Neonatal Hyperbilirubinemia

Number: 0332

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Assessment of Neonatal Hyperbilirubinemia

Aetna considers measurement of glucose-6-phosphate dehydrogenase (G6PD) levels medically necessary for jaundiced infants who are receiving phototherapy, where response to phototherapy is poor, or where the infant is at an increased risk of G6PD deficiency due to family history, ethnic or geographic origin.

Aetna considers measurement of end-tidal carbon monoxide (CO) corrected for ambient CO (ETCOc), used either alone or in combination with the simultaneous measurement of total serum bilirubin (TSB) concentration, experimental and investigational because measurement of ETCOc has not been proven to improve prediction of development of significant neonatal bilirubinemia over TSB alone.

Aetna considers genotyping of BLVRA, SLCO1B1 and UGT1A1 experimental and investigational for assessing risk of neonatal hyperbilirubinemia because the clinical value of this approach has not been established.
Aetna considers transcutaneous bilirubin devices for evaluating hyperbilirubinemia in term and near-term infants while undergoing phototherapy experimental and investigational because this approach is not reliable in infants in this setting.

II. Treatment of Hyperbilirubinemia in Term and Near-Term Infants

Aetna considers phototherapy medically necessary for term and near-term infants according to guidelines published by the American Academy of Pediatrics (AAP). The following are general age-in-hours specific total serum bilirubin (TSB) threshold values for phototherapy based upon gestational age and the presence or absence of risk factors (isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase [G6PD] deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin of less than 3.0 g/dL [if measured]):

<table>
<thead>
<tr>
<th>Age in hours</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>&gt;12</td>
<td>≥10</td>
<td>≥8</td>
</tr>
<tr>
<td>48</td>
<td>&gt;15</td>
<td>≥13</td>
<td>≥11</td>
</tr>
<tr>
<td>72</td>
<td>&gt;18</td>
<td>≥15</td>
<td>≥13.5</td>
</tr>
</tbody>
</table>

* Low Risk: ≥38 weeks gestation and without risk factors; Medium Risk: ≥38 weeks gestation with risk factors or 35 to 37 6/7 weeks gestation without risk factors; High Risk: 35 to 37 6/7 weeks gestation with risk factors.

Notes: Prophylactic phototherapy is considered medically necessary for infants showing a rapid rise in bilirubin (greater than 1 mg/dL/hour) and as a temporary measure when one is contemplating exchange transfusion. Clofibrate in combination with phototherapy for neonatal hyperbilirubinemia is considered experimental and investigational.

Aetna considers exchange transfusion medically necessary for term and near-term infants according to guidelines published by the American Academy of Pediatrics (AAP). The following are general age-in-hours specific TSB threshold values for exchange transfusion based upon gestational age and the presence or absence of risk factors:
factors (isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase [G6PD] deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin of less than 3.0 g/dL [if measured]):

**Table: Age in Hours Specific TSB threshold values for exchange transfusion**

<table>
<thead>
<tr>
<th>Age in hours</th>
<th>Total Serum Bilirubin (TSB) Level in mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Low</td>
</tr>
<tr>
<td>24</td>
<td>&gt;19</td>
</tr>
<tr>
<td>48</td>
<td>&gt;22</td>
</tr>
<tr>
<td>72</td>
<td>&gt;24</td>
</tr>
<tr>
<td>&gt; 72</td>
<td>≥25</td>
</tr>
</tbody>
</table>

Low Risk: ≥38 weeks gestation and without risk factors; Medium Risk: ≥38 weeks gestation with risk factors or 35 to 37 6/7 weeks gestation without risk factors; High Risk: 35 to 37 6/7 weeks gestation with risk factors.

According to available guidelines, inpatient treatment may be considered medically necessary for healthy full-term infants who present with a TSB greater than or equal to 20 mg/dL in the first post-natal week. Inpatient treatment is generally not medically necessary for healthy full-term infants with a TSB less than 20 mg/dL, as these infants can usually be treated with expectant observation or home phototherapy. Inpatient treatment may be medically necessary for pre-term infants who present with a TSB greater than or equal to 18 mg/dL. Inpatient treatment is not generally medically necessary for preterm infants who present with a TSB less than 18 mg/dL, as these infants can usually be treated with expectant observation or home phototherapy.

**III. Criteria for discontinuation of phototherapy**

Consistent with available guidelines, continued phototherapy is not medically necessary for healthy term infants when the following criteria for discontinuation of phototherapy are met:

**Table: Criteria for discontinuation of phototherapy**

http://www.aetna.com/cpb/medical/data/300_399/0332.html
A delay in discharge from the hospital in order to observe the infant for rebound once the bilirubin has decreased is not considered medically necessary. According to available guidelines, no further measurement of bilirubin is necessary in most cases.

### IV. Preterm Infants

Aetna considers management of physiologic hyperbilirubinemia medically necessary in preterm infants (defined as an infant born prior to 37 weeks gestation) according to guidelines published by the AAP. In preterm infants, phototherapy should be initiated at 50 to 70% of the maximum indirect levels below:

#### Table: Phototherapy maximum indirect levels

<table>
<thead>
<tr>
<th>Birth weight in grams</th>
<th>Uncomplicated</th>
<th>Complicated. *</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1,000</td>
<td>≥12</td>
<td>≥10</td>
</tr>
<tr>
<td>1,000 - 1,250</td>
<td>≥12</td>
<td>≥10</td>
</tr>
<tr>
<td>1,251 - 1,499</td>
<td>≥14</td>
<td>≥12</td>
</tr>
<tr>
<td>1,500 - 1,999</td>
<td>≥16</td>
<td>≥15</td>
</tr>
<tr>
<td>2,000 - 2,500</td>
<td>≥20</td>
<td>≥18</td>
</tr>
</tbody>
</table>

*Complications include but are not limited to prenatal asphyxia, acidosis, hypoxia, hypoalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus.

