital staff should be included in the H&P. If the infant is transported by another hospital or admitted from the ER, then it is the responsibility of the resident/NNP/PA to put this data in the admission note. Please obtain and document:

1. Mother's Hepatitis status
2. Mother's group B-streptococcus status (GBS) status
3. Mother's HIV status (including repeat 3rd trimester screen)
4. Maternal prophylactic antibiotics
5. Immunizations given to the patient prior to transport
6. Vitamin K administration to infant
7. Ophthalmic ointment to infant.
8. Whether or not metabolic screen was obtained at referring hospital. (If the information does not arrive with the infant, please call the referring hospital.)

B. Daily Notes:
Daily notes will be reviewed on rounds and finalized, with the attending signing them post rounds.

C. Procedure Notes:
All procedure attempts should be recorded on the appropriate procedure note in Cerner. The note should contain why the procedure was done, if it was done without difficulty, and the results. The universal protocol must be followed and documented, e.g., "time out was performed".

A procedure note is required for placement of UVC/UAC/PICC line. Central lines placed at an outside hospital need to be documented in a vascular access note on admission. This should include the current position of the line on X-Ray. Removal or adjustments of all lines (placed at an outside hospital or here) also need to be documented in a procedure note but addending the original note.

III. MEDICATION RECONCILIATION

A. Admission Medication Reconciliation
The transport nurse will usually complete the medication history for patients transferred from other hospitals. It is the LIPs responsibility to complete the medication history if the

patient is a direct admission to the NICU or an admission from the emergency department and to verify all entered medications. This is especially important to prevent re-dosing medications, including antibiotics.

B. Discharge Medication Reconciliation
Click on discharge medication reconciliation then choose discharge meds that will be continued or add new prescriptions (this option allows you to write in new medications including dose but doesn't need to be printed as a prescription). Discontinue medications that are not going to be used as outpatient. The reconciled medications will now appear on your depart summary.

C. NICU Quality Dashboard
The NICU quality dashboard allows you to determine the patients that have not had their admission medication reconciliation performed yet. Simply click on NICU QDB by exception (figure 1). The NICU quality dashboard will contain several categories including admission medication reconciliation (figure 2). Patients who have not had medication reconciliation performed will appear by room number. Clicking on room number will take you directly to the patient's chart where reconciliation can occur.

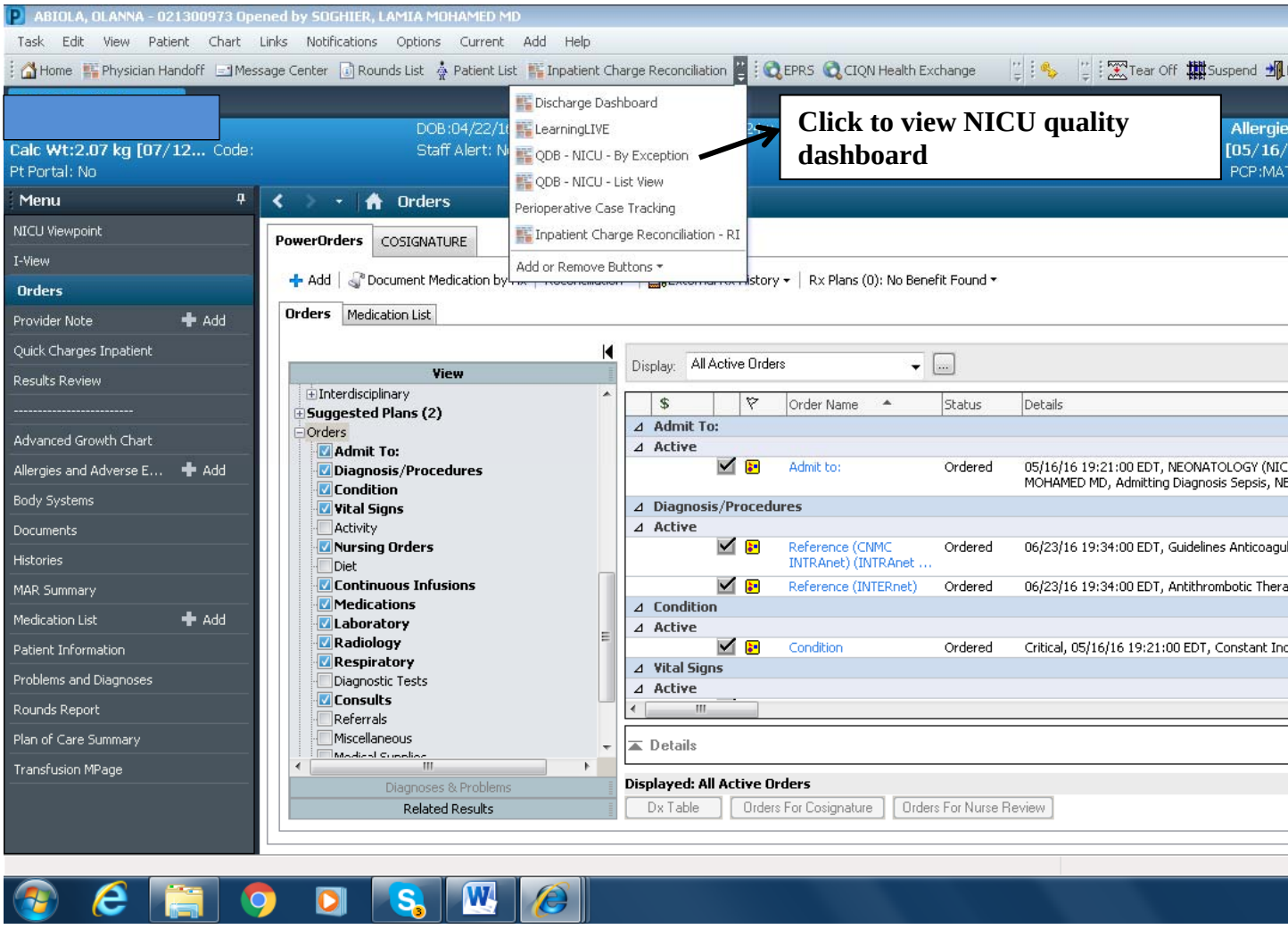

Figure 1: Area to access NICU quality database by exception

Figure 2: NICU quality database by exception

Revised: July, 2016
Lamia Soghier, M.D.

DISCHARGE PLANNING AND OUTPATIENT FOLLOW-UP

I. GENERAL INFORMATION

Advances in NICU have improved the survival of high-risk preterm and critically ill term infants. Infants who are discharged from the NICU require continued comprehensive clinical care done by a primary care and medical specialists.

Before discharged home, all current and anticipated medical and developmental concerns must be identified and communicated to the infant's parents or caregivers. For the infant with ongoing medical problems, the parents should have a good understanding of their infant's problems and be comfortable and proficient in continuing all aspects of care before discharge. Appropriate developmental intervention should be initiated while the infant is in the hospital.

Essential discharge criteria are a physiologically stable infant, a family who can provide the necessary care with appropriate support services in the community, and a primary care physician who is prepared to assume the responsibility with appropriate backup from specialist physicians and other professionals as needed.

The overall goals of the follow-up care are to effectively manage long-term sequelae of preterm birth or other morbidities, facilitate optimal growth and development and integrate the child into the family, school system, and targeted community services.

II. ROUTINE HEALTH MAINTENANCE AND POST-DISCHARGE CONCERNS

A. Growth
NICU babies are at risk for inadequate growth mainly due to their increased caloric and nutrient requirements and poor feeding. Growth failure is more common among infants with VLBW, ELBW, CLD, CHD, Short bowel syndrome and other intestinal anomalies, CNS injuries or birth defects, IEM, chromosomal and/or major malformation syndromes. If growth is inadequate, evaluation of the infant's nutrition and initiation of corrective measures as well as evaluation for contributing conditions is required.

B. Immunization
1. General:
Vaccines should be given based upon chronological age with the same schedule and dose recommended for normal term infants.
2. Hepatitis B:
Patients should have received Hepatitis B before discharge.
3. Palivizumab (Synagis):
Preterm infants with BPD, infants less than 29w, or those with hemodynamically significant congenital heart disease should receive monthly Palivizumab during the RSV season (review AAP guidelines).
4. Influenza vaccine:
Should be administered at six months of chronological age but during influenza season, family members and household contacts should be immunized.
5. Pertussis:
All parents and other care providers should be up to date with the Pertussis booster vaccine.

6. Rotavirus:
   The AAP recommends Rotavirus vaccination following discharge if chronological age is at least 6 weeks, but fewer than 15 weeks of age. However, we do not provide live vaccines, including Rotavirus during inpatient admissions, regardless of age.

C. Newborn metabolic screens
   If not done at birth hospital, will need to be done after 24 hours of age. If blood product/transfusion is warranted before 24 hours of age, send one prior to transfusion, and a second after 24 hours. For Maryland residents, a repeat DC NMS should be sent even if birth hospital nms has been sent. Include nms results on discharge summary. If results not available prior to discharge, please call NMS lab for report; if not finalized, confirm parent and pediatrician contact information so both can be updated regarding results.

D. Critical congenital heart disease screening
   AAP guidelines include screening for critical congenital heart disease (CCHD) for all newborns using pre- and post-ductal pulse oximetry monitoring. While pulse oximetry is routinely used in the NICU, definitive screening for CCHD should be done as close to 24 hours after birth in addition to standard pulse oximetry monitoring. For premature infants, CCHD screening is recommended once weaned from supplemental oxygen, and CCHD screening is not needed if the infant has had an echocardiogram. See appendix for additional information.

