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Clinical Validation for Newborns: New Sepsis and Jaundice Guidelines

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Presented By

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Presented By

Sheilah J. Snyder, MD, FAAP, is a pediatric hospitalist for Children's Hospital and Medical Center in Omaha, Nebraska. Snyder serves as a physician advisor for the Epic inpatient team and CDI program, which allows her to leverage the electronic health record to produce excellent CDI outcomes. Snyder has presented at the ACDIS conference and contributed to the book *Pediatric CDI: Building Blocks for Success*.

Learning Outcomes

- At the completion of this educational activity, the learner will be able to:
  - List the new febrile infant national guidelines and how this has changed our clinical practice in pediatrics
  - Confidently apply August 2022 updated hyperbilirubinemia guidelines to query process and clinical validation reviews
  - Describe how to utilize these new pediatric guidelines to direct clinical validation in CDI through case examples

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Febrile Infant

AAP, 2021 Clinical Practice Guidelines: Evaluation and Management of Well-Appearing Febrile Infants 8-60 days old

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Case Study

- Baby boy was born at premature at 36 weeks gestation. At nine hours old, he had some pauses in breathing. There was no change in heart rate (HR) or O2 sats. Chest X-ray (CXR) was consistent with respiratory distress syndrome (RDS). Blood culture was done, and he started on ampicillin and gentamycin. Baby was transferred to the tertiary care NICU.
- NICU diagnosed with respiratory distress and continued observation for sepsis.

Urinary Tract Infections

- An estimated 10% of febrile infants will have urinary tract infections (UTI)
  - 94% will be positive for leukocyte esterase
- 2021 AAP Clinical Practice Guideline: UTI
  - Pyuria + 50,000 CFU on culture
  - Extend to infants in our age group
- Catheterized specimen
  - Pyuria and fever + 10,000 CFU

Bacteremia

- 3.9% to 5.1% of all febrile infants in this age group
- 20% of infants younger than 28 days with UTI will have bacteremia
- Blood culture needed for identification of organism (and sensitivities) for directed antimicrobial treatment

Meningitis

- The prevalence of meningitis is 0.5%–1.3% in 8–21-day age group.

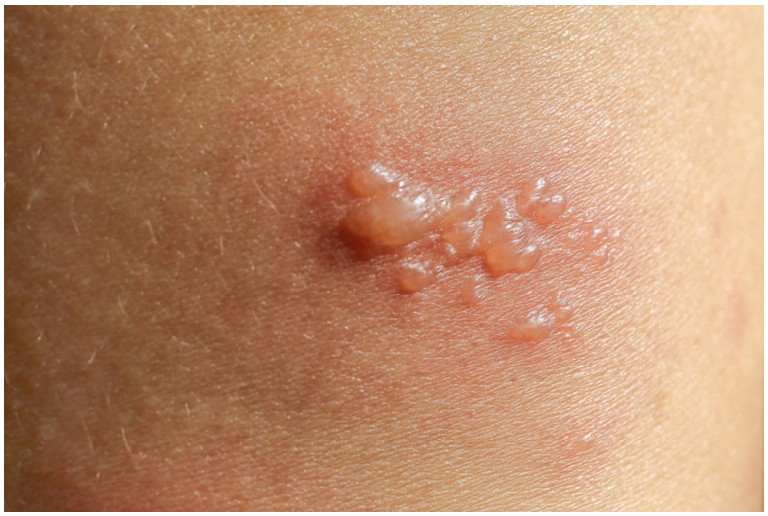
Cerebrospinal Fluid Reference Values for Young Infants Undergoing Lumbar Puncture		
	≤28 days of age	29-60 days of age
CSF WBC counts	High of 15 cell/mm3	9 cells/mm3
CSF protein	High of 127 mg/dL	99 mg/dL
CSF glucose	Low of 25 mg/dL	27 mg/dL

Pediatrics 2018 Mar, Joanna Thomson et al.