### V. Home Phototherapy
Aetna considers home phototherapy for physiologic jaundice in healthy infants with a gestational age of 35 weeks or more medically necessary if all of the following criteria are met:

A. The infant is otherwise ready to be discharged from the hospital; and
B. The infant is feeding well, is active, appears well; and
C. TSB is less than 20 to 22 mg/dL in term infants, or less than 18 mg/dL in preterm infants; and
D. Arrangements have been made to evaluate the infant within 48 hours after discharge by an early office/clinic visit to the pediatrician, or by a home visit by a well-trained home health care nurse who should be able to:

- Be available for follow-up clinical assessments and blood drawing as determined to be necessary by the responsible physician based on changes in bilirubin levels
- Clinically assess the initial level of jaundice
- Draw blood for bilirubin determinations
- Encourage frequent feedings
- Explain all aspects of the phototherapy system to the parents
- Oversee set-up of the phototherapy system
- Weigh the infant in the home

Note: If levels do not respond by stabilizing (+/- 1 mg/dL) or declining, more intensive phototherapy may be warranted.

VI. Metalloporphyrins

Aetna considers the use of metalloporphyrins (e.g., stannsoporfin (tin mesoporphyrin), Stanate, WellSpring Pharmaceutical Corporation, Neptune, NJ) for the treatment of neonatal jaundice experimental and investigational because their safety and effectiveness for this indication has not been established.

VII. Antenatal Phenobarbital

Aetna considers the use of antenatal phenobarbital to reduce neonatal jaundice in red cell isoimmunized pregnant women experimental and investigational because its effectiveness has not been established.
VIII. Zinc Supplementation

Aetna considers zinc supplementation for the prevention of hyperbilirubinaemia experimental and investigational because its effectiveness has not been established.

IX. Massage Therapy

Aetna considers massage therapy experimental and investigational for the treatment of neonatal hyperbilirubinemia because its effectiveness has not been established.

X. Probiotics

Aetna considers probiotics experimental and investigational for the treatment of neonatal hyperbilirubinemia because its effectiveness has not been established.

Background

Aetna's policy on treatment of hyperbilirubinemia in infants is adapted from guidelines from the American Academy of Pediatrics.

There is insufficient evidence to support the use of metalloporphyrins (e.g., stannsoporfin (tin mesoporphyrin), Stanate, WellSpring Pharmaceutical Corporation, Neptune, NJ) for the treatment of neonatal jaundice. Guidelines from the AAP stated: “There is now evidence that hyperbilirubinemia can be effectively prevented or treated with tin-mesoporphyrin, a drug that inhibits the production of heme oxygenase. Tin-mesoporphyrin is not approved by the U.S. Food and Drug Administration. If approved, tin-mesoporphyrin could find immediate application in preventing the need for exchange transfusion in infants who are not responding to phototherapy.” A systematic evidence review prepared for the Cochrane Collaboration (Suresh et al, 2003) concluded that, based upon limitations of the evidence, “[r]outine treatment of neonatal unconjugated hyperbilirubinemia with a metalloporphyrin cannot be recommended at present.”

In a Cochrane review, Thomas et al (2007) stated that neonates from isoimmunized pregnancies have increased morbidity from neonatal jaundice. The increased bilirubin from hemolysis often needs phototherapy, exchange transfusion or both after birth. Various trials in pregnant women who were not isoimmunized but had
other risk factors for neonatal jaundice have shown a reduction in need for phototherapy and exchange transfusion by the use of antenatal phenobarbital. A recent retrospective case-controlled study showed reduction in the need for exchange transfusion for the neonates from isoimmunized pregnancies. These investigators evaluated the effects of antenatal phenobarbital in red cell isoimmunized pregnancies in reducing the incidence of phototherapy and exchange transfusion for the neonate. Randomized and quasi-randomized controlled trials of pregnant women established to have red cell isoimmunization in the current pregnancy during their antenatal testing and given phenobarbital alone or in combination with other drugs before birth were selected for review. All 3 review authors independently assessed study eligibility and quality. No studies met the inclusion criteria for this review. The authors concluded that the use of antenatal phenobarbital to reduce neonatal jaundice in red cell isoimmunized pregnant women has not been evaluated in randomized controlled trials.

Morris and colleagues (2008) compared aggressive versus conservative phototherapy for infants with extremely low birth weight. These investigators randomly assigned 1,974 infants with extremely low birth weight at 12 to 36 hours of age to undergo either aggressive or conservative phototherapy. The primary outcome was a composite of death or neurodevelopmental impairment determined for 91% of the infants by investigators who were unaware of the treatment assignments. Aggressive phototherapy, as compared with conservative phototherapy, significantly reduced the mean peak serum bilirubin level (7.0 versus 9.8 mg/dL [120 versus 168 micromol/L], p < 0.01) but not the rate of the primary outcome (52% versus 55%; relative risk, 0.94; 95% confidence interval [CI]: 0.87 to 1.02; p = 0.15). Aggressive phototherapy did reduce rates of neurodevelopmental impairment (26%, versus 30% for conservative phototherapy; relative risk, 0.86; 95% CI: 0.74 to 0.99). Rates of death in the aggressive-phototherapy and conservative-phototherapy groups were 24% and 23%, respectively (relative risk, 1.05; 95% CI: 0.90 to 1.22). In pre-planned subgroup analyses, the rates of death were 13% with aggressive phototherapy and 14% with conservative phototherapy for infants with a birth weight of 751 to 1,000 g and 39% and 34%, respectively (relative risk, 1.13; 95% CI: 0.96 to 1.34), for infants with a birth weight of 501 to 750 g. The authors concluded that aggressive phototherapy did not significantly reduce the rate of death or neurodevelopmental impairment. The rate of neurodevelopmental impairment alone was significantly reduced with aggressive phototherapy. This reduction may be offset by an increase in mortality among infants weighing 501 to 750 g at birth.
Guidelines from the Canadian Paediatric Society (2007) found that phenobarbitol, studied as a means of preventing severe hyperbilirubinemia in infants with G6PD deficiency, did not improve clinically important outcomes in a randomized controlled clinical study (Murki et al, 2005).

