Case 1

- Length 52.5 cm (75%), FOC 34.8 cm (25-50%)
- Physical exam unremarkable except for peeling hands, deep feet creases, decreased adipose tissue, long slender infant
- Noted to be tremulous
- Initial glucose = 25 mg/dL
- What next?

Hypoglycemia

- Why worry?
- The Brain
- CT scan of term newborn infant with prolonged hypoglycemia of less than 20 mg/dl (1.1 mmol/l) for greater than 48 hours. CT done on DOL 5
Hypoglycemia

• What is hypoglycemia?
  – Determined by glucose level, but what level?
    • Literature does not offer any consistent approach
    • A multinational group of experts examined critically the evidence and considered it impossible to define hypoglycemia as a single blood glucose level and suggested using operational thresholds and therapeutic goals

Operational Thresholds

<table>
<thead>
<tr>
<th>Plasma Glucose Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical condition</td>
</tr>
<tr>
<td>All babies</td>
</tr>
<tr>
<td>Abnormal neurological signs or systemically sick</td>
</tr>
<tr>
<td>All babies with no abnormal neurological signs</td>
</tr>
<tr>
<td>Persistent hyperinsulinemia</td>
</tr>
</tbody>
</table>

1. Blood sample should be free flowing venous or from warm heel
2. Blood glucose can be low due to dilution by red cells
   Value can be 10-15% lower than plasma glucose values

My personal bias – 45 mg/dL or higher (plasma)

At Risk Infants (Physician List)

• Infant of diabetic mother
• Preterm (< 37 weeks)
• Intrauterine growth restriction
• Polyhydramnia
• Abnormal neurological signs
• Acute illness (sepsis)
• Hypoxic-ischemic encephalopathy
• Maternal beta-blocker medication
• Suspected hyperinsulinism
  – Beckwith-Wiedemann syndrome
  – Beta-cell gene mutations
• Suspected inborn error of metabolism / endocrine disorder

Signs & Symptoms of Hypoglycemia

• Jitteriness
• Irritability
• Hypotonia
• Lethargy
• High-pitched cry
• Hypothermia
• Poor suck
• Tachypnea
• Cyanosis
• Apnea
• Seizures
• Cardiac arrest

Transition Nursery Guidelines (Nursing)

• Feed at risk babies soon after birth (if able)
  – Breast feeding is adequate feeding
• Glucose checked per protocol 30 min later

Transition Nursery Guidelines (Nursing)

• Glucose Protocol
  – Infants of diabetic mothers
  – Infants > 4000 grams or LGA by Ballard
  – Infants < 2500 grams or SGA by Ballard
  • Glucose checked every 30 mins x 4 then prefeed q8h for 48 hours
    – Note: May be changed in individual cases by faculty, fellows or NBN resident
  – Note: Other at risk infants are determined by the physician

UH NBN Guidelines
Case 1

• Our infant glucose post feed
  – 30 min = 43 mg/dL
  – 60 min = 36 mg/dL
  – Still tremulous
• What do we do now?

Further Intervention

• Asymptomatic infants with 2 consecutive blood glucose < 36 mg/dL
• Any baby whose blood glucose < 20 mg/dL
• Any baby with abnormal clinical neurological signs

Intervention

• If early enteral feeds are not appropriate/tolerated or enteral feedings do not prevent fall in blood glucose < 20 mg/dL
  – Start IV fluids with glucose infusion rates of 4-6 mg/kg/min
  – Infants with abnormal neurological signs or very low levels,
  – Mini-bolus of glucose = 2 ml/kg of 10% dextrose (= 200 mg/kg/min)
  – Followed with a constant glucose infusion of 4-6 mg/kg/min
  – If glucose remains below operational thresholds, increase infusion rate by 1-2 mg/kg/min and recheck levels
  – Continue feedings if tolerated even if IV fluids are needed