Herpes Simplex Virus (HSV)

- Incidence is increasing: From 2000 to 2015, 3.75 to 5.3 per 10,000 live births
- Transmission
  - 85% acquire HSV perinatally/peripartum period
  - 10% are infected with HSV postnatally
  - 5% acquire the infection during intrauterine period

HSV Rash



Risk of Neonatal Disease From Maternal Infection

- Maternal infection/Ab status (primary vs recurrent)
- Longer duration of rupture of membranes
- Integrity of mucocutaneous barriers (using fetal scalp probe, incisions…)
- Mode of delivery (cesarean versus vaginal delivery)
- History of seizures or seizures at presentation
- Severe illness
- Hypothermia
- Lethargy
- Conjunctivitis
- Vesicles on skin
- Hepatosplenomegaly
- CSF with pleocytosis without bacterial source
- Thrombocytopenia
- Leukopenia
- Elevated LFTs

Disease Classification of Neonatal HSV

Disease classification	% of those diagnosed	Typical age at presentation (day)	Clinical presentation	Diagnostic testing
SEM	45	10-12	Vesicular lesions or ulcerations on eye or mucosa	Skin/mucosa culture/PCR + CSF PCR – Blood PCR +/- ALT normal
CNS	30	16-19	Irritability, seizures, temp instability, lethargy, poor feeding	Skin/mucosa culture/PCR +/- CSF PCR + Blood PCR +/- ALT normal
Disseminated	25	10-12	Acute respiratory failure, encephalitis, hepatic failure, shock, DIC	Skin/mucosa culture/PCR +/- CSF PCR +/- Blood PCR +/- ALT elevated

Risk Factors for Invasive HSV Infection

- Age
- Prematurity
- Seizure at home
- Ill appearance
- Abnormal triage temperature
- Vesicular rash
- Thrombocytopenia
- CSF pleocytosis

Cruz et al, Pediatrics 2021

What Is New About Neonatal Fever?

- **Inflammatory markers play a new role**
- Historically, WBC, ANC, and band count combined with clinical appearance and UA have been the foundation of early clinical prediction models for sepsis
- With E. coli replacing GBS as the most common bacterial pathogen, these markers became less reliable

Procalcitonin

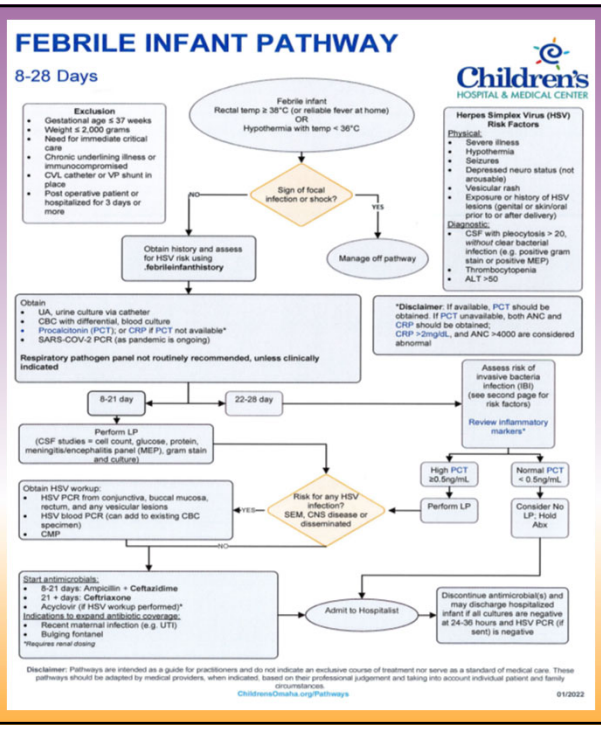
- Produced in the thyroid in response to infection and significant tissue injuries
- Benefits:
  - Rises quicker than other IMs
  - More specific for bacterial infection than other IMs
- Downsides:
  - Not available everywhere
  - Prolonged turnaround
- It's a good IM, but shouldn't be used on its own, better sensitivity with UA, ANC, other IM

Bugs and Drugs: Treatment Based on Pathogens

- E coli has been the most common pathogen detected, with a prevalence of:
  - 70% to 90% of UTIs,
  - 30% to 60% of bacteremia infections
  - 15% to 30% of bacterial meningitis.
- Overall, for studies since the year 2000 in infants <90 days of age, Gram-negative organisms have been responsible for the majority of infections (60% to 80%).
- The prevalence of GBS infection in the first week of life has declined because of prenatal screening and peripartum antimicrobial prophylaxis but is still encountered in >20% of febrile infants with bacteremia after the first week.
- In a 2013 series, GBS was the most common pathogen in the second month and was the most common cause of meningitis in the 2019 Reducing Variability in the Infant Sepsis Evaluation study.