E. Hearing
   The rate of bilateral sensorineural hearing loss is 10 to 20 times higher among infants admitted to the NICU than in healthy term neonates. Hearing screening is performed at the time of discharge for all NICU infants; infants must be out of the isolette, off high-flow respiratory support and off antibiotics prior to screen. If the infant does not pass the OAE screen after two attempts, he/she is referred for BAER and audiology follow-up is recommended. All infants admitted to the NICU for more than 5 days are recommended to undergo a repeat hearing screen in the first year of life, or sooner if they are any risk factors or concerns. Ideal follow-up is at 4 – 6 months corrected age, even if OAE was normal.

F. Vision
   VLBW and ELBW infants are at increased risk for ophthalmologic abnormalities, especially ROP (refer to ROP chapter). NICU graduates are also at risk for visual disorders such as: reduced visual acuity, strabismus, myopia, anisometropia, (the two eyes have unequal refractive power), amblyopia, cataracts, nystagmus, and late retinal detachment. All premature infants should be evaluated by a pediatric ophthalmologist at 9 to 12 months of age. <u>Infants at risk for ROP must sign the Discharge ROP form by the parents and physician/NNP/PA who has explained the urgency for follow-up.</u>

G. Car safety seats
   Premature infants are at increased risk for cardiopulmonary compromise and clinicians need to be familiar with the AAP guidelines for proper selection of car safety seats and positioning to minimize their risk. All infants undergo car seat safety test, which included cardio-respiratory monitoring for 90 minutes in a car

seat. Car beds are suggested for infants with documented cardiopulmonary compromise in standard car seats.

H. Psychosocial concerns
Bringing home a NICU graduate can be very challenging to parents because of social, financial, and psychological stresses. The incidence of maternal depression and anxiety can be higher during their infant's NICU stay and in the first months after discharge home.

Another difficulty that can be present with NICU graduates is the “vulnerable child syndrome,” described as a set of clinical features in which unfounded parental anxiety about the health of a child results in disturbances of the parent-child interaction. The parents’ perception of their child as being vulnerable can lead to maladaptive behaviors.

I. Daycare
Some NICU graduates may be too unstable initially to be placed in formal daycare. If possible, some patients should be kept out of daycare if they are at high risk for infection, especially if they are being discharged home in the fall or winter months when seasonal viruses are more prevalent.

J. Hospital readmissions
NICU graduates have a 10 to 20% increased risk for readmissions to the hospital. They are twice as likely to be readmitted as term infants during the first year of life. The risk of readmission increases with decreasing GA. Parents should be made aware of the increased potential of readmissions for their premature infant.

K. SIDS
Preterm infants are at a greater risk for SIDS compared with term infants, with a peak risk at 50 to 52 weeks postmenstrual age. Education should be focus on "Back to Sleep" as well as other evidence based interventions. These include: breastfeeding, using a firm sleep surface, room-sharing without bed-sharing, immunizations, and avoidance of soft bedding, overheating and exposure to tobacco, alcohol and illicit drugs.

III. NEURODEVELOPMENTAL FOLLOW UP

Although advances in NICU care have improved survival rates of high-risk neonates, this improvement has not been accompanied by a proportional decrease in certain neurologic/neurodevelopmental morbidities. Risk factors for neurodevelopmental impairment include <28 GA, multisystem congenital malformations, and a neonatal course that includes one or more of the following conditions: severe asphyxia, IUGR, IVH, PVL or infarction, meningitis, seizures, or respiratory failure requiring mechanical ventilation. These abnormalities include:

- Learning disabilities
- Cognitive abnormalities
- Attention and behavior problems
- Cerebral palsy
- Mild fine or gross motor delay
- Hearing and vision deficits

- Specific neuropsychological deficits (eg, visual motor integration, executive dysfunction)

The risk of impairment increases with decreasing GA with a 6-8% risk in LBW, 14-17% in VLBW and 20-34% risk ELBW infants. In comparison, major disabilities occur in only 5% of full-term infants. These rates have remained relatively constant over the last decade.

The overall management goal is to identify all infants at risk for subsequent long-term neurodevelopmental disability and those who would benefit from developmental and /or neurology clinic follow up and early intervention programs. Because of limited of availability of reliable tools for prediction, follow-up care is initially broad and focused on identifying and following at-risk infants at discharge. The degree of neurodevelopmental follow-up and interventions needed are modified based on additional information gathered over the first few years of life as the neurodevelopmental outcome is assessed more accurately at school age. Over time, there is cognitive recovery as the brain continues to develop. Early assessment can identify preterm infants who have severe impairment that probably will not resolve and those who can benefit from early intervention.

The prediction of complex academic, behavioral, and functional outcomes for high risk NICU graduates can be imprecise because of the limitations of available clinical tools to accurately prognosticate long-term neurodevelopmental outcomes for individuals at school age, at adolescence, and as adults. The available clinical tools to predict outcome include neuroimaging and early childhood clinical assessments during the first two years of life. These consist of neurologic examinations, evaluation of cognitive, motor function, language, social development and behavior.

Advances in the development and utilization of HUS and MRI have enhanced detection of brain injury in preterm infants and improved the understanding of the links between brain injury and neurodevelopmental outcomes. Neuroimaging is able to identify preterm infants with significant brain injury, who are at-risk for neurodevelopmental impairment. However, these modalities can´t be use as the *sole* predictor of long-term neurodevelopmental outcome. Although patients with abnormal HUS are more likely to have long-term neurodevelopmental outcome impairment, a significant number of patients with a normal ultrasound may still have delays. It also remains uncertain whether grade I and II IVH have an impact on the outcomes of extremely low GA infants due to conflicting data. Neonatal MRI studies have shown that the majority of very preterm infants have white matter abnormalities which include increasing ventricular size, decreasing white matter volume, increasing intensity of white matter signal, and evidence of decreasing myelination. There is evidence that these findings are useful in predicting long-term neurodevelopmental outcome. However, as mentioned above, using MRI data alone is insufficient to predict neurodevelopmental outcomes and the results should be integrated with the entire clinical picture.

A. High risk patients
    1. Infants born at a GA <34 weeks
    2. Perinatal complications including severe asphyxia
    3. Medical history of IUGR, meningitis, seizures, PPHN and/or ECMO
    4. Respiratory disease requiring prolonged ventilation or oxygen
    5. Congenital or genetic anomalies

6. Infants with abnormal HUS or MRI
7. Children who fail a screening test, or in whom there is a concern for neurodevelopmental delay or neurologic abnormality.

B. Procedures for screening high risk patients
   1. Request a formal developmental consult before discharge
   2. Additional outpatient appointments as follows:
      a. Premature infants: at 3-4 months corrected age
         Term infants: 2 months for FT infants
         Referral to EI should be initiated
      b. At 8 -12 months corrected age
         To evaluate for early signs suggestive of CP or other neurologic abnormalities
      c. At 18 to 24 months corrected age
         For ongoing assessment of cognitive, motor, social and language evaluation
      d. Additional follow-up is dependent on the needs of the child based on previous assessment and may include further cognitive testing and academic achievement standardized testing.
   3. Infants not discharged to home
      a. To another tertiary center: No follow-up is planned by our clinic, receiving hospital should be advised on discharge summary that follow-up is recommended. On page 3 of the discharge form, circle "necessary and to be scheduled".
      b. To other nurseries outside geographic area: Receiving hospital should be advised on discharge summary if follow-up is recommended.

C. Neonatology-Development follow-up clinic
   1. Fellow responsibilities
      a. Review each patient that will be evaluated in the clinic
      b. Review neuroradiology imaging prior to the visit
      c. Read at least 1 paper related to <u>one</u> of the scheduled patients and include it in case presentation
      d. Submit draft notes for review with developmental psychology team
      e. Finalize notes in Cerner in order to send the letter to the primary care physician and parents and will be readily accessible to other medical specialists
      f. Any medical or developmental concerns that need to be communicated urgently require a same day phone call to the pediatrician by the fellow.
   2. If the fellow would like to see her/his patient at follow-up, ask the clinic to page when for subsequent visits

IV. DISCHARGE PLANNING

Given the complex nature of many patients, discharge planning should begin on the day of admission and be an ongoing discussion with the clinical coordinator, primary nurse, Attending physician, fellow social worker and case manager.

A. General concepts
   1. Over half of our children are discharged home, while others are back-transferred to their referring hospital or to a chronic care facility. If going home,

nursing has a protocol of parent teaching that must be done. Adequate time has to be given for this to occur. Managed care will not allow continued hospitalization for discharge teaching. Therefore we must anticipate discharge plans early and start discharge teaching prior to the day of discharge.