Glucose Infusion Rate

• (% gluc X 10) (rate infusion/hr)
  60 X weight (kg)

  Or

• (%gluc) (rate infusion/hr) (0.167)
  Weight (kg)

Case 1

• Transferred to extended NBN
  – Given an IV bolus of D10 (2ml/kg)
  – PIV fluids at 80ml/kg/day
  – Repeat glucose 77 and prefeed glucose = 66
• Next 24 hours
  – Serial prefeed glucose 43, 70, 41, 35, (changed to D12.5 at 100ml/kg/day), 70, 62, 78 on feeds
• 24-48 hours
  – Failed to wean with glucose 47, 46 at 36 hr and again at 48 hrs with glucose as low as 39 (on 120ml/kg/day oral intake formula and 120ml/kg/day D12.5)

Case 1

• What is the normal course for glucose metabolism transition in an infant?
• Is this the expected course for our infant?
Quick Review of Glucose Metabolism

Maintaining Adequate Glucose Levels

- Hepatic glycogenolysis
  - Immediate source of fasting glucose
  - 50-75 g glucose (200-300 cal) /kg of liver
  - Sufficient for 2 hours
- Hepatic gluconeogenesis
  - Sole source when glucose stores depleted
  - Precursors – AA, glycerol, lipolysis, lactate
- Lipolysis
  - Releases FFA
  - Heart, kidneys, skeletal muscles can use directly
  - LCFA do not cross BBB so brain can not use
- Fatty acid oxidation and ketogenesis
  - Partial oxidation to produce ketones, B-hydroxybutyrate, acetoacetate
  - Brain can use
- Endocrine control
  - Insulin, cortisol, GH

Avery's Diseases of the Newborn 8th ed

Maintaining Adequate Glucose Levels

- In infants, the fasting response is more rapid
  - Due to greater brain weight/body mass
  - Term: 2-3 x adults
    - 4-6 mg/kg/min
  - Preterm higher than term
    - 5-8 mg/kg/min

Maintaining Adequate Glucose Levels

- Not all systems are functional at birth
  - Hepatic glycogenolysis
    - Glycogen filled 3rd trimester
  - Hepatic gluconeogenesis
    - Several enzymes not present
  - Lipolysis
    - Fat stores filled 3rd trimester
  - Fatty acid oxidation and ketogenesis
    - Not present till after birth
  - Endocrine control
    - Not mature at term

Maintaining Adequate Glucose Levels

- Timing of complete maturation of these fasting systems is not fully known
  - Possibly as early as 24 hours
  - Probably before 1 week of age
  - Maintain > 45 mg/dL at 24 hours old - (Heck, 1987)
  - Day 3 mean fasting glucose = 73 mg/dL (all >50)
    - [Trinaman, et al, 1988]
  - Preprandial glucose levels by days 3 to 4 greater than 50 mg/dL - [Luberscho and Bard, 1972]

Avery's Diseases of the Newborn 8th ed

Case 1

- Our infant’s clinical response is not the expected course in maturation of the glucose homeostasis system
  - Further workup
    - Dx: Persistent Hyperinsulinemia that responded well to diazoxide
    - His jitteriness resolved by DOL 3 and was most likely due to caffeine withdrawal
Summary

- Appropriate glucose levels in term NB are based on operational thresholds and therapeutic goals, not a single value
- Feed at risk infants early if feasible
- Start IV glucose (with a bolus) if indicated
- Term infants should maintain good glucose control as early as 24 hours
- Failure to maintain glucose control > 48hr or GIR at an excessive level warrants further evaluation

MELLOW YELLOW

Case 2

- 3185 gm term African-American female
- G2P1001, O+, serology neg
- Uncomplicated pregnancy
- SVD, Apgars 9/9, taken to NBN
- Noted to be jaundice 4 hours after birth

Hyperbilirubinemia

- Why do we worry about bilirubin?
  - At high levels, bilirubin causes

  Kernicterus
  (Postkernicteric Bilirubin Encephalopathy)
  