In a prospective double-blind study, De Luca et al (2008) compared the accuracy of a new transcutaneous bilirubinometer, BiliMed (Medick SA, Paris, France) with BiliCheck (Respironics, Marietta, GA), a widely available instrument, and with total serum bilirubin (TSB) measurement. A total of 686 healthy newborns needing measurement of their bilirubin were enrolled over a 4-month period. Serum and transcutaneous bilirubin (TcB) measurements were taken with both devices within 15 mins. The order of use of the instruments was randomized. The linear regression analysis showed a better correlation between BiliCheck and serum bilirubin \( r = 0.75 \) than between BiliMed and serum bilirubin \( r = 0.45 \). BiliCheck variability \( (+/- 2 \text{ SD of the mean bias from serum bilirubin}) \) was within -87.2 to 63.3 micromol/L, while BiliMed variability was within -97.5 to 121.4 micromol/L. The receiver operating characteristic analysis (for serum bilirubin levels greater than 205.2 micromol/L or greater than 239.4 micromol/L) showed significantly higher areas under the curve for BiliCheck than those for BiliMed \( (p < 0.001) \). The authors concluded that despite the potential practical advantages of BiliMed, its reduced diagnostic accuracy in comparison with BiliCheck does not justify its use in clinical practice.

Trikalinos et al (2009) reviewed the effectiveness of specific screening modalities to prevent neonatal bilirubin encephalopathy. These researchers identified studies through Medline searches, perusing reference lists and by consulting with United States Preventive Services Task Force (USPSTF) lead experts. They included English-language publications evaluating the effects of screening for bilirubin encephalopathy using early TSB, TcB measurements, or risk scores. Severe hyperbilirubinemia was used as a surrogate for possible chronic bilirubin encephalopathy (CBE), because no studies directly evaluated the latter as an outcome. These investigators calculated the sensitivity and specificity of early TSB, TcB measurements, or risk scores in detecting hyperbilirubinemia. A total of 10 publications (11 studies) were eligible. Seven (2 prospective) studies evaluated the ability of risk factors \( (n = 3) \), early TSB \( (n = 3) \), TcB \( (n = 2) \), or combinations of risk factors and early TSB \( (n = 1) \) to predict hyperbilirubinemia (typically TSB greater than 95th hour-specific percentile 24 hours to 30 days post-partum). Screening had good ability to detect hyperbilirubinemia: reported area-under-the-curve values.
ranged between 0.69 and 0.84, and reported sensitivities and specificities suggested similar diagnostic ability. Indirect evidence from 3 descriptive uncontrolled studies suggested favorable associations between initiation of screening and decrease in hyperbilirubinemia rates, and rates of treatment or re-admissions for hyperbilirubinemia compared with the baseline of no screening. No study assessed harms of screening. The authors concluded that effects of screening on the rates of bilirubin encephalopathy are unknown. Although screening can predict hyperbilirubinemia, there is no robust evidence to suggest that screening is associated with favorable clinical outcomes.

The USPSTF and the Agency for Healthcare Research and Quality (2009) reported on the effectiveness of various screening strategies for preventing the development of CBE. The USPSTF reviewed experimental and observational studies that included comparison groups. For harms associated with phototherapy, case reports or case series were also included. The USPSTF concluded that the evidence is insufficient to assess the balance of benefits and harms of screening for hyperbilirubinemia to prevent CBE.

Hulzebos and associates (2011) examined the relationship between early postnatal dexamethasone (DXM) treatment and the severity of hyperbilirubinemia in extremely low birth weight (ELBW) preterm infants. In 54 ELBW preterm infants, TSB and phototherapy (PT) data during the first 10 days were evaluated retrospectively. These ELBW infants had participated in a randomized controlled trial of early DXM therapy that aimed to evaluate effects on chronic lung disease. Infants had been treated with DXM (0.25 mg/kg twice-daily at postnatal day 1 and 2) or with placebo (normal saline). Analysis was performed on an intention-to-treat basis. A total of 25 infants had been randomized into the DXM group; 29 into the placebo group. Mean TSB (120 +/- 19 μmol/L versus 123 +/- 28 μmol/L, DXM versus placebo, respectively) and maximum TSB (178 +/- 23 μmol/L versus 176 +/- 48, DXM versus placebo, respectively) concentrations were similar. Total serum bilirubin concentrations peaked 30 hours earlier in the DXM group (p ≤ 0.05). The need for PT as well as the duration of PT were similar in both groups. The authors concluded that early DXM treatment does not affect the severity of neonatal hyperbilirubinemia in ELBW preterm infants. These findings seem compatible with the concept that factors other than bilirubin conjugation capacity are important for the pathophysiology of neonatal jaundice in ELBW preterm infants.
It is also important to note that there are serious health risks associated with corticosteroid therapy. In a Cochrane review on early (less than 8 days) postnatal corticosteroid treatment for preventing chronic lung disease in preterm infants, Halliday et al (2010) concluded that the benefits of early postnatal corticosteroid treatment, especially DXM, may not outweigh the known or potential adverse effects of this treatment. Although early corticosteroid treatment facilitates extubation and reduces the risk of chronic lung disease and patent ductus arteriosus, it causes short-term adverse effects including gastro-intestinal bleeding, intestinal perforation, hyperglycaemia, hypertension, hypertrophic cardiomyopathy and growth failure. Long-term follow-up studies reported an increased risk of abnormal neurological examination and cerebral palsy. However, the methodological quality of the studies determining long-term outcomes is limited in some cases; the surviving children have been assessed predominantly before school age, and no study has been sufficiently powered to detect important adverse long-term neurosensory outcomes. The authors concluded that there is a compelling need for the long-term follow-up and reporting of late outcomes, especially neurological and developmental outcomes, among surviving infants who participated in all randomized trials of early postnatal corticosteroid treatment.