2. A pediatrician or clinic must be identified for primary care of each infant. The discharge summary should contain all appropriate addresses for parents and primary care physicians, so both can be reached as needed.
3. Changes in medications or other types of care should **never** be done just prior to discharge. The infant must be stable with the current medications and care. It is a nursing practice guide that all prescriptions be filled prior to discharge. Some medications are difficult to find and /or need preauthorization (i.e. Prevacid, Actigall, cholecalciferol, erythromycin). *Give the case manager prescriptions at least 2 days, and preferably 1 week, before discharge so they can work with the family to find a pharmacy provider.*
4. Communicate the results of eye and ear exams as well as final ultrasound reports with the family and document discussions in the medical record. If they are abnormal you may want to have the fellow or attending with you. The results of this test should be listed on the discharge summary along with medications the patient is on and immunizations given during hospitalization. Pretend that you are the pediatrician getting this patient for the first time...what information would you need to make a good assessment of the infant and start taking over the baby's care?
5. Assess the need for Synagis therapy and initiate first dose prior to discharge.
6. Contact the pediatrician prior to discharge, as the summary is likely to arrive after the first visit. Offer to provide a faxed copy. Give the parents a copy of the discharge to take with them.
7. Case Managers will assist the family with scheduling of follow-up appointments.
8. Advise the family on healthy sleep position.
9. Include recommendations about hearing screening follow-up in the discharge summary (see above)
10. Provide details regarding formula advancements or plans for allowing oral attempts if child is going home strictly tube fed.

B. Coordination of care

Babies are discharged from the NICU several ways. It is important that the Case Manager is involved in all of the ways to insure coordination of care and to avoid delays and denials related to 3rd party payers. Most 3rd party payers need to be kept updated in the plans of care (this is routinely done by the case manager) and need to give authorization for services /transfers outside of the NICU. Parents should also be actively involved in their child's care through rounds or family meetings.

1. Discharge to an acute care facility for continued acute care
   CNMC NICU supports back transfer of babies to birth hospitals (particularly within the city) when the reason the child was transferred has been met and the birth hospital can accommodate the child's medical needs. (i.e. PDA ligation in premies after the chest tube has been pulled)
   a. Physician discusses plan with family
   b. Medical team/LIP must call receiving Attending MD for acceptance
   c. Case Manager must secure authorization
   d. Resident/LIP must complete transfer summary
   e. RN or Case Manager must get written permission from family for transfer

f. Case Manager arranges transfer based on acuity & third party payor

2. Discharge to subacute or transitional care facility
   3rd party payers want babies transferred to a lower level of care as soon as they become medically stable. The 2 primary referrals centers used are Hospital for Sick Children or Mount Washington Pediatric Hospital.
   a. Team discusses plan with family
   b. Case Manager initiates referral
   c. LIP must call receiving Attending MD
   d. LIP must complete transfer summary
   e. RN or Case Manager secures permission to transport from family
3. Discharge to home.
   Resident along with medical and nursing team assures the coordination of care and ongoing continuing care needs. All of these are addressed in the discharge summary (2 copies should be given to the family on discharge)
   a. Parents should be actively involved either in rounds or in family meeting in their child's plan of care so they are not surprised by the discharge date or all the information they need to master before discharge.
   b. Resident should call pediatrician and give summary or update to make sure pediatrician is comfortable with the care needs; PMD appointment should be made within first 3 days after discharge.
   c. Case Manager will arrange for home nursing and any equipment or supplies needed; case manager will also help with setting up initial follow up appointments.
   d. Medications are sometimes difficult to find so case manager should be alerted to help identify a pharmacy that is able to compound small doses or difficult to find medications. Some medications (especially Prevacid) needs pre authorization before pharmacies will fill.

C. Pediatrician
   Many families have not thought about who they want for a pediatrician or will want to change, often leaving this until discharge. They frequently need suggestions or will want to interview the practice; therefore this needs to be addressed early on. In addition, most pediatricians would like to hear from the resident before discharge, especially if there will be matters they need to monitor closely (i.e. NG feeds-most PMD's do not feel comfortable managing this).

D. Complex Care Team
   Infants that require multiple services for follow may benefit from followup with the complex care team. Referral can be made through the NICU Case Manager.

E. Follow-up appointments
   Because of the difficulty in getting appointments, it is strongly recommended that the first follow up appointments be made and included on the discharge summary. The case manager can help in setting these.

F. Feeding plan
   Many babies go home on high calorie or special formulas, and may not be eating all by mouth. Families need time to learn how to place NG tubes and to get the formula and learn to make it. Families also need time to find formulas or to make WIC appointments. Sometimes samples can be given for short period.

G. Sleep

Back to sleep position should be included in the discharge summary and parents should be educated on the recommendation. For infants unable to sustain standard sleep positions should have discussions for home monitoring with the Attending Physician. Infants that require sleep studies should have tests arranged well in advance of the projected discharge date because of the time it takes for results to become available.

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Natalia Isaza, M.D.

CHRONIC LUNG DISEASE

I. GENERAL INFORMATION

The nature of chronic lung disease (CLD) and bronchopulmonary disease (BPD) in newborns has changed over the past 40 years. In 1967 Northway characterized BPD according to the timing of CXR findings:

A. Stage I: Days 1 – 3, hazy micro-atelectatic lung fields, we now call this hyaline membrane disease (HMD)

B. Stage II: Days 4 – 10, more complete white out, obscuring of heart border; this is late HMD, evolving into CLD

C. Stage III: After 10 days, small bubbly appearance, progressively evolving CLD

D. Stage IV: One month and beyond, fibrotic, cystic lungs, true BPD

The Northway progression was accurate from the 60's through the mid 80s when larger premature babies with stiff lungs from HMD were managed on relatively simple ventilators using ventilation strategies and blood gas goals that were not ideal for limiting lung injury. Currently, most micro premies are managed with surfactant and gentle modes of respiratory support such as endotracheal tube delivered Synchronized Intermittent Mechanical Ventilation (SIMV) using a low PIP, short I-Time, Pressure Supported spontaneous breaths approach or nasal prong delivered Nasal Intermittent Positive-Pressure Ventilation, (NIPPV), conventional CPAP or High Flow Nasal Cannula (HFNC) techniques. Permissive hypercapnia (CO_2s 50-60) is common practice. These patients develop a more subtle form of disease in which after doing well for a week or so their X-rays begin to get hazy or bubbly while simultaneously their oxygen and/or pressure requirements increase. Terminology varies. Many Neonatologists are now using either the definition of *an O2 requirement at 28 days of post natal age (if born at >32wk GA) or an O2 requirement at 36 weeks post conceptional age (if born at < 32wk GA),* coupled with X-ray changes to define CLD or BPD. Also, some people use CLD for the milder more recent and common form of lung disease and reserve BPD for Northway's stage IV type of disease.

II. PATHOPHYSIOLOGY

Hypothesized etiologies are many, well demonstrated etiologies few. Essentially anything that can cause tissue injury and consequent inflammatory reaction in the fragile structurally immature lung can contribute to the onset and progression of this disease process. Examples include:

A. Barotrauma: high PIP with sharp onset (from high gas flows) is thought to be the worst offender.

B. Oxidant injury: recall that the fetal lung in-utero sees very low oxygen tensions. Room air is hyperoxia to a 25 wk gestation lung in which the anti-oxidant enzyme systems have yet to develop. This is made worse by the high oxygen tensions that the babies undoubtedly require in order to support their other organs.

C. Nutritional deficiency: growth and development require energy to promote an anabolic state, macromolecular building blocks (amino acids, fatty acids, complex carbohydrates) and precursors of signaling molecules that direct development (e.g. Vitamin A). Lung disease itself increases work of breathing and therefore calorie demands. Sustaining an anabolic state is necessary for lung growth and healing. Nutrition needs to be an early and consistent priority.

D. Inflammation arising from mechanical or oxidative lung injury or from primary pulmonary or systemic infection, can lead to cytokine fluxes that impact the lung. The innate immune response to injury or pathogens (TLR mediated) if excessive can also contribute to lung injury. A strong relationship between severity of certain features of chronic lung disease (alveolar simplification) and exposure to prenatal inflammatory environment has been described.

E. Growth factor and cytokine changes associated with life outside the womb may be sub-optimal for processes that were meant to occur in the womb.

F. Excessive fluid and sodium administration has been implicated in CLD. For similar reasons PDA is also a risk factor.

III. PREVENTIVE MANAGEMENT

The goal is preventive management through eliminating or minimizing of the presumed causes of CLD as listed above:

A. Prenatal steroids: Given to the mother expected to deliver prematurely and/or use of surfactant in the baby with HMD both improve lung function and allow more conservative respiratory management. While surfactant has not been shown to decrease the incidence of CLD, it does increase survival and decreases the severity of CLD.

B. Gentle ventilation: This means accepting blood gas values such as $\underline{CO_2}$ 45 to 60, $\underline{PaO_2}$ 50 to 60, sats 87 to 94%, even in first week of life. Specific parameters are to be set with the team as babies differ and different attendings might have different preferences. For non-paralyzed babies on the vent synchronization with baby's breaths is essential. Use of pressure support (often) and assist control modes (occasionally) can greatly assist weaning from the conventional ventilator. The oscillator with its very small pressure swings at the alveolar level is gentle on the lung parenchyma but has an impact on venous return and is probably uncomfortable for the patient. Nasal prong based modes of support such as continuous positive airway pressure (CPAP), Nasal Intermittent Positive-Pressure Ventilation (NIPPV), and High Flow Nasal Cannula (HFNC) are being increasingly used.

C. Oxygen exposure: Minimizing excessive oxygen exposure and optimizing nutrition including antioxidant vitamin levels. Vitamin A is an antioxidant but also likely signals as a retinoid.

D. Pulmonary toilet: Adequate pulmonary toilet to prevent pathogen seeding or spread together with rapid recognition and treatment of lung and other infections, can be very helpful.