  - Today, kernicterus is almost 100% preventable

Bilirubin has good properties

- Antioxidant
  - Contributes up to 10% to 30% of total antioxidants of premature infants (Hammerman, C. et al, Clin Chem, 1998)
  - Unconjugated and conjugated bilirubin can serve as antioxidants, protecting human LDL from lipid peroxidation in vitro against peroxyl radicals (Wu T-W, et al., Biochem Pharmacol, 1996)
  - Cardioprotection against postischemic-reperfusion injury (Sukekiyo et al., Am J Physiol Heart Circ Physiol 2003)
  - Protective in ischemia-reperfusion injury in the rat intestine (Hammerman, C. et al, J Ped Gastroenterol Nut, 2001)
  - Paradoxically, bilirubin is neuroprotective at very low nanomolar concentrations (Kato Y, et al., Proc Nat Acad Sci, 2001)
  - Both UCB and biliverdin display immunoprotective effects on murine liver and cardiac grafts (Kato Y, et al., Hepatology 2003)

Hyperbilirubinemia

- Prior to birth, bilirubin is cleared by the placenta
- After birth, the term infant is at risk of increased bilirubin load from:
  - Increased red cell mass
  - Decreased red cell half life
  - Decreased conjugation
  - Increased enterohepatic circulation
  - Decreased oral intake
  - Decreased albumin level
Hyperbilirubinemia

- Indirect-reacting bilirubin in UC is 1-3mg/dL
- Rate of rise averages 5mg/dL/24h after birth
- Visible at about 6mg/dL in Caucasians
  - (Females detect jaundice at a lower level than males)
- Jaundice present at birth or within the 1st 24hr is pathologic
  - A later presentation is generally physiologic (but not always)
- Most common cause for newborn readmission

Hyperbilirubinemia

- In general, a search to determine the cause of jaundice should be made if:
  - It appears in the first 24 hours of life
  - Serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr
  - Serum bilirubin is >12-13 mg/dL in full-term infants (especially in the absence of risk factors) or 10-14 mg/dL in preterm infants
  - Jaundice persists after 10-14 days of life
  - Direct-reacting bilirubin is >2 mg/dL at any time

Case 2

- Noted to be jaundice 4 hours after birth
- This is abnormal

Laboratory Evaluation of the Jaundiced Infant of 35 or More Weeks’ Gestation

<table>
<thead>
<tr>
<th>Indications</th>
<th>Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice in direct TSB</td>
<td>Measure TSB and/or TBL</td>
</tr>
<tr>
<td>Jaundice appears excessive for infant’s age</td>
<td>Measure TSB and/or TBL, blood type and Coombs test, if not obtained</td>
</tr>
<tr>
<td>Infant not yellow</td>
<td>Complete blood count and smear</td>
</tr>
<tr>
<td>Jaundice in indirect TSB</td>
<td>Measure direct or conjugated bilirubin</td>
</tr>
<tr>
<td>Jaundice appears excessive for infant’s age</td>
<td>It is an option to perform additional tests, G6PD and ETOX, if available</td>
</tr>
<tr>
<td>Infant not yellow</td>
<td>Complete blood count and smear, measuring infant’s age and TSB level</td>
</tr>
<tr>
<td>Jaundice presenting exchange transfusion or not responding to phototherapy</td>
<td>Perform electrolytes, glucose, albumin, ETOX, if available</td>
</tr>
<tr>
<td>Jaundice present at or beyond age 3 wks, or sick infant</td>
<td>Evaluate for sepsis or other diseases, history and physical examination</td>
</tr>
</tbody>
</table>

Note: If direct bilirubin elevated, evaluate for causes of dehydration.