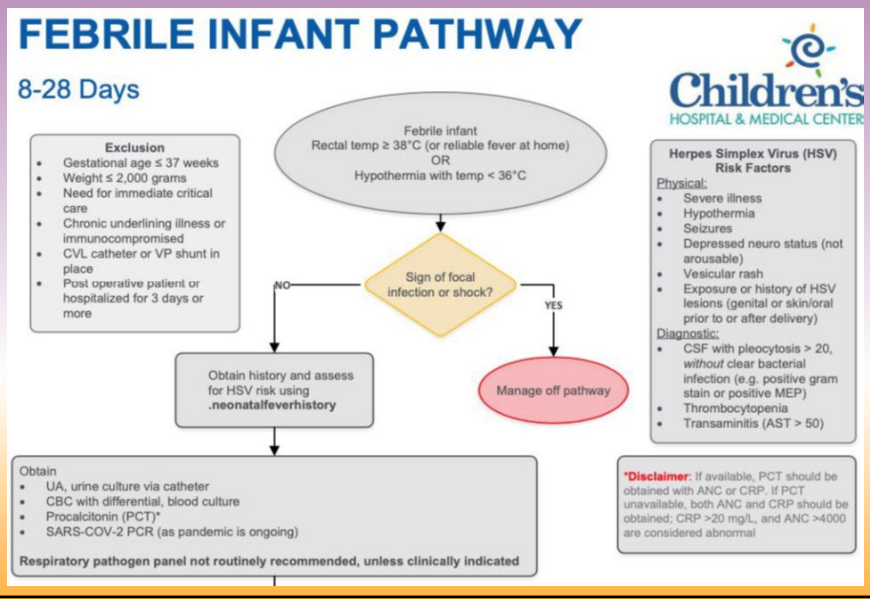
Sepsis Practice Changes: 8–28 days

- Division of 22–28-day olds
- Standardization of the HSV workup
- Use of IM to influence need for an LP for older infants
- Change from gent to ceftazidime
- Anticipated discharge at 24–36 hours



https://www.childrensomaha.org/clinical-pathways/

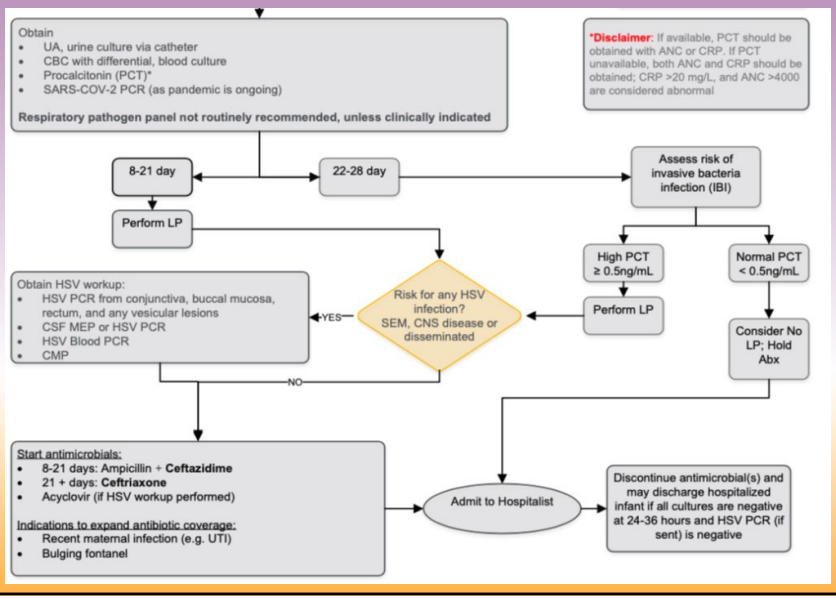
Febrile Infants: Practice Changes 8–28 days



Why Separate 22–28-Day Olds?!

