**Summary of Version Changes**

- Meets discharge criteria
- NICU Consult Criteria

**Automatic NICU Admission Criteria**
- Signs of acute bilirubin encephalopathy
- TSB > 5 mg/dL above exchange transfusion threshold
- Include NICU attending on calls for patients that meet NICU direct admit criteria.

**Exclusion Criteria**
- Direct hyperbilirubinemia
- Meets NICU Direct Admit Criteria
- TSB > 5 mg/dL above exchange transfusion threshold
- Signs of acute bilirubin encephalopathy
- Suspected sepsis or ill-appearing

**Inclusion Criteria**
- Previously healthy
- Age ≤ 14 days
- Born at ≥ 35 wks gestational age

**Pathophysiology**

**Risk for Kernicterus**

**Initial Assessment**
- Clinical History / Physical Exam
- Blood Glucose only if symptomatic
- Total Serum Bilirubin with conjugated fraction (use Heelstick sample)
- Send G-6-PD screen if patient is male and is from an ethnic region at risk for the disease (Afro-Caribbean, West Africa, India, Pakistan, Bangladesh, East African, Asian, Cyprus, Middle East (Iran, Lebanon), China, Italy.
- Initiate ED Hyperbilirubinemia (Neonatal) Orders
- Start phototherapy while awaiting results if clinically indicated
- Determine exchange transfusion threshold using AAP nomogram
- Determine phototherapy threshold using 
- Web Link to 

**Evaluate for Discharge**
- TSB below phototherapy threshold
- Follow-up appointment arranged for next day
- Feeding adequately
- No concern for significant hemolysis

**Evaluate for NICU Consult Criteria**
- TSB within 2 mg/dL of exchange transfusion threshold
- Age ≤ 24 hours
- High suspicion for or lab evidence of hemolysis (e.g. DAT positive)

**Evaluate for Inpatient Admission**
- TSB above phototherapy threshold but not within 2 mg/dL of exchange transfusion threshold (e.g. at 72 hours of age, exchange transfusion threshold 24 and TSB 21)

**ED Management**
- Give effective phototherapy
- Encourage feeding
- The infant should not be removed from bili lights for > 20 mins in any 3 hour period. Use bottle if needed.
- DO NOT interrupt phototherapy for patients nearing exchange transfusion threshold or with rapidly rising TSB
- Use maternal EBM for supplemental feeds, when available
- Give 20 mL/kg NS bolus then maintenance IV fluids for patients that meet NICU consult criteria
- Consider additional labs

**Place PIV only if patient meets NICU Admission Criteria or NICU Consult Criteria**

**Admit to NICU**

**NICU (Off Pathway)**

**Admit on phototherapy**

**Inpatient Admission**

**Discharge**
Neonatal Jaundice for Infants ≥ 35 Weeks Gestational Age v4.0

**PHASE II (INPATIENT)**

**Inclusion Criteria**
- Previously healthy
- Age ≤ 14 days
- Born at ≥ 35 wks gestational age

**Exclusion Criteria**
- Direct hyperbilirubinemia
- Meets NICU Direct Admit Criteria
- TSB > 5mg/dL above exchange transfusion threshold
- Signs of acute bilirubin encephalopathy
- Suspected sepsis or ill-appearing

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**Inpatient Management**
- Initiate Hyperbilirubinemia (Neonatal) Admit Orders
- If direct admit, obtain baseline total serum bilirubin (TSB)
- Continue effective phototherapy until TSB at least 3 mg/dL below phototherapy threshold
- Encourage feeding. The infant should not be removed from bili lights for > 20 mins in any 3 hour period. Use bottle if needed.
- If patient unable to maintain normal temperature in an open crib, place in isolette per Isolette Use Policy & Procedure (for SCH only)
- Consider additional labs for patients meeting NICU consult criteria
- Run maintenance IV fluids for patients within 2 mg/dL of exchange transfusion threshold or with rapidly rising TSB. Stop IVF once TSB has fallen to at least 2 mg/dL below exchange transfusion threshold and feeding well (e.g. at 72 hours of age, exchange transfusion threshold 24 and TSB less than 22)