In a Cochrane review, Gholitabar et al (2012) examined the safety and effectiveness of clofibrate in combination with phototherapy versus phototherapy alone in unconjugated neonatal hyperbilirubinemia. Randomized controlled trials were identified by searching MEDLINE (1950 to April 2012) before being translated for use in The Cochrane Library, EMBASE 1980 to April 2012 and CINAHL databases. All searches were re-run on April 2, 2012. These investigators included trials where neonates with hyperbilirubinemia received either clofibrate in combination with phototherapy or phototherapy alone or placebo in combination with phototherapy. Data were extracted and analyzed independently by 2 review authors (MG and HM). Treatment effects on the following outcomes were determined: mean change in bilirubin levels, mean duration of treatment with phototherapy, number of exchange transfusions needed, adverse effects of clofibrate, bilirubin encephalopathy and neonatal mortality. Study authors were contacted for additional information. Studies were analyzed for methodological quality in a “Risk of bias” table. A total of 15 studies (2 including preterm neonates and 13 including term neonates) were included in this review. All but 1 of the included studies were conducted in Iran. For preterm neonates, there was a significantly lower bilirubin level in the 100 mg/kg clofibrate group compared to the control group with a mean difference of -1.37 mg/dL (95% CI: -2.19 mg/dL to -0.55
mg/dL (-23 µmol/L; 95 % CI: -36 µmol/L to -9 µmol/L) after 48 hours. For the term neonates, there were significantly lower bilirubin levels in the clofibrate group compared to the control group after both 24 and 48 hours of treatment with a weighted mean difference of -2.14 mg/dL (95 % CI: -2.53 mg/dL to -1.75 mg/dL) (-37 µmol/L; 95 % CI: -43 µmol/L to -30 µmol/L) and -1.82 mg/dL (95 % CI: -2.25 mg/dL to -1.38 mg/dL) (-31 µmol/L; 95 % CI: -38 µmol/L to -24 µmol/L), respectively. There was a significantly lower duration of phototherapy in the clofibrate group compared to the control group for both preterm and term neonates with a weighted mean difference of -23.82 hours (95 % CI: -30.46 hours to -17.18 hours) and -25.40 hours (95 % CI: -28.94 hours to -21.86 hours), respectively. None of the studies reported on bilirubin encephalopathy rates, neonatal mortality rates, or the levels of parental or staff satisfactions with the interventions. The authors concluded that there are insufficient data from different countries on the use of clofibrate in combination with phototherapy for hyperbilirubinemia to make recommendations for practice. They stated that there is a need for larger trials to determine how effective clofibrate is in reducing the need for, and duration of, phototherapy in term and preterm infants with hyperbilirubinemia.

Watchko and Lin (2010) noted that the potential for genetic variation to modulate neonatal hyperbilirubinemia risk is increasingly being recognized. In particular, polymorphisms across 3 genes involved in bilirubin production and metabolism: (i) glucose-6-phosphate dehydrogenase (G6PD), (ii) uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1), and (iii) solute carrier organic anion transporter polypeptide 1B1 (SLCO1B1)] may interact with each other and/or environmental contributors to produce significant hyperbilirubinemia. Variant gene co-expression including compound and synergistic heterozygosity enhances hyperbilirubinemia risk, contributing to the etiologic heterogeneity and complex nature of neonatal jaundice.

Liu et al (2013) examined if 3 variants (388 G>A, 521 T>C, and 463 C>A) of SLCO1B1 are associated with neonatal hyperbilirubinemia. The China National Knowledge Infrastructure and MEDLINE databases were searched. These researchers performed a systematic review with meta-analysis including genetic studies, which assessed the association between neonatal hyperbilirubinemia and 388 G>A, 521 T>C, and 463 C>A variants of SLCO1B1 between January of 1980 and December of 2012. Data selection and extraction were performed independently by 2 reviewers. A total of 10 articles were included in the study. The results revealed that SLCO1B1 388 G>A is associated with an increased risk of
neonatal hyperbilirubinemia (odds ratio [OR], 1.39; 95 % CI: 1.07 to 1.82) in Chinese neonates, but not in white, Thai, Latin American, or Malaysian neonates. The SLCO1B1 521 T>C mutation showed a low risk of neonatal hyperbilirubinemia in Chinese neonates, while no significant associations were found in Brazilian, white, Asian, Thai, and Malaysian neonates. There were no significant differences in SLCO1B1 463 C>A between the hyperbilirubinemia and the control group. The authors concluded that the findings of this study demonstrated that the 388 G>A mutation of the SLCO1B1 gene is a risk factor for developing neonatal hyperbilirubinemia in Chinese neonates, but not in white, Thai, Brazilian, or Malaysian populations; the SLCO1B1 521 T>C mutation provides protection for neonatal hyperbilirubinemia in Chinese neonates, but not in white, Thai, Brazilian, or Malaysian populations.

Petersen and colleagues (2014) stated that extreme hyperbilirubinemia (plasma bilirubin greater than or equal to 24.5 mg/dL) is an important risk factor for severe bilirubin encephalopathy. Several risk factors for hyperbilirubinemia are known, but in a large number of patients, a causal factor is never established. UGT1A1 is the rate-limiting enzyme in bilirubin's metabolism. The genotype of Gilbert syndrome, the UGT1A1’28 allele, causes markedly reduced activity of this enzyme, but its association with neonatal hyperbilirubinemia is uncertain and its relationship with extreme hyperbilirubinemia has not been studied. These researchers examined whether the UGT1A1’28 allele is associated with extreme hyperbilirubinemia. The UGT1A1’28 allele was assessed in a case-control study of 231 white infants who had extreme hyperbilirubinemia in Denmark from 2000 to 2007 and 432 white controls. Cases were identified in the Danish Extreme Hyperbilirubinemia Database that covers the entire population. Genotypes were obtained through the Danish Neonatal Screening Biobank. Subgroup analysis was done for AB0 incompatible cases. No association was found between the UGT1A1’28 allele and extreme hyperbilirubinemia. With the common genotype as reference, the odds ratio of extreme hyperbilirubinemia was 0.87 (range of 0.68 to 1.13) for UGT1A1’28 heterozygotes and 0.77 (range of 0.46 to 1.27) for homozygotes. Also, no association was found for AB0 incompatible cases. The authors concluded that the UGT1A1’28 allele was not associated with risk for extreme hyperbilirubinemia in this study.