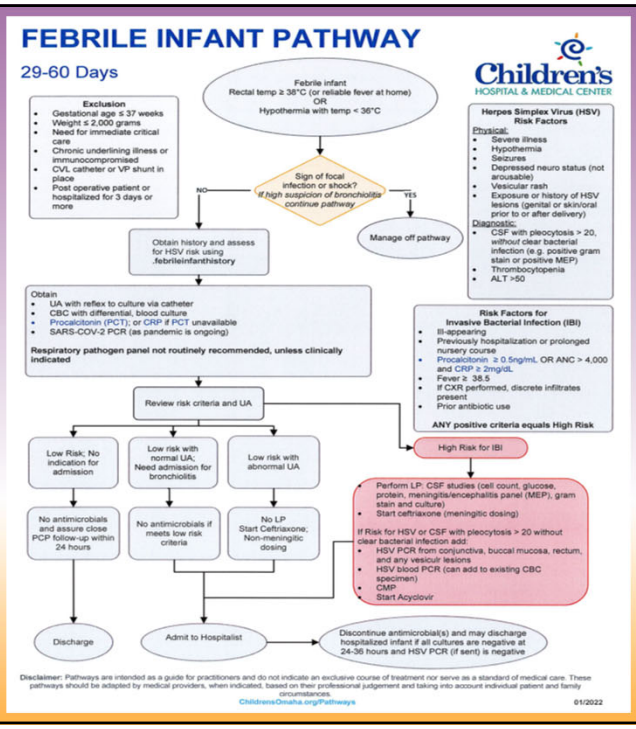
- Prospective national surveillance study in England analyzed 22,075 episodes of IBI from 2010–2017, documented a dramatic decrease in IBI after the first week of life, followed by a continuous stepwise decrease in population incidence over the next eight weeks.
- PECARN: Pediatric Emergency Care Applied Research Network showed there was a significantly lower rate of bacteremia in the fourth week (1.6%) compared with weeks two (5.3%) and three (3.3%) and no difference from weeks five and six (P =0.76).
- IMHC, University of Utah/Intermountain Healthcare –Pantell, JAMA 2004.
- FYIRC: Febrile Young Infants Research Collaborative -Scoring system developed by Aronson et al identified age >21 days to be useful in identifying low-risk infants.
- PROS: Pediatric Research in Office Settings study indicated that when combined with other variables, infants >25 days of age were at low risk for IBIs, 0.4%.
- European Collaborative Group developed and validated the step-by-step approach with a combination of clinical and laboratory variables that included 22- to 28-day-old infants, capable of identifying infants at low risk for IBIs, 0.2% to 0.7%.

Febrile Infants 8–28 Days (cont.)

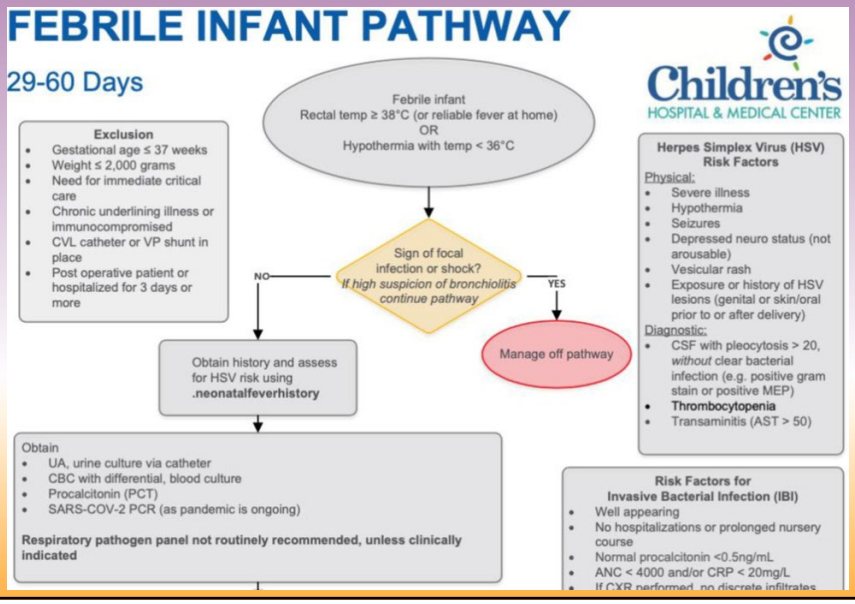


Sepsis Practice Changes: 29–60 Days

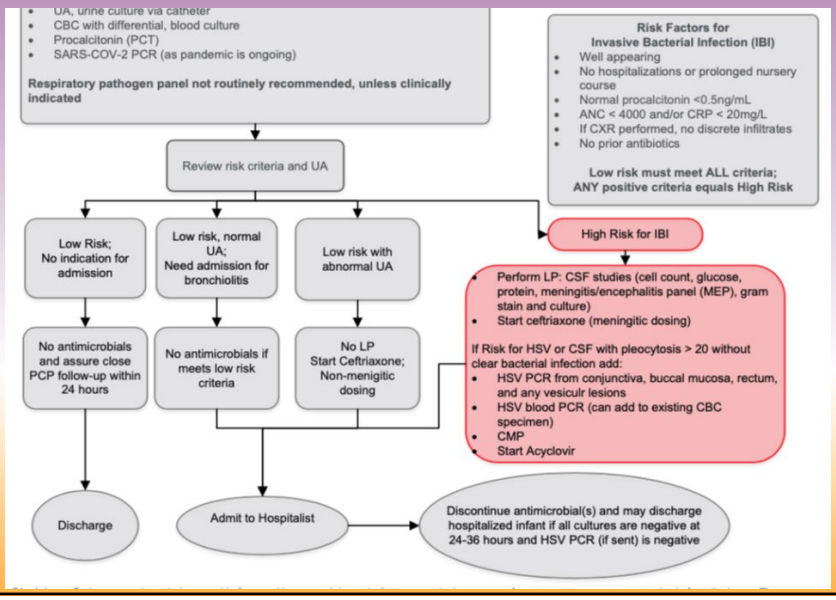
- Reinforces no LP initially
- Use of risk criteria for invasive bacterial infection (IBI)