---

**TSB within 2 mg/dL of exchange transfusion threshold, age <72 hours, or known/suspected hemolysis?**

- Yes
  - **Subsequent Labs**
    - TSB every 4 hours until TSB falling
    - G6PD (for unexplained hemolysis)
  - Meets **Discharge Criteria**
    - Patient off phototherapy and otherwise well
    - Follow-up appointment arranged for next day
    - No concern for significant ongoing hemolysis
  - **Discharge**

- No
  - **Subsequent Labs**
    - TSB approximately 12 hours after starting phototherapy (or with routine AM labs)
    - Subsequent checks as clinically indicated

---

For questions concerning this pathway, contact: NeonatalJaundice@seattlechildrens.org

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Ordersets

Updated Ordersets:

Use for patients age 0 to 14 days with hyperbilirubinemia
  • ED Hyperbilirubinemia (Neonatal) Orders
  • Hyperbilirubinemia (Neonatal) Admit Orders

Ordersets are intended for use with patients on the neonatal jaundice pathway.
  • For patients with neonatal jaundice who do not meet inclusion criteria, please uncheck “Follow Neonatal Jaundice Pathway” order
  • For patients meeting exclusion criteria, uncheck “Follow Neonatal Jaundice Pathway” order and check “Exclude from Neonatal Jaundice Pathway” selecting the specific exclusion criteria satisfied
Key Pathway Features

- Tools to identify phototherapy and exchange transfusion thresholds built into CIS
- Fewer tests
- IV hydration limited to infants at high risk for exchange transfusion
- New phototherapy equipment introduced with tools to ensure delivery of effective phototherapy
- Emphasis on regular feeding
**Background**

**“Jaundice”**
- Yellowing of the skin, conjunctivae and other mucous membranes
- Increased circulating bilirubin
- Deposits in tissues
- Progresses caudally
- One of the most common conditions leading to medical evaluation in neonates

**“Hyperbilirubinemia”**
- Total serum bilirubin (TSB) >95th percentile for age in hours
- Jaundice does not necessarily = hyperbilirubinemia

**Epidemiology**

Visible Jaundice is Common
- ~60% of term and ~80% of preterm infants will be visibly jaundiced in the first week of life

Need for Treatment is Less Common
- ~4% of neonates in a U.S. study population met criteria for phototherapy (Atkinson 2003)
- TSB is ≥ 20 mg/dL in 1 - 2% of infants born at ≥ 35 weeks gestational age (Newman 1999, Eggert 2006)

Variation in Hospital Treatment Exists
- 0.5 – 8% of infants born at ≥ 35 weeks gestational age receive phototherapy in the hospital (before nursery discharge or readmitted) (Bhutani 2006, Eggert 2006, Malcelsi 1998)

**Epidemiology – Blood Group Incompatibility**

In the United States
- Rh sensitization
  - 10 per 10,000 births
- ABO incompatibility
  - 12% of pregnancies
- Significant hemolysis due to ABO incompatibility
  - <1% of births
  
  (Wagle 2011)
Neonatal Physiologic Jaundice

Newborns have:
- Shorter red blood cell lifespan
- Higher red blood cell concentration
- Slower metabolism and excretion of bilirubin

This is considered physiologic

Direct Hyperbilirubinemia is NOT Physiologic

- Conjugated bilirubin ≥ 2 mg/dL or ≥ 20% of total serum bilirubin (TSB)
- Pathologic causes: hepatobiliary disease, infection, metabolic disease
- The terms “direct” and “conjugated” are used interchangeably

Why Treat?

- Acute Bilirubin Encephalopathy: signs & symptoms of bilirubin neurotoxicity in the first few weeks of life
- Kernicterus: chronic, irreversible signs & symptoms of bilirubin neurotoxicity as a consequence of acute bilirubin encephalopathy
Progression of Hyperbilirubinemia

Factors Contributing to Pathologic Hyperbilirubinemia

- **Increased hemolysis of red blood cells** (Blood group incompatibility, G-6-PD deficiency, hereditary spherocytosis)
- **Breastfeeding jaundice** (inadequate fluid/nutrient intake → dehydration → increased enterohepatic circulation)
- **Breast milk jaundice** (increased enterohepatic circulation due to enzyme in breast milk)
- **Polycythemia** (delayed cord clamping, high altitude gestation, maternal smoking)
- **Extravasated blood** (bruising, cephalohematoma, subgaleal hemorrhage, intraventricular hemorrhage)
- **Stress-related Heme-oxygenase induction** (hypoxia, infection, hypothermia)
Signs of Adequate Breastfeeding