E. Glucocorticoids: Postnatal steroids are effective in reducing lung inflammation arising from a number of etiologies but because of their side effects must be used very carefully,

and *after discussion with the attending or fellow*. Trials of newer anti-inflammatory agents and recombinant antioxidant enzymes are ongoing but for now remain in the future.

F. Fluid and salt administration: Judicious use of fluids and salt, along with rapid recognition and treatment of fluid overload or PDA make sense.

IV. MANAGEMENT STRATEGIES

A. General treatment strategies:
   1. Fluids: Careful fluid management with relative restriction together with diuretics.

   2. Broncho-dilators: Bronchodilators can be very helpful. Albuterol (levalbuterol/xopenex if cardiac symptoms are an issue), and ipratropium (atrovent) aerosols are frequent choices; metaporterenol should be used as an adjunct to beta agonist therapy and should be delivered in the same aerosol as the beta agonist, often with every other albuterol. Inhaled steroid (pulmicort) treatments tend to reduce inflammation (Section IV D) but also to sustain beta agonist effects of albuterol through up regulation of beta-2 receptors and down regulation of phosphodiesterase activity.

   3. Xanthine: parenteral aminophylline or enteral theophylline are very seldom used but they can be effective agents if needed. They have a narrow therapeutic index and are not used lightly or frequently. Caffeine, originally approved by the FDA for treatment of apnea of prematurity, has also been shown to decrease the use of mechanical ventilation, supplemental oxygen and postnatal corticosteroids; early use of caffeine (within 3 days of birth) is also associated with lower rates of BPD/CLD.

   4. Steroids: Nebulized or systemic steroids are effective but again the complications are significant and have to be weighed against the anticipated benefit.

   5. Respiratory Support: Avoiding excessive barrow trauma and oxygen toxicity remains important. This must be balanced against a growing need to prevent excessive drops in alveolar and arterial oxygen tension and to avoid excessive hypercapnia, because of the effects these have on the pulmonary circulation (see below).

   6. Nutrition: The importance of adequate nutrition, at each step of the disease process, cannot be overestimated.

   7. Infection: Timely recognition and antibiotic treatment of infections, local and systemic.

   8. Future therapies:
      a. Cyclic GMP (cGMP): Agents which act through nitric oxide and cGMP pathway have well-known effects on vascular and airway smooth muscle, increased cGMP seems to increase alveolar septation; and this addresses a prominent pathologic component of CLD/BPD, which is decreased alveolar surface area.
      b. Retinoic Acid: Retinoic acid has also been shown to increase alveolar septation, not in current use and safety issues need to be addressed, but may be an important treatment in future
      c. Nitric oxide (NO): Some feel treatment of premature infants with lung disease with

Nitric Oxide can increase vascularization and septation and in this way it may reverse some of the pathophysiologic features of BPD but support for this in clinical trials has been inconsistent.

d. Stem cells: Recent studies have shown benefit of infusing bone marrow derived mesenchymal stem cells or factors derived from them in animal models of lung injury.

B. Suggested management for infants with CLD once they are convalescing (>36 weeks)

1. Oxygen goals:
   a. Keep $PaO_2 > 60$ or 70 and the O_2 saturation 92-96% in a $FiO_2 < 0.30$ if possible. Balance limiting oxygen injury and keeping pulmonary vascular resistance (PVR) low.
   b. Strive to maintain arterial $PaO_2 \geq 60$; can monitor blood gas status with an oximeter, but need to correlate the saturation with an arterial gas periodically.
   c. When weaning FiO_2, use a pulse oximeter correlated to arterial pO_2. Oxygen status needs to be assessed during all states, especially sleeping, feeding and increased activity. These are times when pO_2 tends to fall. Also remember conditions in the home may not be as controlled as those in the NICU.
   d. In stage III-IV CLD, do not push to wean rapidly below 30% O_2. More damage may be done by too rapid weaning of FiO_2 than by remaining O_2 dependent. These are the infants who are potential candidates for home O_2.
   e. If CLD infants require home O_2, **Pulmonary Medicine** should be contacted and will need to follow these infants. **(Ext.2128)**
   f. Home oxygen is usually administered via nasal cannula (except for tracheostomy patients). Since blenders are not available for use with a home cannula, O_2 must be regulated by titrating liter flow of pure O_2. One cannot equate liter flow with a given FiO_2 so adequacy is assessed by pulse oximetry. Most babies can go home on 1/8 to 1/2 L of 100% O_2.
   g. Tracheostomy patients receive FiO_2 using a blender. Discuss discharge settings with Pulmonary Medicine as they will follow patient after discharge.

2. Ventilation goals:
   a. Keep arterial $PaCO_2 < 60$ if possible; do not discharge if $pCO_2 > 65$, unless stable and well compensated. Again, PVR must be a consideration and both pH and $PaCO_2$ affect PVR, in order to avoid progression of pulmonary hypertension.
   b. Strive to maintain $pCO_2 \leq 65$. Levels higher than this are an indication of a severely reduced pulmonary reserve and should not be accepted even though the infant appears "comfortable". pCO_2's in the 50's –65's are acceptable if adequate pharmacologic therapy has been tried and the infant is growing. High pCO_2's may reflect not only reactive airway disease, but also poor air entry for other reasons. Still the reactive component should be optimized. A patient does not have to be wheezing to derive some benefit from a bronchodilator.

3. Fluids and Nutrition:
   a. Aim for steady weight gain, at least 10 gm/day minimum and avoid fluid & salt overlod
   b. Assess fluid status and "wetness" of lungs. Most infants with significant CLD require aggressive diuresis on a regular, not p.r.n., basis. Use K^+ sparing agents (i.e. Aldactone) as needed.

4. Bronchodilator use

Bronchodilators are used to reduce $PaCO_2$ and improve PaO2 by improving overall ventilation and V/Q matching by helping to control baseline airway smooth muscle tone and to decrease reactive airway disease exacerbations.

a. Albuterol: Aerosols Usually given q. 4-6 hrs; dose and frequency can be titrated by respiratory response as well as heart rate; heart rate should not exceed 200 and should return to baseline within 1/2 hour of treatment. Aerosols should always be accompanied by chest physiotherapy and suctioning. If significant tachycardia, Xopenex can be used. It is unclear that it helps. Terbutaline is also an option.
b. Atrovent (Ipratropium), an atropinic agent, can be helpful, should be given with beta agonist. Can cause drying out of secretions.
c. Albuterol Oral suspension; may be considered as alternative to theophylline; begin at 0.3 mg/kg/d divided q. 8 hours; increase by 0.05 mg./kg./d. until effect is achieved or patient becomes tachycardic. This is very rarely used in the NICU.
d. Theophylline: If infant is on caffeine for apnea and has significant reactive airway disease not adequately controlled with inhaled agents, one could try switching caffeine to theophylline for added diaphragm, bronchodilator and diuretic effects; maintain <u>level 14-16 peak, 9 trough</u>. Theophylline may lead to or make GER worse. Not used regularly for reactive airway disease any longer, PMDs may be less familiar with managing the drug, so use <u>only if necessary and provide good discharge instructions.</u>

5. Steroids use

Either inhaled or systemic steroids can be considered, again this should be done in consultation with Neonatology fellow or attending. For use in convalescent CLD *prednisone* is steroid of choice for chronic *oral* use, *pulmicort* for chronic *aerosol* use. Aerosolized steroids have far fewer side effects and though less effective they are preferred as first line steroid treatment. Pulmicort in particular is becoming a first line treatment for CLD both for its impact on airway resistance and for its anti-inflammatory effects.

a. Systemic dexamethasone: short and long course

Decadron (dexamethasone) was once a mainstay of the management of severe CLD. Standard practice was to start at 0.5 mg/Kg/day divided then to taper over 42 days. Because some studies suggested neurological side effects (e.g. increased risk of cerebral palsy) as well as immune and adrenal suppression problems, it is currently used much less frequently and when it is used, it is done in a much more judicious way. We include the full long course high dose protocol to preserve it for the rare times it is needed as well as a more commonly used shorter course protocol.

i. Short course

One currently widely used protocol taken from a clinical trial is the DART protocol: 150 mcg/kg/day in two divided doses for 3 days followed by 100 mcg/kg/day for 3 days, 50 mcg/kg/day for 2 days and 20 mcg/kg/day for 2 days; total dose of 0.89 mg/kg over 10 days. Discuss details with Fellow or Attending.

ii. Long course (42 day)

We only very rarely use the high dose long course protocol to wean a baby from mechanical ventilation, when we do the protocol below can be used. Even with the long taper, weaning from the high doses of dexamethasone utilized in the protocol can be risky because of both the possible adrenal suppression and BPD rebound during and after the wean. For these reasons it had been standard practice to observe several weeks after long term dexamethasone

was stopped before discharging. With the Pulmonary Service's involvement in discharge planning and follow up, more timely discharge can be considered, assuming patient is otherwise ready. Remember to consider an increase in steroid dose during times of "stress," and a stress dose warning should also be added to the discharge summary. This should be discussed with parents and follow-up pediatrician.