How Do 29–60-Day Olds Fit In?



29–60-Day Old (cont.)



Back to Our Case Study

- Baby boy was born at premature at 36 weeks gestation. At nine hours old, he had some pauses in breathing. There was no change in HR or O2 sats. CXR was consistent with RDS. Blood culture was obtained, and he started on ampicillin and gentamycin. Baby was transferred to the tertiary care NICU.
- NICU diagnosed with respiratory distress and continued observation for sepsis.
- Is there an opportunity for improvement in this documentation?

Impact of Sepsis

Principal diagnosis	Respiratory distress	Respiratory distress
Secondary diagnosis	Z051, Observ for sepsis	P360, Sepsis of newborn due to group B strep
APR-DRG	625, Neonate BW 2000-2499grams with other significant condition	623, Neonate BW 2000-2499grams with congenital/perinatal infection
Severity of illness	1	1
Risk of mortality	1	2
Relative weight	1.3666	2.1514 **57%**

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Updated Hyperbilirubinemia Guidelines

AAP, 2022 Clinical Practice Guidelines Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More weeks of Gestation

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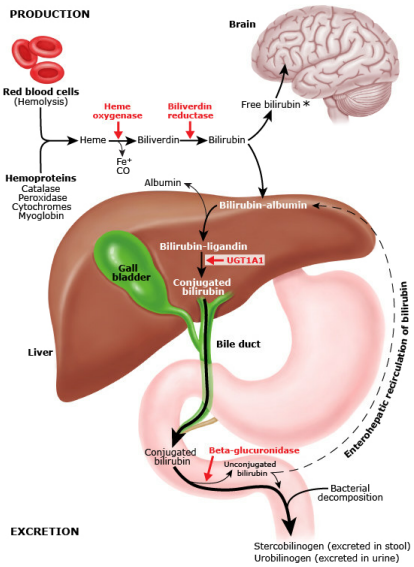
Bilirubin Production, Metabolism, and Excretion



Factors That Impact on Bilirubin Load

Rate of bilirubin rise (load) measured in mg/dL/hr = **Bilirubin production rate** MINUS **Bilirubin elimination rate**

- Bilirubin production rate ← Increased by hemolysis
- Bilirubin elimination rate → Hepatic function (decreased by impaired conjugation)
- Bilirubin elimination rate → Gut function:
  - Increased by increasing stooling frequency and volume
  - Increased by intestinal bacterial breakdown of unbound ("free") bilirubin (UB)
  - Decreased by increasing enterohepatic recirculation of bilirubin

- **All infants require total serum bilirubin (TSB)**
  1. Visual assessment for jaundice every 12 hours after delivery
  2. TcB 24–48 hours after birth

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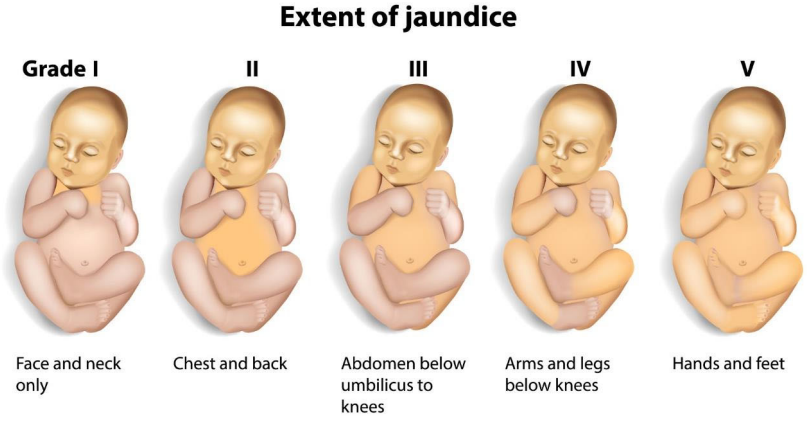
Neonatal Jaundice