Travan et al (2014) examined if UGT1A1 promoter polymorphisms associated with Gilbert Syndrome (GS) occur with a greater frequency in neonates with severe hyperbilirubinemia. In a case-control study performed at a single hospital center in
Italy, 70 subjects with severe hyperbilirubinemia (defined as bilirubin level greater than or equal to 20 mg/dL or 340 μmol/L) and 70 controls (bilirubin level less than 12 mg/dL or 210 μmol/L) were enrolled. Both case and control subjects were full term newborns. Polymerase chain reaction analysis on blood spot was performed to determine the frequency of UGTA1A1 promoter polymorphisms in cases and controls. No statistical difference in the prevalence of UGTA1A1 gene variants was found between cases and controls (p = 1). Thirteen infants homozygous for (TA)7 polymorphism associated with GS were in the case group (18.6 %) and 14 in the control group (20.0 %). A heterozygous group was also equally distributed between cases (44.3 %) and controls (42.9 %). No (TA)8 repeat was found in the 2 groups. The authors concluded that in this study population, GS polymorphism alone did not appear to play a major role in severe neonatal hyperbilirubinemia in neonates without signs of hemolysis.

An UpToDate review on “Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants” (Wong and Bhutani, 2015) does not mention genotyping of SLCO1B1 and UGT1A1 as management tools.

Zinc Supplementation for the Prevention of Hyperbilirubinemia

In a Cochrane review, Mishra and colleagues (2015) examined the effect of oral zinc supplementation compared to placebo or no treatment on the incidence of hyperbilirubinaemia in neonates during the first week of life and to evaluate the safety of oral zinc in enrolled neonates. These investigators searched CENTRAL (The Cochrane Library 2014, Issue 1), MEDLINE (1966 to November 30, 2014), and EMBASE (1990 to November 30, 2014). Randomized controlled trials were eligible for inclusion if they enrolled neonates (term and pre-term) to whom oral zinc, in a dose of 10 to 20 mg/day, was initiated within the first 96 hours of life, for any duration until day 7, compared with no treatment or placebo. These researchers used the standard methods of the Cochrane Collaboration and its Neonatal Review Group for data collection and analysis. Only 1 study met the criteria of inclusion in the review. This study compared oral zinc with placebo. Oral zinc was administered in a dose of 5 ml twice-daily from day 2 to day 7 post-partum. The drug was administered into the mouth of the infant by the plastic measure provided with the bottle or with a spoon. Incidence of hyperbilirubinaemia, defined as serum total bilirubin (STB) greater than or equal to 15 mg/dL, was similar between groups (n = 286; risk ratio (RR) 0.94, 95 % CI: 0.58 to 1.52). Mean STB levels, mg/dL, at 72 ± 12 hours were comparable in both the groups (n = 286;
mean difference (MD) -0.20; 95 % CI: -1.03 to 0.63). Although the duration of phototherapy in the zinc group was significantly shorter compared to the placebo group (n = 286; MD -12.80, 95 % CI: -16.93 to -8.67), the incidence of need for phototherapy was comparable across both the groups (n = 286; RR 1.20; 95 % CI: 0.66 to 2.18). Incidences of side effects like vomiting (n = 286; RR 0.65, 95 % CI: 0.19 to 2.25), diarrhea (n = 286; RR 2.92, 95 % CI: 0.31 to 27.71), and rash (n = 286; RR 2.92, 95 % CI: 0.12 to 71.03) were found to be rare and statistically comparable between groups. The authors concluded that the limited evidence available has not shown that oral zinc supplementation given to infants up to 1 week old reduces the incidence of hyperbilirubinaemia or need for phototherapy.

Furthermore, an UpToDate review on “Treatment of unconjugated hyperbilirubinemia in term and late preterm infants” (Wong and Bhutani, 2016) does not mention zinc supplementation as a management tool.

Sharma and colleagues (2017) examined the role of oral zinc supplementation for reduction of neonatal hyperbilirubinemia in term and preterm infants. The literature search was done for various randomized control trial (RCT) by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, Web of Science, Scopus, Index Copernicus, African Index Medicus (AIM), Thomson Reuters (ESCI), Chemical Abstracts Service (CAS) and other data base. This review included 6 RCTs that fulfilled inclusion criteria. One study evaluated the role of zinc in very low birth-weight (VLBW) infants and remaining enrolled neonates greater than or equal to 35 weeks of gestation. The dose of zinc varied from 5 to 20 mg/day and duration from 5 to 7 days. All the studies used zinc sulfate, only 1 study used zinc gluconate. The total number of neonates enrolled in these different RCT were 749. The authors concluded that the role of zinc in the prevention of neonatal hyperbilirubinemia is not supported by the current evidence. Only 1 study was able to show reduction in the mean TSB level and requirement of phototherapy with zinc, and the remaining studies did not report any positive effect. None of the studies showed any effect on the duration of phototherapy, incidence of phototherapy, age of starting of phototherapy and any serious adverse effect.