LONG COURSE DEXAMETHASONE FOR BPD/CLD

Day	Daily Dose (mg/Kg)	Frequency		Day	Daily Dose (mg/Kg)	Frequency
1 to 3	0.5	divided q12h		19 to 21	0.18	divided q12h
4 to 6	0.3	divided q12h		22 to 24	0.16	divided q12h
7 to 9	0.27	divided q12h		25 to 27	0.14	divided q12h
10 to 12	0.24	divided q12h		28 to 30	0.12	divided q12h
13 to 15	0.22	divided q12h		31 to 36	0.1	divided q12h
16 to 18	0.2	divided q12h		37 to 42	0.05	q24h

iii. Stress coverage:

Despite slow weaning of long course (42 day) dexamethasone, adrenal suppression is possible, and may last for up to 6 months. A single A.M. serum cortisol level of >15 is considered by some to indicate sufficiency; this is a high bar. The best determination of adrenal suppression is by a stimulation test which will test the entire HPA axis, however this is seldom done. If felt to be necessary, an Endocrinology consult would be indicated.

If the baby has weaned entirely off dexamethasone, but needs steroid coverage for stress during the period of possible adrenal suppression, the recommended treatment is *Hydrocortisone 20 to 30* ***mg/m^2/day*** IV in 2 to 4 divided doses**.** NOTE THE UNITS and see table below for conversion. If surgery is planned, the stress protocol should be started the day prior to the surgery if possible, and also given at least on the day of surgery and for a day or two more. If the baby is unstable/in shock/acutely ill, then continue until the baby improves. If the baby is on stress dosage for more than a few days, then the hydrocortisone may need to be tapered slowly.

CONVERSIONS FOR SURFACE AREA ARE:

Weight (kg)	SA (m^2)	Weight (kg)	SA (m^2)
0.6	0.08	2	0.15
1	0.1	3	0.2
1.4	0.12	4	0.25

If the baby is still on a Decadron taper but needs surgery or has an acute illness for which stress coverage is desired, dexamethasone can be continued as an acceptable means of coverage. Dose adjustment follows:

- Current dose $\leq$ 0.14mg/kg/day divided q12 hours (i.e. day 25-42):
  The easiest modification is to add an extra dose per day so that medication is given Q8 hours.
  For example, if the scheduled dose is 0.12mg/kg/day (0.06mg/kg q12 hours), when stress dosage is begun the baby should get 0.06 mg/kg Q8

hours (or a total of 0.18mg/kg/day).
If the baby is receiving Decadron every other day (usually 0.1mg/kg/day dose, day 38-42) the Decadron for stress coverage should be given every day.
After the period of stress is over, the extra stress dose should be stopped, and continue to taper the Decadron.

- Current dose is > 0.14 mg/kg/day (days 1-24) extra coverage for stress is probably not needed. As always, if an individual baby is in shock and not improving, dosage may have to be adjusted. The electrolytes must always be monitored.

b. Systemic steroids: hydrocortisone
As noted above, concern for neurological side effects has led to a general reluctance to employ high dose, long duration dexamethasone treatments to improve lung function in babies with BPD. Reasoning that the very long half-life and high potency of dexamethasone might be in part responsible for neurological side effects, some groups have trialed a steroid treatment regimen based on hydrocortisone that appears to be free of neurological sequealae.

i. One well studied protocol follows (See ref. Rademaker et. al. 2007):
1.25mg/Kg/dose given every 6 hours (5mg/Kg/day), for 7 days
1.25 mg/Kg/dose given every 8 hours (3.75mg/Kg/day) for 5 days
1.25 mg/Kg/dose given every 12 hours (2.5mg/Kg/day) for 5 days
1.25 mg/Kg/dose given every 24 hours (1.25mg/Kg/day) for 5 days

As with the dexamethasone protocol, adjustments can be made based on the babies response to hydrocortisone weaning, such as extending the duration of the more frequent dosing period. These decisions should be made by the Neonatology attending.

6. Feeding and nutrition
   a. Adequate nutrition is essential for growth and development in any infant with BPD. Caloric demands are higher than normal because of increased work of breathing. However, adequate intake is often difficult due to fluid restrictions and inability to feed without distress.
   b. Caloric intake should be 130-140 kcal/kg of ideal weight. Formula may be concentrated up to 30 kcal/oz as tolerated in order to spare fluid intake. Some babies may need severe fluid restriction. Electrolytes need to be followed in these patients.
   c. Monitor infant during nipple feeding for any signs of distress such as decreased O_2 saturation, increased CO_2, increased RR, chest wall retractions, increased As, Bs or Ds, changes in ability to P.O. feed, arching and emesis.
   a. Be aware that pushing the infant too hard to exclusively nipple feed may set him up for food refusal later; in addition, many of these babies may have oral-motor CP or have problems handling various tastes and textures due to low oral tone or oral hypersensitivity; nipple feeding time should be $\leq$ 30 min; consider alternate feeding methods if unable to consistently take adequate calories (NG, NJ, GT feeding)
   d. Feeding schedule can also be altered; sometimes continuous overnight feeds can be very helpful.

7. Other Monitoring:

a. Cardiovascular: infants need ongoing blood pressure monitoring because of late onset hypertension in BPD or hypertension secondary to steroid therapy; ECHO and ECG should be checked at least monthly and prior to discharge to monitor for development of pulmonary hypertension, RVH or LVH.
b. Renal: Ultrasound to look for calcifications and stones secondary to Lasix should be done if an infant has hematuria.

V. IMPACT AND CO-MORBIDITIES

A. Cardiac implications

One of the most ominous complications of CLD is *pulmonary hypertension* which results from pulmonary vascular smooth muscle hypertrophy and hyper responsiveness as well as a decrease in the cross sectional area of the pulmonary vascular bed. It is only recently that the importance of a simplified vascular tree and the decreased alveolarization that goes along with it have been recognized to be components of CLD/BPD. Once >36wk adjusted GA, normalizing alveolar gas tensions and systemic blood gases, including during times of feeding and sleep, can help mitigate this process, and should be a high priority. It has been the current authors practice to screen babies with severe BPD for pulmonary hypertension about once a month by echocardiogram, sooner if signs or symptoms warrant it. Practices differ and this should be discussed with your attending.

B. Development

Delayed motor and cognitive development are often seen in patients with BPD. Its hard to separate the effects of accompanying illness (infection, anemia, IVH etc.), of marginal blood gases over a prolonged periods of time and of behavioral limitations imposed by CLD. Limited movement and experience resulting from prolonged intubation can take a toll on development. Tracheotomy can help improve the social and experiential activity for the baby if very prolonged ventilatory support will be required. Of course the benefits must be weighed against the risks inherent in a tracheostomy.

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Revised: June, 2016
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NEWBORN CIRCUMCISION

I. GENERAL INFORMATION

AAP Circumcision Policy Statement: "Existing scientific evidence demonstrates the potential medical benefits of neonatal circumcision; however it is not sufficient to recommend it as routine. Parents should be encouraged to make an informed choice by being provided unbiased information about potential risks and benefits. If decision for circumcision is made, procedural analgesia should be provided" (please read, Pediatrics, 2012;130:585–586, AAP Policy Statement on Circumcision).

The World Health Organization (WHO) recently stated that "male circumcision should now be recognized as an additional important intervention to reduce the risk of heterosexually acquired HIV infection in men."
(http://www.unaids.org/en/PolicyAndPractice/Prevention/MaleCircumcision, 2009).

II. POTENTIAL BENEFITS

A. Decreased risk of penile cancer

B. Cervical cancer in sexual partners

C. Penile problems (e.g. phimosis/ paraphimosis, balanitis)

D. Urinary tract infections (10X less risk in circumcised vs uncircumcised in 1st year of life)

E. Decreased sexually transmitted diseases
   1. HSV2 (decreased 28-34%)
   2. HPV (decreased 32-35%)
   3. HIV (decreased 53-60%).

III. POTENTIAL RISKS/ NEGATIVES

A. Incidence of UTI and penile cancer in males is rare and may not justify routine circumcision

B. Risk of certain penile problems (e.g. meatitis, meatal ulcers) occurs exclusively in circumcised males

C. Behavioral practices are a far more important risk factor for STD (HIV) transmission than circumcision status

D. There is a perception that circumcision will negatively impact sexual function and pleasure later in life (evidence unclear)

E. Ethical issues have been raised regarding patient autonomy when parents are deciding on circumcision for their child

F. Complications

   1. Exact incidence is unknown, complication rate estimated to be 0.2-1%

2. Most common complications are bleeding and local infection
3. Complications due to local anesthesia consist mainly of hematomas and local skin necrosis
4. Rare complications include urinary retention, chordee, unsatisfactory cosmesis, penile amputation, sepsis, meningitis, death

IV. PATIENT REQUIREMENTS

The Department of Urology will perform circumcisions in infants *up to 45 days post term* and weight < 10 pounds who are medically stable (see contraindications below). Discuss with Case Manager to arrange prior to discharge or schedule as outpatient*. If baby will need circumcision outpatient the baby must have valid insurance or his own MA number.* Infants with contraindications to outpatient circumcision must then be referred to Urology and/or General Surgery.

V. CONTRAINDICATIONS

A. Unstable or sick infant
Circumcision is contraindicated if the baby is unstable or sick. Circumcision is elective and, as with other medically elective procedures, it should be delayed until the baby is well. Signs of stability include normal feeding, elimination, and maintenance of normal body temperature without support. A period of observation after the infant's birth may allow for recognition of abnormalities or illnesses (eg, serious jaundice, infection, or manifest bleeding disorder) that should be addressed before this elective surgery.

B. Prematurity
Circumcision should be deferred in a preterm infant until he meets criteria for discharge from the hospital.