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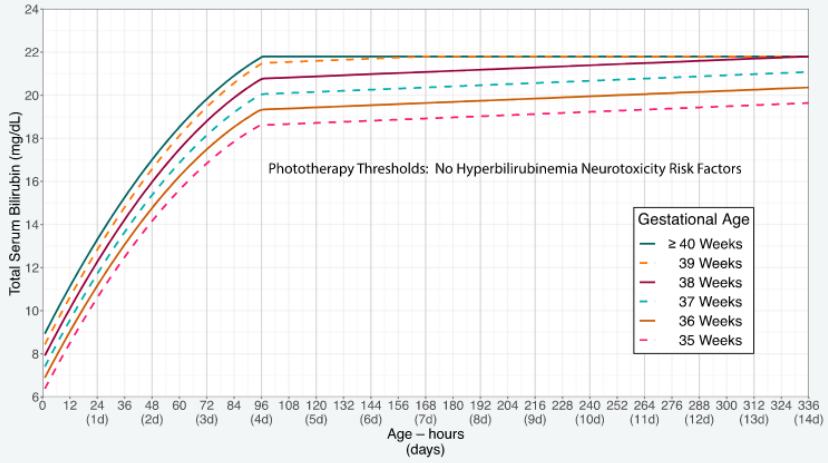
Bilirubin Normograms

Phototherapy Thresholds:
No Hyperbilirubinemia Neurotoxicity Risk Factors Other than Gestational Age



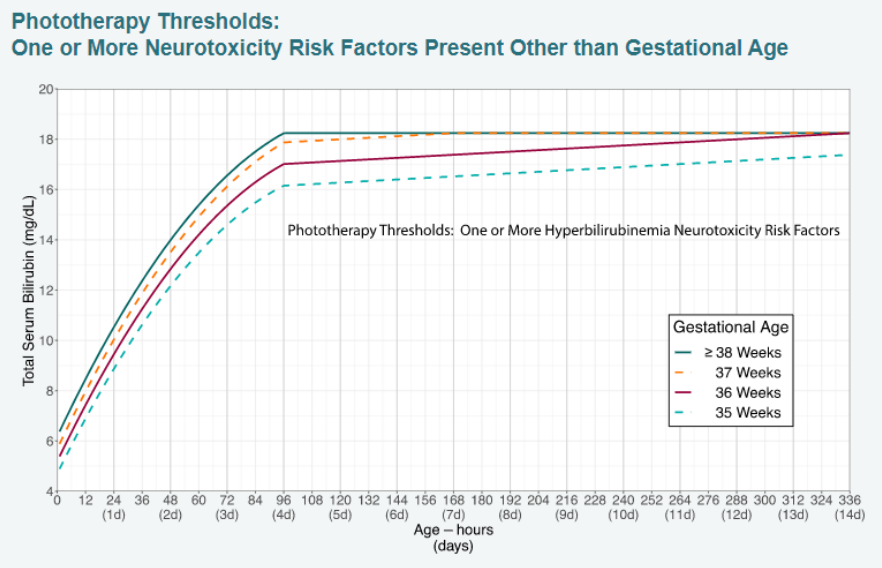
Risk Factors for Developing Significant Hyperbilirubinemia:

Lower gestational age (i.e., risk increases with each additional week less than 40 weeks)
Jaundice in the first 24 hours after birth
Predischarge transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) concentration close to the phototherapy threshold
Hemolysis from any cause, if known or suspected based on a rapid rate of increase in the TSB or TcB of >0.3 mg/dL per hour in the first 24 hours or >0.2 mg/dL per hour thereafter
Phototherapy before discharge
Parent or sibling requiring phototherapy or exchange transfusion
Family history or genetic ancestry suggestive of inherited red blood cell disorders, including glucose-6-phosphate dehydrogenase (G6PD) deficiency
Exclusive breastfeeding with suboptimal intake
Scalp hematoma or significant bruising
Down syndrome
Macrosomic infant of a diabetic mother

Breastfeeding-Associated Jaundice

- **Clarification of breastfeeding-associated jaundice:**
  - Suboptimal Intake hyperbilirubinemia
    - Formerly known as breastfeeding jaundice attributed to suboptimal intake, peaks at 3–5 days “suboptimal intake hyperbilirubinemia”
  - Breast milk jaundice syndrome
    - Prolonged elevated unconjugated hyperbilirubinemia that persists with adequate milk intake that can last up to three months

Bilirubin Normograms



Clinical Case

- 4-day old baby boy born at 38 weeks gestation with normal prenatal care and maternal labs who went to his pediatrician today and was found to have an elevated bilirubin level of 21mg/dl.
  He is exclusively breastfeeding, gaining weight, and making a good number of wet diapers.
- He was sent to the ED for further work up.