By day of life 4:
- ≥ 4 wet diapers per 24 hours
- ≥ 3 stools per 24 hours
- Transitioning stools (meconium → yellow, seedy)

Other signs in term infants:
- Peak weight loss by ~5 days old
- Average peak weight loss = 7% from birth weight, maximum of 10%
- Regain birth weight by ~10 days old

AAP. Pediatrics 2004;114(1):297-318; Spenoor 2012
Evidence of Hemolysis

- Jaundice evident in the first 24 hours of life
- Rapidly rising total serum bilirubin
- Total serum bilirubin rising or unchanged despite effective phototherapy

Blood Group Incompatibility

- Rh disease
- ABO incompatibility
- Minor blood group incompatibility
  - e.g. Kell, Duffy
  - Rare
Pathophysiology of ABO Incompatibility

Almost exclusively O mothers with A or B fetus

- A, B mothers make IgM antibodies
- O mothers make IgG antibodies
- IgM does not cross the placenta; IgG does

Less severe than Rh disease

- “Distraction” (A & B antigens are widely expressed in various tissues so RBCs are not the only target)
- Low A & B surface Ag expression on fetal RBCs = fewer reactive sites
Major Risk Factors for Severe Hyperbilirubinemia

- High-risk TSB or TcB before nursery discharge
- Jaundice in the first 24 hours of life
- Blood group incompatibility with positive direct antiglobulin test (DAT) or other known hemolytic disease (e.g. G6PD deficiency)
- Gestational age 35 - 36 weeks
- Previous sibling received phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding
- East Asian race

AAP. Pediatrics 2004;114(1):297-318

Factors that Lower Risk for Severe Hyperbilirubinemia

- Low-risk TSB or TcB
- Gestational age ≥ 41 weeks
- Exclusive bottle feeding
- Black race
- Nursery discharge after 72 hours of life

AAP. Pediatrics 2004;114(1):297-318
Risk Factors for Acute Bilirubin Encephalopathy

- Blood group incompatibility (a.k.a. isoimmune hemolytic disease)
- G6PD deficiency
- Asphyxia
- Significant lethargy
- Temperature instability
- Sepsis
- Acidosis

AAP. Pediatrics 2004;114(1):287-298
Pathway Inclusion and Exclusion Criteria

Included
• Previously healthy
• Age ≤ 14 days
• Born at ≥ 35 weeks gestational age

Excluded
• Direct hyperbilirubinemia
• Meets NICU Direct Admit Criteria
  • TSB > 5 mg/dL above exchange transfusion threshold
  • Signs of acute bilirubin encephalopathy
• Suspected sepsis or ill-appearing
Guidelines for **Initiation of Phototherapy**
In Hospitalized Infants of 35 or More Weeks’ Gestation

These levels are approximations representing a consensus based on limited evidence.
[LOE: E (AAP 2004)]

- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.
These levels are approximations representing a consensus based largely on the goal of keeping TSB levels below those at which kernicterus has been reported. [LOE: E (AAP 2004)]

- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrococollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 μmol/L) above these lines.
- Risk factors: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.
How to Use BiliTool™

Step 1: Click on the Bilirubin laboratory result to invoke a result pop-up window.

![Bilirubin Laboratory Results]

Step 2: The Bilitool™ button will display in the top right of this pop-up window when a bilirubin sum is available. Click the button.

![Bilirubin Unconj/Conj/Sum]

How to Use BiliTool™, cont’d

Step 3: Enter patient’s age in hours at the time the TSB was drawn. If older than 168 hours enter 168.

![Press Submit for Bilitool]

Step 4: Bilitool.org is opened, passing the age and result information.

![BiliTool EMR™]
NICU Direct Admit Criteria

Directly admit infants with TSB >5 mg/dL above exchange transfusion threshold or with signs of acute bilirubin encephalopathy to the NICU for exchange transfusion.