C. Genital anomalies
Infants born with genital anomalies (e.g. hypospadias) should not be circumcised. The foreskin may be needed for the surgical correction of the anomalies.

D. Bleeding problems
Whenever there is a family history of bleeding disorders, appropriate laboratory studies should be performed to make certain the baby himself has not inherited the bleeding disorder.

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Updated: October, 2016
Nickie Andescavage, M.D.

Critical Congenital Heart Disease Screening Program:

Screening Protocol Diagram

Measurement #1
Pulse Ox on Right Hand (RH) and One Foot After 24 Hours of Age

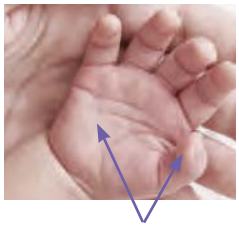
FAIL	RETEST	PASS
Pulse ox of 89% or less in either the RH or foot Action: Do Not Repeat for Screening, Refer for Immediate Assessment	Pulse ox of 90-94% in BOTH the RH and foot OR a difference of 4% or more between the RH and foot Action: Repeat pulse ox measurements in 1 hour	Pulse ox of 95% or more in RH or foot AND difference of 3% or less between the two Action: Do Not Repeat for Screening, Provide Normal Newborn Care

Measurement #2
Pulse Ox on Right Hand (RH) and One Foot 1 Hr After Measurement #1

FAIL	RETEST	PASS
Pulse ox of 89% or less in either the RH or foot Action: Do Not Repeat for Screening, Refer for Immediate Assessment	Pulse ox of 90-94% in BOTH the RH and foot OR a difference of 4% or more between the RH and foot Action: Repeat pulse ox measurements in 1 hour	Pulse ox of 95% or more in RH or foot AND difference of 3% or less between the two Action: Do Not Repeat for Screening, Provide Normal Newborn Care

Measurement #3
Pulse Ox on Right Hand (RH) and One Foot 1 Hr After Measurement #2

FAIL	RETEST	PASS
Pulse ox of 89% or less in either the RH or foot Action: Do Not Repeat for Screening, Refer for Immediate Assessment	Pulse ox of 90-94% in BOTH the RH and foot OR a difference of 4% or more between the RH and foot Action: Do Not Repeat, Clinical Assessment	Pulse ox of 95% or more in RH or foot AND difference of 3% or less between the two Action: Do Not Repeat for Screening, Provide Normal Newborn Care



RH Application Sites

Foot Application Sites

REMINDER ALGORITHM FOR SCREENERS

- Confirm that the infant is at least 24 hours of age and eligible for screening.
- Help the parent to warm and calm the infant in a quiet and peaceful environment.
- Describe the pulse ox test to the parent.
- Select a site on the right hand and one foot that is clean and dry
- Place the pulse ox sensor and perform the pulse ox test.

ASSESSMENT OF BABIES WITH FAILING SATURATIONS

1. Babies with saturation of 89% or less in RH or foot should have immediate assessment.
2. Babies with Failing Saturations:
   - Clinical Assessment
   - Complete echocardiogram
   - Infectious and Pulmonary pathology should be excluded
   - If symptomatic, referral to Pediatric Cardiology immediately
   - If asymptomatic referral to Pediatric Cardiology in timely manner

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

I. GENERAL INFORMATION

Congenital diaphragmatic hernia (CDH) affects approximately 1 in 2500-4000 live births. Over the past 20 years, advances in technology such as the use of permissive hypercapnia, high frequency ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation (ECMO) have been incorporated into treatment strategies for babies with CDH. The timing of surgical repair has transitioned from emergent perinatal surgery to delayed elective repair after transition/ stabilization of pulmonary hypertension after birth. Despite all these changes, mortality and morbidity of infants affected by CDH remains high. Mortality rates range from 30% to as high as 50% in high-risk cases, (i.e. infants having respiratory symptoms within six hours after birth and/or requiring ECMO). More recently, several centers have reported improved outcomes with use of standardized postnatal treatment protocols. Surviving infants with moderate to severe CDH may develop long term morbidities falling into 3 categories: 1) neurodevelopmental impairment in up to 25%, 2) chronic pulmonary hypertension or some degree of pulmonary injury (5%) leading to an increased incidence of asthma and recurrent pneumonias during the first 1-3 years of life, and 3) feeding difficulties relating to oral aversion and/or gastroesophageal reflux.

II. CLINICAL MANAGEMENT GUIDELINES

A. Respiratory management

1. Gentle ventilation strategy– utilize lowest pressure that provides adequate chest movement and gas exchange

PARAMETER	GOAL	THRESHOLD
Preductal oxygen sats	>90	>88*
Postductal oxygen sats	>70	>60*
$PaCO_2$	40-65	<70
PIP	20-25	28
MAP	14-16	18

*Tolerate preductal sat > 85%, postductal > 60% only if perfusion is satisfactory (e.g. non-acidotic and lactic acid not increasing).
If pCO_2> 65 at rapid rate or PIP > 25, consider early use of HFOV

2. Initiate inspired oxygen at 100%; weaning commences at 6-8 hours if stable and PaO_2> 150. Wean FiO_2 by 1-2% as tolerated every 1-2 hrs if pre-ductal sats > 90
3. Management of pulmonary hypertension
   a. iNO has not been shown to keep CDH patients off ECMO, so it is primarily used to stabilize pre-ECMO patients as surgery is being prepared or on transport. Consider nitric oxide @ 20ppm if:
      i. Post-ductal O_2 sats>10 point less than preductal sats
      ii. Post-ductal PaO_2 <100 on FiO_2 100%
      iii. Echo demonstrates evidence of pulmonary artery hypertension
   b. Shunting episodes (>10 point difference between pre and post ductal saturation)
      i. Best therapy is prevention; common triggers include: ETT suctioning, stimulation of the patient, acidosis, increased pCO_2, and hypoxemia.
         - CDH babies should be premedicated with sedation medication boluses for all care
      ii. Treatment of shunting episodes
         - Optimize systolic blood pressure through IVF boluses and pressors

- Correct acidosis
- Administer sedation boluses and increase infusion rates

B. Sedation
   1. Non-pharmacologic: minimal handling of the infant, noise and stimulation
   2. Pharmacologic: first-line: morphine and midazolam infusions

C. Fluids
   1. Maintenance fluid of stock D10 + Ca @ 80 cc/kg/day
   2. Day 1 start TPN @ 80 cc/kg/day and continue TPN until initiation of enteral feeds (post repair).
   3. Volume bolus as needed for hypotension – NS boluses in 10 cc/kg increments
   4. Avoid colloid – except PRBCs
   5. Avoid acidosis – consider bicarb if pH < 7.2 (consider THAM if pCO_2>40, but remember hyperosmolality, risk for arrhythmias and hypoglycemia as potential side effects of THAM infusion)

D. Hemodynamic support for hypotension
   1. Dopamine started @ 5 mcg/kg/min and titrated to support mean arterial blood pressure at or above the patient's gestational age in weeks – max 20 mcg/kg/min
   2. Hydrocortisone when approaching dopamine >15 mcg/kg/min.

E. Studies/Monitoring
   1. Continuous pre and post ductal oxygen saturation monitors
   2. Continuous cerebra saturation monitors (NIRS)
   3. Make sure sump tube is working well to decompress bowel
   4. Labs:
      a. Type and cross, CBC with diff, PT/PTT/fibrinogen along with BMP/Mg/Phos; Lactate on admission and with each blood gas
   5. Radiology:
      a. CXR: on arrival and as appropriate for vent mode and change in status, surveillance of over/under inflation
      b. HUS: on arrival and repeated as clinically indicated
   6. Echocardiogram:
      a. As soon as appropriate following admission to NICU to define cardiac anatomy (especially pulmary veins), cardiac function, intra-cardiac shunts, PA diameter, and assess pulmonary hypertension
      b. Prior to discharge to document pulmonary artery pressure

F. ECMO
   1. "Honeymoon period" – in the first 24-48 hours babies can exhibit a period of relative stability and then go on to deteriorate rapidly
   2. Indications and considerations for ECMO
      a. Refractory hypoxemia, inability to maintain pre-ductal sats>85%
      b. Using injurious settings to achieve satisfactory oxygenation (eg PIP>28 MAP>18)
      c. Pressor resistant hypotension
      d. Persistent metabolic acidosis
      e. Inability to wean FiO_2 from 100% in the first 72 hours
   3. Contraindications for ECMO
      a. Weight < 2kg
      b. Presence of greater than Grade 2 IVH

c. Gestational age <34 weeks
d. Presence of other significant congenital or chromosomal abnormalities
e. Inability to achieve a $PaCO_2$ <70

G. Timing of Surgical Repair
1. Delay at least until day of life 2 to get beyond honeymoon period
2. Wait for resolution of pulmonary hypertension
3. FiO_2<50%, PIP <25, MAP<12 in order to have ability to increase your ventilator support if needed post repair
4. Nearly ready to come off ECMO or already off ECMO
5. If on ECMO for repair, consider Amicar infusion. Loading dose: 100 mg/kg followed by infusion rate: 20 mg/kg/hr.
6. Resolution of anasarca
7. Normal acid-base balance

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CAFFEINE CITRATE

I. DESCRIPTION

Caffeine is a methylxanthine and CNS stimulant. It increases medullary respiratory center sensitivity to carbon dioxide, stimulates central inspiratory drive and improves skeletal muscle contraction.