Impact of Breast Milk Jaundice

Principal diagnosis	Hyperbilirubinemia	Hyperbilirubinemia
Secondary diagnosis	Neonatal jaundice, unspecified	Neonatal jaundice from **breast milk inhibitor**
APR-DRG	Normal newborn or neonate with other problem	Normal newborn or neonate with other problem
Severity of illness	1	2
Risk of mortality	1	1
Relative weight	0.1277	0.2019 ↑ **58%**

Clinical Case

- 4-day old baby boy born at 38 weeks gestation with normal prenatal care and maternal labs who went to his pediatrician today and was found to have an elevated bilirubin level of 20mg/dl.
  He had dysmorphic facies noted at birth that was clinically concerning for trisomy 21 and had a genetic evaluation.
- He was sent to the ED for further work up.

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Impact of Trisomy 21

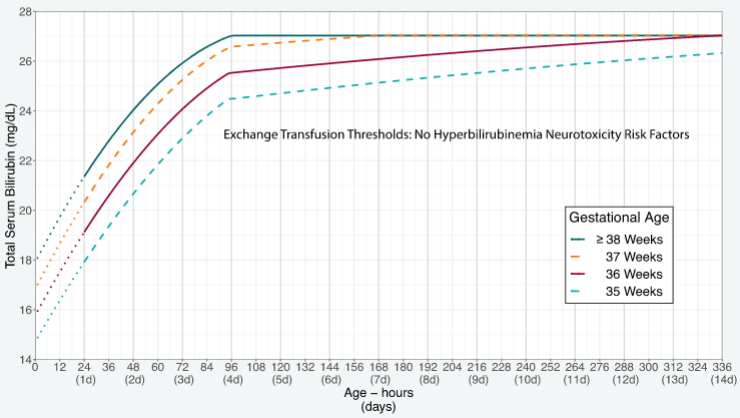
Principal diagnosis	Hyperbilirubinemia	Hyperbilirubinemia
Secondary diagnosis		Trisomy 21
APR-DRG	Normal newborn or neonate with other problem	Neonate BW >2499G with major anomaly
Severity of illness	1	1
Risk of mortality	1	1
Relative weight	0.1277	0.6060 ↑ **375%**

Exchange Transfusion Levels of Hyperbilirubinemia:

- **Recommend intensive phototherapy:**
  - Use double bank of phototherapy lights
  - Use bili blanket as available
  - Maximize area of skin exposed
    - E.g., small diapering area, allow feeding under phototherapy lights
- Recommend intravenous fluids for suspected dehydration:
  - Normal saline bolus, 20 ml/kg
  - For infants feeding pumped breastmilk or formula:
    - D10, 0.45% NaCl at TFL of 100-120 ml/kg/day
  - For infants NPO:
    - D10, 0.45% NaCl at TFL of 150 ml/kg/day if significant risk of exchange transfusion
- Place moistened gauze on umbilical stump in preparation for exchange transfusion
- Double volume exchange transfusion
- Consider IVIG if DAT+ and exchange threshold exceeded
  - 0.5-1 g/kg over 2 hours, may be repeated in 12 hours

Exchange Transfusion Thresholds: No Neurotoxicity Risk

Exchange Transfusion Thresholds:
No Hyperbilirubinemia Neurotoxicity Risk Factors Other than Gestational Age