Rationale:
Exchange transfusion during the intermediate stage of acute bilirubin encephalopathy may lead to reversal of neurotoxicity and prevent kernicterus

[LOE: very low quality ✦✦✦ (Harris 2001), Local Expert Opinion]
NICU Consult Criteria: ED

- Bilirubin within 2 mg/dL of exchange transfusion threshold
- Age less than 24 hours
- Evidence of hemolysis

[LOE: Local Expert Opinion]
**Effective Phototherapy**

Use blue – green spectrum (460 – 490 nm) light with irradiance (“dose”) of at least 30 μW/cm²/nm covering maximal body surface area

**Rationale:**

Bilirubin best absorbs blue light (~460 nm). Light absorption converts unconjugated bilirubin into bilirubin photoproducts. The most effective light in practice is probably in the blue-to-green spectrum (~460 – 490 nm) due to properties of the skin.

[LOE: high quality ★★★★★ (AAP 2011)]

Studies have demonstrated both a minimal dose and a saturation point for effective phototherapy. Within that range, the response is dose-dependent.

[LOE: moderate quality ★★★★★ (Tan 1977; Tan 1982)]

---

**Type of Phototherapy**

Use LEDs (light emitting diodes).

**Rationale:**

Studies show no significant differences between LED and conventional phototherapy lights in terms of total duration of phototherapy, rate of fall of TSB, phototherapy failure incidence, or incidence of rebound requiring re-initiation of therapy.

[LOE: high quality ★★★★★ (AAP 2011)]

Compared to conventional phototherapy, LED lights have a longer lifespan, lower heat output, low infrared emission and no UV emission.
Lab Frequency

Check TSB every 4 hours until it is falling if TSB is within 2 mg/dL of exchange transfusion threshold, age <72 hours, or known/suspected hemolysis.

-otherwise-

Check TSB ~12 hours after starting phototherapy or with routine AM labs.

Rationale:

There are no good studies looking at lab timing. Frequencies recommended in various guidelines span a wide range. Recommendations are aimed at detecting rapidly rising bilirubin, identifying phototherapy failure, and avoiding unnecessary testing in select infants.

[LOE: Local Expert Opinion]
Additional Labs

Obtain the following labs only if patient meets NICU consult criteria:

- Hematocrit
- Blood type
- Direct Antibody Test (DAT)
- Reticulocyte count

Rationale:
Evidence does not support the routine use of DAT in healthy babies. In identifying significant hemolysis requiring treatment, the positive predictive value of the DAT has been shown to be only 23% with a sensitivity of 86%.

[LOE: Very low quality 🌟🌟🌟 (NICE 2010, Murray 2007)]

Worldwide pooled data show increasing prevalence of blood group incompatibility and G6PD deficiency as etiologic factors in neonatal hyperbilirubinemia as serum bilirubin levels rise.

[LOE: Very low quality 🌟🌟🌟 (NICE 2010)]

Additional Labs, cont’d

Do not measure serum albumin routinely.

Rationale:
Evidence for the bilirubin:albumin (B/A) ratio as a predictor of neurotoxicity is either of poor quality or demonstrates no statistically significant advantage. Do not use the B/A ratio in making decisions about the management of neonatal hyperbilirubinemia.

[LOE: E (NICE 2010)]
Feeding

- Encourage feeding. The infant should not be removed from bili lights for > 20 mins in any 3 hour period. Use bottle while remaining under bili lights if needed
- Use maternal expressed breast milk for supplemental feeds, when available
- Lactation consultation if mom desires to breast feed

Rationale:

Formula feeds and breastfeeding are equally effective at reducing serum bilirubin during phototherapy.

[LOE: moderate quality ⭐⭐⭐⭐ (NICE 2010)]
Feeding, cont’d

Give enteral feeds but DO NOT interrupt phototherapy for patients nearing exchange transfusion threshold or with a rapidly rising TSB.

Rationale:

There is no statistically significant difference in duration of phototherapy or mean change in serum bilirubin between continuous and interrupted phototherapy when initiated at low serum bilirubin levels. There is no data to support interrupted phototherapy at high serum bilirubin levels.

[LOE: moderate quality ☺☺☺☺ (NICE 2010)]

Feeding improves stool output which in turn decreases enterohepatic circulation.
IV Fluids

- Do not routinely supplement with IV fluids
- In the ED: Give 20 mL/kg NS bolus then maintenance IV fluids for patients that meet NICU consult criteria
- On admission to floor:
  - Give maintenance IV fluids for patients within 2 mg/dL of exchange transfusion threshold or with rapidly rising TSB
  - Stop IVF once TSB has fallen to at least 2 mg/dL below exchange transfusion threshold and patient is feeding well

Rationale:
Routine use of supplemental IV fluids is not supported by the evidence and can interfere with breastfeeding. Because supplemental IV fluids can reduce the number of exchange transfusions required, it is recommended that infants at risk for exchange transfusion be given supplemental IV fluids.