Yang and colleagues (2018) noted that zinc sulfate may be a promising approach to treat neonatal jaundice. However, the results remain controversial. These investigators conducted a systematic review and meta-analysis to examine the safety and efficacy of zinc sulfate on hyperbilirubinemia among neonates. PubMed, Embase, Web of science, EBSCO, Cochrane library databases, Ovid, BMJ
database, and CINAHL were systematically searched; RCTs evaluating the effect of zinc sulfate versus placebo on the prevention of jaundice in neonates were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. The primary outcomes were TSB on 3 days and 7 days, the incidence of hyperbilirubinemia. Meta-analysis was performed using random- or fixed-effect models. A total of 5 RCTs involving 645 patients were included in the meta-analysis. Overall, compared with placebo, zinc sulfate supplementation failed to significantly reduce TSB on 3 days (MD = 0.09 mg/dL; 95% CI: -0.49 to 0.67; p = 0.77), TSB on 7 days (MD = -0.37 mg/dL; 95% CI: -0.98 to 0.25; p = 0.25) as well as the incidence of hyperbilirubinemia (OR = 1.14; 95% CI: 0.74 to 1.76; p = 0.56). Zinc sulfate showed no influence on phototherapy requirement (OR = 0.90; 95% CI: 0.41 to 1.98; p = 0.79), but resulted in significantly decreased duration of phototherapy (MD = -16.69 hours; 95% CI: -25.09 to -8.3 hours; p < 0.0001). The authors concluded that zinc sulfate could not reduce the TSB on 3 days and 7 days, the incidence of hyperbilirubinemia and phototherapy requirement, but resulted in significantly decreased duration of phototherapy.

Transcutaneous Bilirubin Devices for Evaluation of Hyperbilirubinemia in Term and Near-Term Infants Exposed to or Undergoing Phototherapy

In a prospective study, Casnocha and colleagues (2016) tested the accuracy of TcB measure in newborns undergoing phototherapy. A total of 150 term Caucasian neonates, 255 measurements of TSB and TcB concentration were obtained 2 hours after discontinuing phototherapy. TcB measurements obtained on the forehead, sternum, abdomen and covered lower abdomen were statistically compared with the corresponding TSB. TcB consistently under-estimated TSB levels significantly. The smallest but significant difference between TSB and TcB was found on the lower abdomen. The correlation between TSB and TcB was found to be moderately close (r = 0.4 to 0.5). TcB measurements were inaccurate, regardless of phototherapy technique (Bilibed, conventional phototherapy). The authors concluded that phototherapy significantly interfered with the accuracy of transcutaneous bilirubinometry; TcB measurements performed 2 hours after stopping phototherapy were not reliable, even if they were performed on the unexposed body area. They stated that TSB assessment remains necessary, if treatment of hyperbilirubinemia is being considered.
Nagar and associates (2016) noted that TcB devices are commonly used for screening of hyperbilirubinemia in term and near-term infants not exposed to phototherapy. However, the accuracy of TcB devices in infants exposed to phototherapy is unclear. These researchers conducted a systematic review of studies comparing TcB devices with TSB in infants receiving phototherapy or in the post-phototherapy phase. Medline, Embase, Cochrane Library, CINAHL and Scopus databases (from inception to May 8, 2014) were searched. Additional citations were identified from the bibliography of selected articles and from the abstracts of conference proceedings. The studies were included if they compared TcB results with TSB in term and near-term infants during phototherapy or after discontinuation of phototherapy. Two reviewers independently assessed studies for inclusion, and discrepancies were resolved with consensus. Risk of bias was assessed using the QUADAS-2 tool. A total of 14 studies were identified. The pooled estimates of correlation coefficients (r) during phototherapy were: covered sites 0.71 (95% CI: 0.64 to 0.77, 11 studies), uncovered sites 0.65 (95% CI: 0.55 to 0.74), 8 studies), forehead 0.70 (95% CI: 0.64 to 0.75, 12 studies) and sternum 0.64 (95% CI: 0.43 to 0.77, 5 studies). Two studies also provided results as Bland-Altman difference plots (mean TcB-TSB differences -29.2 and 30 µmol/L, respectively). The correlation coefficient improved marginally in the post-phototherapy phase (r = 0.72, 95% CI: 0.64 to 0.78, 4 studies). The authors found a moderate correlation between TcB and TSB during phototherapy with a marginal improvement in the post-phototherapy phase. They stated that further research is needed before the use of TcB devices can be recommended for these settings.

Furthermore, an UpToDate review on “Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants” (Wong and Bhutani, 2017) states that “TcB measurements are not reliable in infants undergoing phototherapy. TcB should not be used in patients undergoing phototherapy.”

Massage Therapy

Garg and colleagues (2017) stated that neonatal hyperbilirubinemia (NNH) is one of the leading causes of admissions in nursery throughout the world. It affects approximately 2.4 to 15% of neonates during the first 2 weeks of life. These researchers evaluated the role of massage therapy for reduction of NNH in both term and preterm neonates. The literature search was done for various RCTs by searching the Cochrane Library, PubMed, and Embase. This review included total of 10 RCTs (2 in preterm neonates and 8 in term neonates) that fulfilled inclusion
criteria. In most of the trials, Field massage was given; 6 out of 8 trials reported reduction in bilirubin levels in term neonates. However, only 1 trial (out of 2) reported significant reduction in bilirubin levels in preterm neonates. Both trials in preterm neonates and most of the trials in term neonates (5 trials) reported increased stool frequencies. The authors concluded that the role of massage therapy in the management of NNH was supported by the current evidence. However, they stated that due to limitations of the trials, current evidence is insufficient regarding the use of massage therapy for the management of NNH in routine practice.