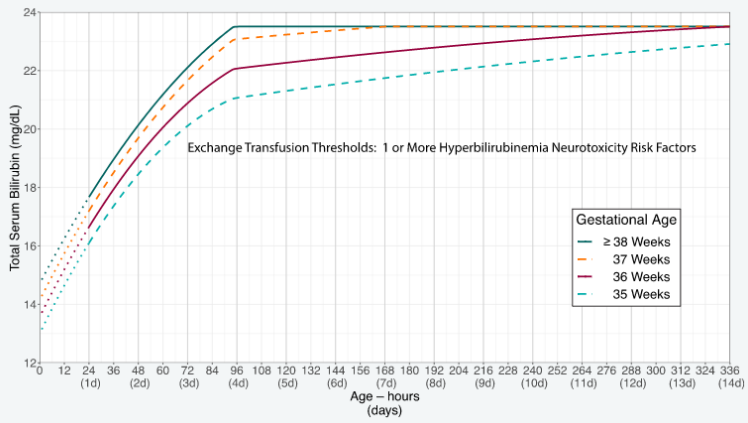


Hyperbilirubinemia Neurotoxicity Risk Factors

- Gestational age <38 weeks and this risk increases with the degree of prematurity
- Isoimmune hemolytic disease
  Infant can be treated as DAT negative if:
  1. Mother was RhD antibody negative prior to receiving RhIG during pregnancy
  2. ***And*** infant is DAT positive to anti-RhD only
- Other hemolytic diseases (e.g., G6PD deficiency)
- Significant clinical instability in the previous 24 hours:
  - Sepsis
  - Acidosis
  - Asphyxia
  - Significant lethargy
  - Temp instability
- Albumin < 3.0 g/dL

Exchange Transfusion Thresholds: With Neurotoxicity Risk

Exchange Transfusion Thresholds:
One or More Hyperbilirubinemia Neurotoxicity Risk Factors Other than Gestational Age



Clinical Case

- 4-day old baby boy born at 36 weeks gestation with no prenatal care who received phototherapy prior to discharge for an elevated bilirubin level of 10mg/dl; most likely due to a large caput noted on his newborn exam. He was off phototherapy and formula feeding well at discharge.
  He went to his pediatrician today and was found to have an elevated bilirubin level of 23mg/dl and jaundice to his feet on exam.
- He was sent to the ED for further work up where he was admitted to the NICU for potential exchange transfusion.

Impact of Kernicterus

Principal diagnosis	Hyperbilirubinemia	Hyperbilirubinemia
Secondary diagnosis		Kernicterus, unspecified
APR-DRG	Normal newborn or neonate with other problem	Neonate with other significant condition
Severity of illness	1	1
Risk of mortality	1	1
Relative weight	0.1277	**0.9295** ↑ **628%**

Resolution of Hyperbilirubinemia

- **Discontinuing phototherapy**
  - Discontinue if TSB is more than 2 mg/dL below the phototherapy threshold used for initiation of phototherapy (not current hour of life phototherapy threshold).
- **Rebound bilirubin: Monitoring TSB after phototherapy**
  - Measure TSB after phototherapy based on the risk of rebound hyperbilirubinemia.

Conclusions

- Incorporate the new febrile infant national guidelines and how this has changed our clinical practice in pediatrics.
- Confidently apply August 2022 updated hyperbilirubinemia guidelines to query process and clinical validation reviews.

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Thank you. Questions?

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Clinical Review

- Summary of Changes in AAP 2022 Guidance
- AAP. 2022 Clinical Practice Guidelines Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation
- Prevention and early identification of infants at risk for hyperbilirubinemia who may require treatment are again emphasized:
  - All infants require TSB
    - Visual assessment for jaundice every 12 hrs after delivery
    - TcB 24-48 hrs after birth
  - Continued risk factors clarification:
    - Hyperbilirubinemia Risk Factors
    - Hyperbilirubinemia Neurotoxicity Risk Factors
  - Raised thresholds for Phototherapy Initiation and Exchange Transfusion delineated by gestational age
  - Infant can be treated as DAT negative if:
    - Mother was RhD antibody negative prior to receiving RhIG during pregnancy
    - And, infant is DAT positive to anti-RhD only
- Updated Bilitool™
- New guidance on phototherapy discontinuation thresholds. Consider discontinuing if TSB decreased by at least 2 mg/dL below the hour-specific threshold at the initiation of phototherapy:
  - E.g., not the current age phototherapy threshold when repeat TSB drawn
- Transcutaneous bilirubin (TcB) is a reliable screening test and has a good correlation with TSB:
  - Laboratory Studies, TcB Interpretation
- New guidance on measuring rebound TSB following discontinuation of phototherapy:
  - Rebound Testing
- New guidance on home biliblanket usage:
  - Phototherapy Thresholds
  - Home LED-based Phototherapy
- Clarification of breastfeeding-associated jaundice:
  - Suboptimal Intake Hyperbilirubinemia
    - Formerly known as breastfeeding jaundice attributed to suboptimal intake, peaks at 3-5 days “suboptimal intake hyperbilirubinemia”
  - Breast Milk Jaundice Syndrome
    - Prolonged elevated unconjugated hyperbilirubinemia that persists with adequate milk intake that can last up to 3 months