[LOE: very low quality 🅢〇〇〇 (Kaplan 2006)]
Stopping Phototherapy

Discontinue phototherapy when the TSB is at least 3 mg/dL below the phototherapy initiation threshold.

Rationale:

One RCT from Israel compared two thresholds for stopping phototherapy, 1 mg/dL and 3 mg/dL below phototherapy initiation level. There was no significant difference in duration of phototherapy or in need for retreatment between the two thresholds.

[LOE: high quality ◆◆◆◆ (Barak 2009)]

Because we are not recommending routine use of rebound labs, the more conservative of these two thresholds was chosen. This is also consistent with the NICE guideline.

[LOE: E (NICE 2010); Local Expert Opinion]

Stopping Phototherapy, cont'd

A longer course of therapy may be indicated in certain circumstances, including the following:

- Ongoing feeding difficulty
- Prematurity (gestational age <37 weeks)
- Higher bilirubin level at the start of therapy, particularly if close to exchange threshold
- Hemolytic jaundice

[LOE: Local Expert Opinion]
Discharge Readiness

• Discharge once off phototherapy and otherwise well
• Discharge when there is no concern for significant ongoing hemolysis
• Do not routinely check rebound TSB (i.e. TSB after some interval of time following phototherapy cessation) before discharge
• Ensure follow-up on the day after discharge

Rationale:
An uncontrolled study from Israel showed 9.6% (22/226) of infants needed a second course of phototherapy for rebound. The majority were infants who were first treated at <72 hours of age.

[LOE: very low quality 1 1 1 (Kaplan 2006)]

A retrospective review from the US found only 0.7% (1/144) of infants readmitted for phototherapy after nursery discharge needed retreatment while 8.2% (13/158) of infants treated with phototherapy while still in the nursery needed a second course of phototherapy.

[LOE: very low quality 1 1 1 (Maisels 2002)]

Discharge Criteria: Inpatient

• Patient off phototherapy and otherwise well
• Follow-up appointment arranged for next day
• No concern for significant ongoing hemolysis

Discharge
Discharge Criteria: ED

- TSB below phototherapy threshold
- Follow-up appointment arranged for next day
- Feeding adequately
- No concern for significant hemolysis

Discharge

Return to ED Management  Return to Inpatient Management
## Value Analysis: Blood Glucose

### Value Analysis Tool

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Care Option A</th>
<th>Care Option B</th>
<th>Preferred Option</th>
<th>Assumptions Made</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description of care treatment option</strong></td>
<td>Obtain serum blood glucose on all patients admitted with neonatal jaundice</td>
<td>Do not routinely obtain blood glucose levels on patients unless symptomatic</td>
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<tr>
<td><strong>Operational factors</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Percent adherence to care (goal 80%)</td>
<td>Neutral</td>
<td>Neutral</td>
<td>NEUTRAL</td>
<td></td>
</tr>
<tr>
<td>Care delivery team effects</td>
<td></td>
<td>Preferred</td>
<td>OPTION B</td>
<td></td>
</tr>
<tr>
<td><strong>Benefits / harms (quality/outcome)</strong></td>
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<td></td>
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<td>Degree of recovery at discharge</td>
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<tr>
<td>Effects on natural history of the disease over equivalent time</td>
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<td>Neutral</td>
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</tr>
<tr>
<td>Potential to cause harm</td>
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<tr>
<td>Population-related benefits</td>
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<tr>
<td>Threshold for population-related benefits reached</td>
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<tr>
<td><strong>Cost (arising from Options A or B) - express as cost per day</strong></td>
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<tr>
<td>“Room rate” ($ or time to recovery)</td>
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</tr>
<tr>
<td>“Dx/Rx” costs ($)</td>
<td>Preferred</td>
<td>OPTION B</td>
<td>SAVINGS: $1,333/yr</td>
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<tr>
<td><strong>Cost (complications/adverse effects arising from Options A or B) - express as cost per day</strong></td>
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### Value Analysis Grid