Probiotics

Chen and co-workers (2017) stated that probiotics supplementation therapy could assist to improve the recovery of neonatal jaundice, through enhancing immunity mainly by regulating bacterial colonies. However, there is limited evidence regarding the effect of probiotics on bilirubin level in neonates. These researchers systematically evaluated the safety and efficacy of probiotics supplement therapy for pathological neonatal jaundice. Databases including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wan Fang Database (Wan Fang), Chinese Biomedical Literature Database (CBM), VIP Database for Chinese Technical Periodicals (VIP) were searched and the deadline was December 2016; RCTs of probiotics supplementation for pathological neonatal jaundice in publications were extracted by 2 reviewers. The Cochrane tool was applied to assessing the risk of bias of the trials. The extracted information of RCTs should include efficacy rate, serum total bilirubin level, time of jaundice fading, duration of phototherapy, duration of hospitalization, adverse reactions. The main outcomes of the trials were analyzed by Review Manager 5.3 software. The RR or MD with a 95 % CI was used to measure the effect. A total of 13 RCTs involving 1,067 neonatal with jaundice were included in the meta-analysis.

Probiotics supplementation treatment showed efficacy \[\text{RR: 1.19, 95 \% CI: 1.12 to 1.26, } p < 0.00001\] in neonatal jaundice. It not only decreased the total serum bilirubin level after 3 days \[\text{MD: -18.05, 95 \% CI: -25.51 to -10.58, } p < 0.00001\], 5 days \[\text{MD: -23.49, 95 \% CI: -32.80 to -14.18, } p < 0.00001\], 7 days \[\text{MD: -33.01, 95 \% CI: -37.31 to -28.70, } p < 0.00001\] treatment, but also decreased time of jaundice fading \[\text{MD: -1.91, 95 \% CI: -2.06 to -1.75, } p < 0.00001\], as well as the duration of phototherapy \[\text{MD: -0.64, 95 \% CI: -0.84 to -0.44, } p < 0.00001\] and hospitalization \[\text{MD: -2.68, 95 \% CI: -3.18 to -2.17, } p < 0.00001\], when compared with the control group. Additionally, no serious adverse reaction was reported. The
authors concluded that this meta-analysis showed that probiotics supplementation therapy was an effective and safe treatment for pathological neonatal jaundice. Moreover, they stated that as the quality of included studies and the limitations of samples, the long-term safety and efficacy still need to be confirmed by long-term and high-quality research.

The authors stated that this study had several drawbacks. First, because the value of jaundice fading in each guideline was different, the heterogeneity was high in time of jaundice fading. It suggested that these researchers should use the same guideline to detect the time of jaundice fading in future study. Second, according to Cochrane risk of bias estimation, randomized allocation of participants was mentioned in 9 trials. Most of the included studies only mentioned the use of random allocation, but they did not describe the specific random allocation method. So, it was hard for these investigators to determine whether the allocation scheme was appropriate and whether blinding of participants and personnel was implemented. Some studies showed that unclear random allocation and allocation plan might exaggerate the hidden effect of up to 30 to 41 %. Third, since RCTs of included studies centered in a short observation period and did not follow-up the patients in long-term, the methodological quality of clinical trials with probiotics supplementation therapy for neonatal jaundice needed further improvement. Therefore, well-designed, large randomized, double blind, placebo-controlled trials would be needed to further confirm the efficacy of probiotics. All of the outcome measures should be monitored by a standardized effective report system in clinical trials and rare serious adverse reaction could be observed through epidemiological studies.

Deshmukh and associates (2017) noted that neonatal jaundice requiring phototherapy is associated with significant socioeconomic burden including hospital re-admission, prolonged hospital stay, and separation of the baby from mother. These investigators assessed the safety and efficacy of probiotics in reducing the need for phototherapy and its duration in NNH. They performed a systematic review of RCTs of probiotic supplementation for prevention or treatment of jaundice in neonates (any gestation or weight) using the Cochrane methodology. Primary outcome was the duration of phototherapy. Secondary outcomes included incidence of jaundice, TSB level at 24, 48, 72, 96 hours, and day 7, duration of hospital stay, and adverse effects (e.g., probiotic sepsis). Results were summarized as per GRADE guidelines. A total of 9 RCTs (prophylactic: 6 trials, n=1,761; therapeutic: 3 trials, n=279) with low- to high-risk of bias were included.
Meta-analysis (random-effects model) showed probiotic supplementation reduced duration of phototherapy \([n = 415, \text{MD: } -11.80 (-17.47 \text{ to } -6.13); p < 0.0001; \text{level of evidence (LOE):} \text{low}]\); TSB was significantly reduced at 96 hours [MD: -1.74 (-2.92 to -0.57); \(p = 0.004\)] and 7 days [MD: -1.71 (-2.25 to -1.17); \(p < 0.00001; \text{LOE: } \text{low}\)] after probiotic treatment. Prophylactic probiotics did not reduce the incidence of jaundice significantly \([n = 1,582, \text{RR: } 0.56 (0.25 \text{ to } 1.27); p = 0.16; \text{LOE: } \text{low}]\). There were no probiotic-related adverse effects. The authors concluded that limited low-quality evidence indicated that probiotic supplementation may reduce the duration of phototherapy in neonates with jaundice. Moreover, they stated that routine use of probiotics to prevent or treat neonatal jaundice cannot be recommended; large well-designed trials are needed to confirm these findings.

**Adjuvant Therapies (e.g., Clofibrate, and Metalloporphyrins) and Exchange Transfusion**

In an evidence-based review on “Neonatal hyperbilirubinemia”, Pace and colleagues (2019) stated that clofibrate, metalloporphyrins, and ursodiol have been examined in the management of unconjugated hyperbilirubinemia as augmentation to phototherapy. Honar et al (2016) found that ursodiol added at the time of phototherapy initiation showed a significant reduction in peak bilirubin levels and duration of phototherapy in term infants with unconjugated hyperbilirubinemia without any adverse effects. They stated that a Cochrane review of clofibrate (2012) and metalloporphyrins (2003) found that when added to phototherapy, these medications significantly decreased serum bilirubin levels and duration of phototherapy. However, there was insufficient evidence to recommend their use because of inadequate data on safety and long-term outcomes. Moreover, these investigators stated that infants with bilirubin levels greater than 25 mg/dL, those who are not responding to phototherapy, and those with evidence of acute bilirubin encephalopathy should be treated with exchange transfusion, with initiation based on an infant’s age in hours and neurotoxicity risk factors. Exchange transfusion involves taking small aliquots of blood from the infant and replacing them with donor red cells until the infant’s blood volume has been replaced twice to remove bilirubin and antibodies that may be causing hemolysis. Exchange transfusion should be performed in a neonatal intensive care unit (NICU) due to significant risks.