II. INDICATIONS

Caffeine is indicated for treatment of patients with apnea of prematurity who meet the following criteria:

A. Patient has documented apnea of prematurity
B. Patient < 37 weeks PMA

III. PHARMACOKINETICS

Half-life (in neonates): 40-230 hours

IV. DOSAGE AND ADMINISTRATION

	Loading Dose	Maintenance Dose
IV/PO (dose based on caffeine citrate)	Caffeine-naïve: 20 mg/kg/dose x 1 dose Receiving caffeine maintenance: additional loading dose of 10 mg/kg if patient is symptomatic	5-10 mg/kg/dose every 24 hours Initiate maintenance dose of 8-10 mg/kg/dose, readjust dose when below 5 mg/kg/dose May consider every 12 hour dosing for PMA > 29 weeks and PNA of 1 month
Additional Information	Start maintenance dose 24 hours after load 1:1 IV to PO ratio	

The initial study[1] looked at twice daily dosing but recent literature demonstrates that daily dosing is sufficient. Shortening of half-life can occur with neonatal maturation.[13]

Discontinuation of caffeine should be considered at PMA 34 to 36 weeks[8,10,12]. Weaning (gradual or expedited) prior to discontinuation may not be necessary due to lack of evidence. Rebound apnea has not been noted in the literature.

V. ADVERSE REACTIONS

The most common adverse reactions are tachycardia, restlessness, irritability, hyperactivity, vomiting and gastric irritation. In one study[8] one of 14 patients on high dose (12mg/kg) caffeine was found to experience reflux.

VI. MONITORING

A. Levels:
    1. No routine monitoring of levels is required (e.g. patients with normal heart rate and asymptomatic)

2. Steady-state concentrations may take up to 2 weeks to achieve in caffeine-naïve patients
3. Increase maintenance dose by 1 mg/kg/day if symptomatic

B. Goal levels:
   1. Random level: 8-25 mcg/mL

C. Timing of levels:
   1. May be taken at any time in relation to dose if at steady-state but commonly taken before next dose

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APPENDIX A
FORMULAS & FORTIFIERS

I. HUMAN MILK FORTIFIER

Not available outside the hospital

A. Enfamil Human Milk Fortifier Acidified Liquid
   1. When added to breast milk, provides additional calories, protein, MCT, Ca, Phos, vitamin D, Fe, Zn, and other vitamins and minerals
   2. Adds only 31 mOsm/kg H_2O to breast milk
   3. Discontinue when intake exceeds 20 vials per day

II. PRETERM FORMULAS

Not available outside the hospital

A. Enfamil Premature 24 kcal/oz High-Protein (PE 24)
   1. Higher in calories, protein, Ca, Phos, and other vitamins and minerals to meet the needs of preterm infants
   2. Discontinue use when intake exceeds 355 mL, per manufacturer instructions
B. Enfamil Premature 30 kcal/oz (PE 30)
   1. For use when a fluid restriction is necessary
   2. Can also be mixed 1:1 with PE 24 High Protein to make 27 kcal/oz
   3. Discontinue use when intake exceeds 355 mL, per manufacturer instructions

III. PRETERM DISCHARGE FORMULAS

A. Enfamil Enfacare / Similac Neosure
   1. Standard = 22 kcal/oz
   2. Transition from PE formulas to discharge formula once the infant weighs ~2.5-3 kg, or prior to discharge
   3. Preterm discharge formula contains nutrient levels between those of preterm and term formula
   4. AAP recommends continuing preterm discharge formula up until 9 months CGA, please include these instructions on all discharge summaries

IV. STANDARD TERM FORMULAS

A. Enfamil 20 kcal/oz (E20)
   1. Default formula for infants >37 weeks gestation when breast milk is not available
   2. Can be concentrated to different calorie levels if fluid restriction is necessary – e.g., 22 kcal/oz, 24 kcal/oz (available ready-to-feed), 26 kcal/oz
B. Similac 19 kcal/oz
   1. Ready to feed formula recently changed to 19 kcal/oz
   2. WIC products are currently 20 kcal/oz
   3. Use only with parents' request

V. EXTENSIVELY-HYDROLYZED PROTEIN (SEMI-ELEMENTAL) FORMULAS

A. Pregestimil
   1. Hypoallergenic, can be used for fat malabsorption (e.g., if patient has acholic stools due to cholestasis, but note that premature formulas also contain MCT)
   2. Contains 55% of fat as MCT
   3. Galactose-free
B. Alimentum
   1. Hypoallergenic, can be used for fat malabsorption

2. Contains 33% of fat as MCT
3. Lactose-free

C. Nutramigen
1. Hypoallergenic
2. Contains no MCT
3. Powder form contains L. rhamnosus GG, which helps regain cow's milk protein tolerance
4. Galactose-free

VI. AMINO ACID–BASED (ELEMENTAL) FORMULAS

A. Elecare / Neocate / PurAmino
1. Indicated for severe, life-threatening milk protein allergy, or malabsorption
2. Available in powder only, not sterile
3. Contains 33% of fat as MCT

VII. DISEASE-SPECIFIC FORMULAS

A. Similac PM 60/40
1. Indicated for impaired renal function
2. Lower mineral content – does not meet iron needs
3. Close to human milk

B. Enfaport
1. Indicated for Chylothorax or LCHAD deficiency
2. Contains 84% of fat as MCT

VIII. SOY-BASED FORMULAS

A. Enfamil Prosobee / Similac Isomil
1. Lactose-free; can be used for galactosemia or hereditary lactase deficiency
2. Soy formulas should not be used in preterm infants due to phytic acid and aluminum content, which decreases the bioavailability of calcium and other minerals increasing risk of bone disease

IX. FORMULAS FOR REFLUX/FUSSINESS

A. Similac Sensitive
1. Low lactose formula marketed for fussiness and gas due to lactose intolerance
2. Almost never indicated as lactose intolerance is extremely rare in infants – do not recommend!

B. Enfamil A.R.
1. Added rice starch thickens when it hits the acidic environment of the stomach to help reduce reflux symptoms. Cannot be used with Zantac. May increase residuals.
2. Questionable effectiveness; treats symptoms rather than cause – do not recommend!

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APNEA OF PREMATURITY
OBSERVATION & DISCHARGE GUIDELINES

I. GENERAL INFORMATION

This guideline was developed to outline the length of stay for observation of preterm infants (<37 weeks gestational age) who experience apnea of prematurity (A) or bradycardia (B)/desaturation (D) events related to prematurity. Following review of the literature (1-5) and clinical practice discussion, consensus was reached on the following parameters. This guideline does NOT outline parameter for discharge of patients who require apnea monitors or for full term infants with events.

A. 48 hour observation
   - Self-limiting bradycardia/desaturation events occurring only during feeds that do not require intervention

B. 72 hour observation
   - Significant bradycardic events (<70 beats/min) or desaturations (<80%) occurring during sleep or between feeds that are *self- limiting*
   - Significant bradycardic events (<70 beats/min) or desaturations (<80%) occurring during sleep or between feeds that *require light stimulation*

C. 5 day observation
   - Significant bradycardic events (<70 beats/min) or desaturations (<80%) that require stimulation (moderate or vigorous stimulation, positive pressure ventilation, code event, chest compressions, blow-by oxygen)
   - Clinically observed color change (will likely require stimulation, blow by or have desat event)
   - Any Apneic event (defined as pause >20sec or <20 sec associated with brady/desat event)

D. 7 day observation
   - Not usually performed but can be done under special circumstances as an exception to the guideline (e.g. in cases of ELBW, <40wk PMA, extreme repetitive code events requiring significant rescue)

II. DEFINITIONS

A. Apnea: cessation of breathing for $\geq$ 20 seconds or cessation of breathing $\geq$ 10 seconds with associated bradycardia or cyanosis

B. Bradycardia: varies based on gestational age; for term corrected infants, bradycardia generally considered for resting heart rate < 80 bpm; significant bradycardia is considered when heart rate is below 70 bpm

C. Desaturation: Under physiologic condition, normal saturations are considered > 95%; notable desaturations are noted for pulse oximeter readings < 90% however the context, duration and reliability of pulse oximeter should be considered when interpreting desaturation event; significant desaturation events are considered for values <80%

regardless of duration and context; saturations of at least 95% result in significant increase in pulmonary vasodilation; term corrected infants with CLD who remain optimally oxygenated have improved weight gain and attain development milestones more readily; optimal oxygen administration depends on the corrected gestational age and co-morbid diseases, and should be discussed with the Neonatology attending

D. Self-limiting: no stimulation was required by a caregiver for the infant to recover from the event

E. Light: gentle strokes on the body were required to reduce central cyanosis or recover

F. Moderate: flicking the sole of the foot, or rolling the infant side to side, or using blow-by oxygen or increasing the fraction of inspired oxygen (FiO2) was necessary to reduce central cyanosis or recover

G. Vigorous/severe: ventilation with bag and mask or use of resuscitative drugs was necessary to recover

III. HOME MONITORS

Medical science has failed to demonstrate any link between those who have "apnea of prematurity" in an intensive care unit and those who die of "SIDS". Statistically a greater number of significantly premature infants, BW <1000gms, die of SIDS, but there is no relationship to history of apnea in the NICU and SIDS later in life. There has been no satisfactory demonstration to date that monitors alter the death rate from SIDS. Since there are no reliable tests to tell us who might benefit from home monitoring, we rely on clinical judgment. Thus the following are guidelines only:

A. Home cardiorespiratory monitoring should <u>not</u> be prescribed to prevent SIDS

B. General considerations:
   1. Infants who have experienced an apparent life-threatening event (ALTE)
   2. Infants with tracheostomies or anatomical abnormalities that make them vulnerable to airway compromise such as Pierre Robin infants
   3. Infants with neurologic or metabolic disorders affecting respiratory control
   4. Infants with CLD, who are requiring supplemental oxygen, continuous positive airway pressure, or mechanical ventilation

C. Premature infants – monitors may be warranted in the following conditions:
   1. High risk of recurrent episodes of apnea, bradycardia, and hypoxemia after hospital discharge – criteria include but are not exclusive to the following:
      a. When breathing stops for 20 seconds or longer
      b. When breathing stops for less than 20 seconds, but is associated with bradycardia or cyanosis
      c. Infants on caffeine at the time of discharge, or have been taken off caffeine within a week prior to discharge
      d. When sleep study results indicate the need for home monitoring as determined by the pulmonary attending/fellow
   2. Premature infants who are technology dependent (oxygen, tracheostomy, CPAP), have unstable airways, have rare medical conditions affecting regulation of breathing, or have symptomatic chronic lung disease

D. Special considerations:
    1. Infants going home on continuous feedings overnight where home nursing will not be available during the night feeding period.
        a. The attending physician should determine if monitoring is required
    2. Monitoring of siblings of infants who have died of SIDS –
        a. The risk of SIDS in this population is unclear
        b. Efficacy of monitoring to prevent SIDS in this group is equally unclear
        c. Due to the uncertainty of the relationship and effectiveness of treatment, and the anxiety in most parents who have had a sibling with SIDS, it is recommended that these infants also be monitored, but it is not mandatory if parents do not want home monitoring

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ANEMIA AND TRANSFUSION MEDICINE

I. GENERAL INFORMATION

The critically ill neonate may require the need for transfusion of various blood products throughout the hospital stay. The preterm infant may require multiple blood transfusions due to lower blood hemoglobin concentrations at birth, frequent blood sampling, low total blood volume to blood sampling ratio, and diminished production of erythropoietin[1]. Preterm infants experience a more significant physiologic nadir to a mean hemoglobin level of 7-8gm/dL that is also more prolonged than that of the term infant. Infants with more significant cardiopulmonary disease may require hemoglobin/hematocrit thresholds to be maintained slightly higher to optimize oxygen delivery. Several studies have sought to determine adequate thresholds for transfusion in the neonate. The preterm neonate in particular is subject to a high risk of apnea, intraparenchymal brain hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis[2-3], all of which may be increased with severe or prolonged anemia.

Coagulopathy may also accompany various disease states in the NICU (sepsis, disseminated intravascular coagulation, hypoxic injury, synthetic liver disease, etc.) This may predispose infants to other comorbidities such as intracranial hemorrhage or pulmonary hemorrhage, and necessitate the need for transfusion of platelets, fresh frozen plasma (FFP) or cryoprecipitate.

Estimated blood volume varies with gestational age. In premature infants, estimated blood volume ~ 100 mL/kg, compared to ~85mL/kg blood volume in term infants.

II. GENERAL TRANSFUSION GUIDELINES

A. Red blood cell transfusions (adapted from Stauss, et al[4]):
   1. For severe cardiopulmonary disease (i.e. PPHN, ECMO): maintain hematocrit 40-45%
   2. For moderate cardiopulmonary disease (i.e. requires supplemental O2): maintain hematocrit 30-40%
   3. For major surgery: maintain hematocrit 30-35%
   4. For infants with stable anemia (no respiratory support with evidence of bone marrow production of RBCs): maintain hematocrit > 25%
   5. Consider transfusion in any neonate with symptomatic anemia (tachycardia, tachypnea, frequent cardiorespiratory events, O2 requirement) if hematocrit < 35%

B. Other blood product transfusions[5]:
   1. For sick, preterm neonate in the first week of life or with evidence of active bleeding: maintain platelets > 100K
   2. For sick, term neonate with evidence of active bleeding: maintain platelets > 100K
   3. For all others, maintain platelets > 30-50K
   4. For infants with evidence of bleeding diathesis or at risk for such: maintain INR < 2.0, fibrinogen > 150 with fresh frozen plasma or cyroprecipitate

III. COMPONENT DOSING

A. Red blood cells
   RBCs are used for treatment of anemia in the neonate. Dosing of RBCs is by volume needed, usually 10-15mL/kg, administered slowly, not to exceed 4 hours, via PIV or central line (Broviac only, PICC lines smaller than 3French may clot with the slow rate of infusion).

For select surgical procedures (primarily cardiac) or for ECMO, blood may need to be ordered by unit.

B. Platelets
Platelets are used in the treatment of thrombocytopenia. Platelet dosing is by equivalent unit (EU) per order care-set in Cerner, and specific volume is administered over 30 minutes via PIV or central line (Broviac only); typically volume is 10-15mL/kg.

C. Fresh frozen plasma
FFP is used primarily to treat acquired coagulation factor deficiencies such as disseminated intravascular coagulation (DIC) or synthetic liver dysfunction. Dosing of FFP is typically 10-15mL/kg, and administered over a minimum of 30 minutes, not to exceed 4 hours, via PIV or central line (Broviac only).

D. Cryoprecipitate
Cryoprecipitate is the treatment of choice for congenital factor XIII deficiency (if recombinant product is not available), congenital afibrinogenemias, dysfibrinogenemia and hypofibrinogenemia (< 150mg/dL) associated with bleeding. Dosing of cryoprecipitate is 1 bag per 5kg, and administered over 30 minutes via PIV or central line (Broviac only), where the volume of one bag is 10-15 mL.

To determine how much cryoprecipitate is needed by calculating fibrinogen replacement:

= (desired fibrinogen level – initial fibrinogen level) x plasma volume (mL) x 0.01 dL/mL

Example:

Initial fibrinogen is 40 mg/dL, desired fibrinogen is 200 mg/dL, and Hct 50%
To calculate plasma volume (PV)
= Blood volume[f] x (1 – Hct)
= (85 mL/kg x 2.5 kg) x (1 – 0.5) = 106 mL
[f] Estimating blood volume = 85mL/kg for a term infant
Fibrinogen needed
= (200 mg/dL – 40 mg/dL) x 106 mL x 0.01dL/mL
= 160 mg/dL x 106 mL x 0.01dL/mL
= 170 mg
1 bag of cryoprecipitate contains ~ 250mg fibrinogen/bag

Additional instructions on order care sets and policies can be found on the intranet

IV. BLOOD BANKING FOR NICU PATIENTS

A. Scope
Blood banking for NICU patients has changed from the routine use of O negative washed cells to type specific dedicated units. Up to 3 infants can be assigned per unit, which may be used for up to 42 days. This will allow directed donations from family as well as dedicated units from the blood bank pool, thus decreasing the number of donor exposures.

B. Procedure
1. Routine admissions
All neonates in the NICU must be typed and screened prior to their <u>first</u> transfusion, which includes: ABO grouping, Rh typing, direct and indirect antiglobulin test

2. Transfusion specifics
   a. Specimen collection:
      - A minimum of 2cc of blood in a lavender top tube is necessary for the Type and Screen; all samples must be properly labeled, signed and dated by the procedure drawing the sample and a second health care provider as a witness. The signed label must be affixed to the specimen in the presence of the witness. If using an electronic specimen collection software such as Cerner Bridge Specimen Collection, the software provides positive patient ID (PPID) and requires only one person.
      - Type and screen is required for any blood product transfusion (RBC, platelets, cryoprecipitate or platets)
      - Potential ECMO candidates should have 3 units *crossmatched* for cannulation NOT "type and screen". Type and screen does not set up the units, only processes the type of blood. If the patient does not go on ECMO, the blood bank should be called so the blood can be released.
      - A new Type and Screen specimen is needed after 4 months of age, after a discharge and readmission or for major surgical procedures in which the anticipated blood requirements exceeds one full unit of RBCs.
   b. Irradiation*:*
      - Infants of any size who have received an intrauterine transfusion or who may have an immune deficiency disease should receive irradiated blood.
      - Premature infants with birth weight < 1200 gms, and still currently <2500 grams
      - Infants with congenital heart disease in which the FISH for Di George's Syndrome or other <u>22q11.2 deletion syndromes</u> is unknown; (isolated coarctation of the aorta & patent ductus arteriosus are exceptions).

3. Anticipation for surgical procedures
   Requisition for the blood must be done as soon as the procedure is scheduled
   Order RBCs by the unit, not mL, and choose the justification code "On hold for surgery...."

4. Exchange transfusion
   Any patient from the NICU who <u>requires an exchange transfusion must be crossmatched.</u>

   If exchange transfusion is anticipated, e.g., patient admitted with bilirubin 25 or greater, the Transfusion Medicine Medical Director on-call should be called immediately so they can direct you on the appropriate amount and hematocrit of blood product to use.

5. Emergency release
   NICU patients rarely require emergency release of blood for transfusion. If emergency release is required, call the Blood Bank at 202-476-5347 and inform them of the urgent need. Order a Type and Screen if one is not already on file, and order the blood products desired. Transfusion Medicine must receive a pre-transfusion Type and Screen specimen ASAP but will issue the emergency release blood needed prior to receiving the specimen, if necessary

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