**Cost**

<table>
<thead>
<tr>
<th>A &gt; B</th>
<th>A = B</th>
<th>A &lt; B</th>
<th>Unclear</th>
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<tr>
<td>Make value judgement</td>
<td>B</td>
<td>B</td>
<td>Do B and PDSA in 1 year</td>
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</tbody>
</table>

| A and B costs are the same | A | A or B, operational factors may influence choice | B | A or B, operational factors may influence choice, PDSA in 1 year |

| B costs more than A | A | A | Make value judgement | Do A and PDSA in 1 year |

### Value Statement

**Final CSW Value Statement**

Blood glucose should not be ordered routinely for patients with neonatal jaundice, levels should be obtained only if symptomatic. This recommendation is based on a review of local data, 1 out of 194 blood glucose values was <40mg/dl, this patient was asymptomatic and did not require intravenous glucose. Estimated yearly cost savings is $1,333.
### Value Analysis: PIVs and IV Fluids

#### Value Analysis Tool

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<tr>
<td><strong>Description of Care Treatment Option</strong></td>
<td>Obtain peripheral IV (PIV) upon admission and give IVFs.</td>
<td>Obtain peripheral IV and give IVFs only if patient meets NICU admission or consult criteria.</td>
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<tr>
<td>A and B costs are the same</td>
<td>A</td>
<td>A or B, operational factors may influence choice</td>
<td>B</td>
<td>A or B, operational factors may influence choice, PDSA in 1 year</td>
</tr>
<tr>
<td>B costs more than A</td>
<td>A</td>
<td>A</td>
<td>Make value judgement</td>
<td>Do A and PDSA in 1 year</td>
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#### Value Statement

**Final CSW Value Statement**

Peripheral IVs and IVFs should only be utilized if the patient meets NICU admission or consult criteria. This option is preferred due to lower cost, increased palatability and decreased risk for harm while providing safe and appropriate care. Estimated yearly cost savings is $4,633.
# Neonatal Jaundice Approval & Citation

**Approved by the CSW Neonatal Jaundice for August 16, 2019 go live**

<table>
<thead>
<tr>
<th>CSW Neonatal Jaundice Team:</th>
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<tbody>
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<td>Emergency Dept Owner</td>
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<td>Emergency Dept, CNS</td>
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<td>Neonatology, Stakeholder</td>
<td>Linda Wallen, MD</td>
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<tr>
<td>Operations Director:</td>
<td>Karen Rancich Demmert, BS, MA</td>
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**Please cite as:**
We used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial, or observational studies. The rating is then adjusted in the following manner:

Quality ratings are *downgraded* if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings can be *upgraded* if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

**Quality of Evidence:**

- 🌟🌟🌟🌟 High quality
- 🌟🌟🌟 Moderate quality
- 🌟🌟 Moderate quality
- 🌟🌟🌟🌟 Very low quality

*Expert Opinion (E)*

Bilirubin Monitoring and Measurement

Recommendations for measuring and monitoring for bilirubin have predominantly come from targeted consultations with topic experts and the Clinical Guideline Update Committee, due to a lack of good quality evidence. [LOE: Guideline (NICE 2016)]. The accuracy of bilimeters decreases at levels above 14.6 mg/dL. The Bilicheck correlation ranged between 0.80 and 0.87. The correlation for the Minolta JM-102 showed wider variation between a positive 0.77 to a positive 0.93 [LOE: Guideline (NICE 2016)].

Diagnostic Testing Upon Admission

Obtain serum bilirubin and hematocrit for all patients needing treatment for hyperbilirubinemia. In North America and Europe, blood group incompatibility was implicated in 32.1% of cases where serum bilirubin was > 23.39 mg/dL. Check the maternal and infant blood group and DAT especially if the mother did not receive anti-D immunoglobulin during pregnancy. In North America and Europe, G6PD deficiency was implicated in 5.5% of patients when serum bilirubin was > 23.39 mg/dl or in those receiving exchange transfusions, and in 20.9% of kernicterus cases. Send G6PD if the patient comes from an ethnic group that is at higher risk [LOE: Guideline (NICE 2010)].

Return to ED Management  Return to Inpatient Management
Infant Positioning

There was a trend (that did not achieve statistical significance) in favor of a fixed supine position vs. changing position in the mean duration of treatment $MD = -6.67$ hours (95% CI: −13.50 to 0.15). A trend was also reported for mean change in serum bilirubin $MD = -0.35$ mg/dl (95% CI: −0.87 to 0.16) [LOE: Guideline (NICE 2012)].