**Genotyping of BLVRA**

http://www.aetna.com/cpb/medical/data/300_399/0332.html
Li and colleagues (2019) examined the associations between G6PD 1388 G>A, SLCO1B1 rs4149056 and BLVRA rs699512 variants and the risk of neonatal hyperbilirubinemia in a Chinese neonate population. A total of 447 Chinese neonates with hyperbilirubinemia were selected as the study group and 544 healthy subjects were recruited as the control group matched by baseline sex, age, feeding pattern and delivery mode. Approximately 2 ml of peripheral venous blood was taken from all subjects. The single nucleotide polymorphisms (SNPs) of G6PD 1388 G>A, SLCO1B1 rs4149056 and BLVRA rs699512 loci were examined by the polymerase chain reaction (PCR) and Sanger sequencing technique in the peripheral blood of all subjects. For the G6PD 1388 G>A SNP, individuals carrying the A-allele were associated with a significantly increased risk of neonatal hyperbilirubinemia (adjusted OR = 1.49, p < 0.001, 95 % CI: 1.31 to 1.67). This risk increased significantly in the CC genotype carriers at the rs4149056 locus of the SLCO1B1 gene (OR = 2.17, 95 % CI: 1.87 to 2.33), whereas it decreased significantly in individuals carrying the G-allele at the rs699512 locus of the BLVRA gene (adjusted OR = 0.84, p = 0.01, 95 % CI: 0.75 to 0.95). The G6PD 1388 G>A, SLCO1B1 rs4149056 and BLVRA rs699512 SNPs had a significant impact on STB levels. Moreover, individuals carrying the A-allele of G6PD 1388 G>A and BLVRA rs699512 had a significantly increased risk of developing neonatal hyperbilirubinemia (OR = 5.01, p < 0.001, 95 % CI: 3.42 to 7.85). The authors concluded that genetic variants of bilirubin metabolism genes, including G6PD 1388 G>A, SLCO1B1 rs4149056 and BLVRA rs699512, were associated with the risk of neonatal hyperbilirubinemia, and are potential markers for predicting the disorder.

Genotyping of G6PD

Guidelines from the American Academy of Pediatrics (AAP, 2004) on management of hyperbilirubinemia in the newborn infant state that "Measurement of the glucose-6-phosphate dehydrogenase (G6PD) level is recommended for a jaundiced infant who is receiving phototherapy and whose family history or ethnic or geographic origin suggest the likelihood of G6PD deficiency or for an infant in whom the response to phototherapy is poor (evidence quality C: benefits exceed harms)."

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

http://www.aetna.com/cpb/medical/data/300_399/0332.html 06/26/2019
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36450</td>
<td>Exchange transfusion, blood; newborn</td>
</tr>
<tr>
<td>82247</td>
<td>Bilirubin; total</td>
</tr>
<tr>
<td>82248</td>
<td>direct</td>
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</tbody>
</table>

CPT codes not covered for indications listed in the CPB:

Genotyping of BLVRA - no specific code:

<table>
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<tr>
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<th>Code Description</th>
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<tbody>
<tr>
<td>81328</td>
<td>SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)</td>
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<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) [for assessing risk of neonatal hyperbilirubinemia]</td>
</tr>
<tr>
<td>97124</td>
<td>Therapeutic procedure, 1 or more areas, each 15 minutes; massage, including effleurage, petrissage and/or tapotement(stroking, compression, percussion)</td>
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</tbody>
</table>

Other CPT codes related to the CPB:

<table>
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<th>Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>81247 - 81249</td>
<td>G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis</td>
</tr>
</tbody>
</table>

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E0202</td>
<td>Phototherapy (bilirubin) light with photometer</td>
</tr>
<tr>
<td>S9098</td>
<td>Home visit, phototherapy services (e.g., Bili-lite), including equipment rental, nursing services, blood draw, supplies, and other services, per diem</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

<table>
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<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2560</td>
<td>Injection, phenobarbital sodium, up to 120 mg</td>
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</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

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<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>P55.0 - P55.9</td>
<td>Hemolytic disease of newborn</td>
</tr>
<tr>
<td>P57.0 - P57.9</td>
<td>Kernicterus</td>
</tr>
<tr>
<td>P58.0 - P58.9</td>
<td>Neonatal jaundice due to other excessive hemolysis</td>
</tr>
<tr>
<td>P59.0 - P59.9</td>
<td>Neonatal jaundice from other and unspecified causes</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


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<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>O36.111+</td>
<td>Maternal care for other isoimmunization [not covered for the use of antenatal phenobarbital in red cell isoimmunized pregnant women]</td>
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<tr>
<td>O36.199+</td>
<td>Glucose-6-phosphate dehydrogenase (G6PD) levels:</td>
</tr>
<tr>
<td>Z15.89</td>
<td>Genetic susceptibility to other disease [G6PD deficiency]</td>
</tr>
<tr>
<td>Z83.49</td>
<td>Family history of other endocrine, nutritional and metabolic diseases [G6PD deficiency]</td>
</tr>
<tr>
<td>Z84.81</td>
<td>Family history of carrier of genetic disease [G6PD deficiency]</td>
</tr>
</tbody>
</table>


60. Wong RJ, Bhutani VK. Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2015.


http://www.aetna.com/cpb/medical/data/300_399/0332.html
Amendment to
Aetna Clinical Policy Bulletin Number: 0332 Neonatal Hyperbilirubinemia

There are no amendments for Medicaid.