Pediatrics 2004
Case 2

- Infant B+ (Mother O+)
- DAT +
- Total bili = 9.6 mg/dl @ 4hr
- Hemoglobin = 10.6 g/dl

Risk Factors for Bilirubin Neurotoxicity

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Hyperbilirubinemia Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>Isoimmune hemolytic disease</td>
</tr>
<tr>
<td></td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Asphyxia</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Acetosis</td>
</tr>
<tr>
<td></td>
<td>Albumin &lt; 5.0 mg/dL</td>
</tr>
</tbody>
</table>

Neurotoxicity risk factors are used in making the decision to initiate phototherapy or perform an exchange transfusion.

Interventions are recommended at a lower bilirubin level when any of the neurotoxicity risk factors is present.

Guidelines for phototherapy in infants 35 weeks’ gestation

<table>
<thead>
<tr>
<th>Day</th>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.6</td>
</tr>
<tr>
<td>2</td>
<td>12.1</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
</tr>
<tr>
<td>4</td>
<td>8.3</td>
</tr>
<tr>
<td>5</td>
<td>10.5</td>
</tr>
<tr>
<td>6</td>
<td>13.7</td>
</tr>
<tr>
<td>7</td>
<td>7.5</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Phototherapy started, double lights added on DOL 3 and discontinued on DOL 6

Also was transfused 30ml PRBCs

Maternal anti-B antibody titer 256, G6PD neg, Sickle neg, ID w/u neg

ABO hemolytic disease is more common in African-Americans (B group)

Predischarge Risk Assessment For Subsequent Severe Hyperbilirubinemia

- New evidence suggests that combining a predischarge measurement of TSB or TcB with clinical risk factors might improve the prediction of the risk of subsequent hyperbilirubinemia
- The recommendations are not endorsed by the AAP, but are put forth as clarification by the leading experts and authors of the 2004 AAP recommendations
- There are 3 flow diagrams to use with the bilirubin discharge nomogram depending upon risk factors

Other Risk Factors for Severe Hyperbilirubinemia

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Other Risk Factors for Severe Hyperbilirubinemia</th>
</tr>
</thead>
</table>
| Age and the Predischarge TSB or TcB level | Considered with the Gestational Age and the Predischarge TSB or TcB level (see Figure 3).
| Birth asphyxia, particularly if neurologic defects develop, or significant hypoglycemia or acidemia at birth | Severe hypoglycemia or other hemolytic disease (e.g., G6PD deficiency, hereditary spherocytosis) |
| Premature delivery with patent ductus arteriosus | Perinatal infection with parechymal brain damage |
| Cardiomyopathy or significant intrauterine growth retardation | Neonatal jaundice |
| The predominance of ABO in one group over the other is not the most important factor that helps to predict the risk of hyperbilirubinemia. The risk increases with each increasing week of gestation, as seen in Figure 2. |
Pediatrics Grand Rounds  
13 August 2010  

University of Texas Health Science Center at San Antonio

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**Nomogram for Designation of Risk at Discharge**

[Table or diagram showing the nomogram for risk designation at discharge.]

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**Algorithm providing recommendations for management and follow-up**

A.  
- Gestational age 35–36.9 weeks, no hyperbilirubinemia risk factors
- Gestational age ≥37 weeks, no other hyperbilirubinemia risk factors

B.  
- Predict discharge TcTTPB
- Assign bilirubin risk zone

C.  
- Follow-up at 72 h

---

**Summary**

- Bilirubin is treated to prevent Kernicterus
- An infant jaundice at birth or in the 1st 24h is abnormal
- Management of bilirubin is directed by the AAP Clinical Practice Guideline, 2004
- Recent research indicates a risk based approach in conjunction with the 2004 AAP guidelines provide a better assessment of severe hyperbilirubinemia at discharge

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**Major References for Management**


- Newborn Nursery Guidebook: Laughing (or smiling) your way through Newborn Nursery, 2009-2010. UTSASSA, Blackboard, Pediatric Nursery Rotation.