Eye Protection

There was an increased incidence of purulent eye discharge among the eye patch group when compared to the headbox group, $RR = 2.53$, (95% CI: 1.23 to 5.20). Similarly, there was more conjunctivitis among the eyepatch group when compared to the headbox group, $RR = 6.44$ (95% CI: 1.49 to 27.80). There were no studies of headboxes in preterm patients and the guideline developers concluded that, unless the preterm infant is being treated with fiberoptic phototherapy, appropriate eye protection and eye care should be given, and tinted headboxes should not be used [LOE: Guideline (NICE 2012)].

Breaks off Phototherapy and Supplemental Hydration

There was no statistically significant difference in mean duration of phototherapy when continuous phototherapy was compared to intermittent phototherapy, $MD = -6.97$ hours (95% CI: −26.31 to 12.38 hours). One study reported that fewer infants given additional IV fluids needed exchange transfusion, those with IVF experienced a greater reduction in mean serum bilirubin, and a shorter duration of phototherapy compared with infants given only enteral feeds. The second study did not confirm these results. In one RCT, formula was not advantageous over breastfeeding in reducing serum bilirubin. In another study, lactose-containing formula did not confer benefit over lactose-free formula. No studies examining additional fluids in preterm babies receiving phototherapy were found [LOE: Guideline (NICE 2010)].

Bulb Color

Regarding duration of treatment, green-light phototherapy was statistically significantly shorter than blue-light phototherapy, $MD = 7.03$ hours (95% CI: 6.23 to 7.83), which in turn was statistically significantly shorter than white phototherapy, $MD = -32.00$ hours (95% CI: −44.72 to −19.28 hours).

The mean decrease in serum bilirubin was greater in the multiple phototherapy group $MD = 1.62$mg/dL (95% CI: 0.85 to 2.4). This result was statistically significant. Heterogeneity was significant ($I^2 = 74\%$).

Patients who received fiberoptic phototherapy were more likely to have treatment failures than those in whom LED or fluorescent tube light was used (RR 0.12, 95% CI: 0.02 to 0.92). There was no heterogeneity ($I^2 = 0\%$).

When triple versus double phototherapy was compared, serum bilirubin did not differ between groups at admission ($p = 0.170$), after 8 hours ($p = 0.590$), 16 hours ($p = 0.760$), and 24 hours ($p = 0.370$) [LOE: Guideline (NICE 2012)].
White Sheets to Improve Effectiveness of Phototherapy

Since different time points (4 hours & 24 hours) were used when examining the change in serum bilirubin concentration, results could not be combined. All studies showed a statistically significantly greater decrease in serum bilirubin at the two time-points for patients in the curtained groups. Results were @ 4 hours: 1.4 mg/dL (95% CI: 1.97 to 0.83); @ 24 hours: MD = 1.19 mg/dL (95% CI: 1.84 to 0.54) [LOE: Guideline (NICE 2012)].

Intravenous Gammaglobulin (IVIG)

Patients randomized to receive IVIG needed statistically significantly less exchange transfusions than controls RR 0.31 (95% CI: 0.20 to 0.47). Heterogeneity was I2 = 37%. The RR was similar for both Rh and ABO disease, RR 0.33 (95% CI: 0.20 to 0.52) and RR 0.29 (95% CI: 0.13 to 0.68) respectively. The number needed to treat (NNTB) with IVIG to prevent one exchange transfusion was different in each category of hemolytic disease (Rh disease: NNTB = 2; ABO disease: NNTB = 5) [LOE: Guideline (NICE 2012)].

Alternative Therapies

Agar: Two NRCTs were pooled in a meta-analysis, there was no statistically significant difference between treatment and control groups for mean reduction in serum bilirubin MD = -0.12 mg/dL (95% CI: -1.41 to 1.18). Moreover, there was no statistically significant difference in mean duration of phototherapy, MD = -6.57 hours (95% CI: -16.06 to 2.92 hours). Heterogeneity was I2 = 21%.

Albumin: In one study, there was no statistically significant difference between Double Volume Exchange Transfusion (DVET) and albumin-enriched DVET in mean reduction of bilirubin, the mean duration of phototherapy or the level of rebound bilirubin. There were zero cases of kernicterus or adverse effects in either cohort.

Barbiturates: In one controlled trial, no patient who received phototherapy alone required an exchange transfusion; one who received phenobarbitone + phototherapy had an exchange transfusion which was thought to be caused by extensive bruising. Patients who received phenobarbitone received phototherapy for longer than control patients (72 ± 31 hours versus 67 ± 33 hours).

Clofibrate: Five RCTs (n = 310 participants) examined the mean decrease in serum bilirubin. There was a statistically significant greater decrease in bilirubin in those treated with clofibrate, MD = -3.72 mg/dl (95% CI: -4.01 to -3.43). Heterogeneity was I2 = 95% but the direction of effect favored clofibrate in all five studies. However, it is important to recognize that studies of clofibrate in adults reported significant adverse effects.

Riboflavin: In one RCT (n = 24 participants), riboflavin (sodium phosphate 1.5 mg/kg q 12 hours) was given for 6 hours prior to phototherapy for non-hemolytic hyperbilirubinemia in term patients. Riboflavin was discontinued after 24 hours of phototherapy. In patients receiving riboflavin, there was no mean reduction (not statistically significant) in serum bilirubin after 24 hours, MD = -17.00 mol/L (95% CI: -35.81 to 1.81), MD = 0.99 mg/dl (95% CI: 2.09 to 0.11). [EL 1+] [LOE: Guideline (NICE 2010)].
Yinzhihuang

Yinzhihuang (3ml tid X 5 days, 5 ml tid X 5 days, 5 ml bid X 5 days, 5 ml bid X 7 days) + phototherapy (8-12 hours per day for 5-7 days) was compared to phototherapy in 6 RCTs (n = 1478 participants) to evaluate total serum bilirubin (micromol/L) over a 5 to 7 days follow-up period. The intervention was favored [MD -50.25 micromol/L (95% CI: -64.01 to -36.5)], [MD -2.94 mg/dl (95% CI: -3.74 to -2.13)] This outcome is downgraded for the following reasons: There were serious issues with randomization (4 of 6 studies) and allocation concealment (5 of 6 studies). The point estimates vary widely across studies (I²=99%) [Level of Evidence (LOE): +2 Low certainty (Wu 2018)].

Massage

Massage and phototherapy (2 times a day for 15-20 minutes) was compared to phototherapy (2 times a day for 15-20 minutes) in 2 RCTs (n = 54 participants) to evaluate serum bilirubin over a within 4-days. The intervention was favored MD -2.31 mg/dL (95% CI: -2.92 to -1.7). This outcome is downgraded for the following reason: The intervention tested was significantly different than our intervention of interest (intensity of phototherapy). [Level of Evidence (LOE): +2 Low certainty (Zhang.2018)]

Home Phototherapy

No high quality studies were found that addressed this question.
• **Version 1.0 (5/31/2012):** Go live
• **Version 2.0 (4/2/2013):** Added recommendation for ED to notify NICU attending if patient meets NICU admission criteria; established recommendations for removal from phototherapy for feeding.
• **Version 3.0 (5/10/2016):** Added Value Analysis #1 (Glucose Testing)
• **Version 4.0 (8/16/2019):** Added updated evidence synthesis statements for all recommendations, added guidance in algorithm for G-6-PD testing, IVIG use and infant positioning.
Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children’s Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.
Studies were identified by searching electronic databases using search strategies developed and executed by a medical librarian, Jamie Graham. Searches were performed on July 7th-8th, 2011 in the following databases: on the Ovid platform – Medline (1996 to date), Cochrane Database of Systematic Reviews (2005 – June 2011); elsewhere the National Guidelines Clearinghouse, Clinical Evidence, DynaMed and TRIP were searched. Retrieval was limited to English language, literature from 2001 forward, and newborn infants. In Medline, appropriate Medical Subject Headings (MeSH) were used, along with text words, and the search strategy was adapted for other databases using their controlled vocabularies, where available, along with text words. Results were restricted to high levels of evidence where appropriate using the following publication limits; consensus development conference, consensus development conference (NIH), guideline, meta-analysis or practice guideline.

Terms: jaundice, neonatal; hyperbilirubinemia, neonatal; kernicterus; icterus neonatorum; exchange transfusion, whole blood; IVIG; immunoglobulins, intravenous

Jamie Graham, MLS
5/23/2012

Flow diagram adapted from Moher D et al. BMJ 2009;339:bmj.b2535


