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In This Issue…

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Neonatal Jaundice

Jaundice is a yellow discoloration of the skin and eyes caused by hyperbilirubinemia. The serum bilirubin level required to cause jaundice varies with skin tone and body region, but jaundice usually becomes visible on the sclera at a level of 2-3 mg/dL and on the face at about 4-5 mg/dL. With increasing bilirubin levels, jaundice seems to advance in a head-to-foot direction. Slightly over 50% of all neonates become visibly jaundiced in the first week of life.

CONSEQUENCES OF HYPERBILIRUBINEMIA

Hyperbilirubinemia may be harmless or harmful depending on its cause and the degree of elevation. Some causes of jaundice are intrinsically dangerous whatever the bilirubin level. But hyperbilirubinemia of any etiology is a concern once the level is high enough. The threshold for concern varies by age, degree of prematurity, and health status.

Among healthy term infants, the threshold typically is considered to be a level > 18 mg/dL. However, infants who are premature, small for gestational age, and/or ill are at much greater risk. In such infants, although risk increases with increasing hyperbilirubinemia, there is no level of hyperbilirubinemia that is considered safe.

Neurotoxicity is the major consequence of neonatal hyperbilirubinemia. An acute encephalopathy can be followed by a variety of neurologic impairments, including cerebral palsy and sensorimotor deficits; cognition is usually spared. Kernicterus is the most severe form of neurotoxicity. Although it is now rare, kernicterus still occurs and can nearly always be prevented. Kernicterus is brain damage caused by unconjugated bilirubin deposition in basal ganglia and brain stem nuclei, caused by either acute or chronic hyperbilirubinemia. Normally, bilirubin bound to serum albumin stays in the intravascular space. However, bilirubin can cross the blood-brain barrier and cause kernicterus in certain situations:

- When serum bilirubin concentration is markedly elevated
- When serum albumin concentration is markedly low (eg, in preterm infants)
- When bilirubin is displaced from albumin by competitive binders

Competitive binders include drugs (eg, sulfisoxazole, ceftriaxone, aspirin) and free fatty acids and hydrogen ions (eg, in fasting, septic, or acidotic infants).

PATHOPHYSIOLOGY

The majority of bilirubin is produced from the breakdown of hemoglobin into unconjugated bilirubin (and other substances). Unconjugated bilirubin binds to albumin in the blood for transport to the liver, where it is taken up by hepatocytes and conjugated with glucuronic acid by the enzyme uridine diphosphogluconurate glucuronosyltransferase (UGT) to make it water-soluble. The conjugated bilirubin is excreted in bile into the duodenum. In adults, conjugated bilirubin is reduced by gut bacteria to urobilin and excreted. Neonates, however, have fewer bacteria in their digestive tracts. They also have the enzyme β-glucuronidase, which deconjugates bilirubin. The now unconjugated bilirubin can be reabsorbed and recycled into the circulation (enterohepatic circulation of bilirubin).

ETIOLOGY & CLASSIFICATION

Because transient jaundice is common among healthy neonates (unlike adults, in whom jaundice always signifies a disorder), hyperbilirubinemia can be classified by whether the hyperbilirubinemia is unconjugated, conjugated, or both. It can be classified. It also can be classified by etiology or mechanism.

Mechanisms of hyperbilirubinemia

Hyperbilirubinemia can be caused by one or more of the following processes:

- Increased production
- Decreased hepatic uptake

- Decreased conjugation
- Impaired bile flow (cholestasis)
- Impaired excretion
- Increased enterohepatic circulation

Most cases involve unconjugated hyperbilirubinemia. Some of the most common causes of neonatal jaundice include:

- **Physiologic hyperbilirubinemia:** occurs in almost all neonates. Shorter neonatal RBC life span increases bilirubin production; deficient conjugation due to the deficiency of UGT decreases clearance; and low bacterial levels in the intestine combined with increased hydrolysis of conjugated bilirubin increase enterohepatic circulation. Bilirubin levels can rise up to 18 mg/dL by 3 to 4 days of life (7 days in Asian infants) and fall thereafter.
- **Breastfeeding jaundice:** develops in one sixth of breastfed infants during the first week of life. Breastfeeding increases enterohepatic circulation of bilirubin in some infants who have decreased milk intake and who also have dehydration or low caloric intake. The increased enterohepatic circulation also may result from reduced intestinal bacteria that convert bilirubin to nonresorbed metabolites.
- **Breast milk jaundice:** is different from breastfeeding jaundice. It develops after the first 5 to 7 days of life and peaks at about 2 wk. It is thought to be caused by an increased concentration of β-glucuronidase in breast milk, causing an increase in the deconjugation and reabsorption of bilirubin.
- **Pathologic hyperbilirubinemia due to hemolytic disease:** in term infants is diagnosed if jaundice appears in the first 24 h, after the first week of life, or lasts > 2 wk
  - Total serum bilirubin (TSB) rises by > 5 mg/dL/day
  - TSB is > 18 mg/dL
  - Infant shows symptoms or signs of a serious illness

  Some of the most common pathologic causes are
  - Immune and nonimmune hemolytic anemia
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Hematoma resorption
  - Sepsis
  - Hypothyroidism

Liver dysfunction (eg, caused by parenteral alimentation causing cholestasis, neonatal sepsis, neonatal hepatitis) may cause a conjugated or mixed hyperbilirubinemia.

TREATMENT

Treatment of hyperbilirubinemia is directed at the underlying disorder. In addition, treatment for hyperbilirubinemia itself may be necessary.

Medication

Medications are not usually administered in infants with physiologic neonatal jaundice. However, in certain instances, phenobarbital, an inducer of hepatic bilirubin metabolism, has been used to enhance bilirubin metabolism. Several studies have shown that phenobarbital is effective in reducing mean serum bilirubin values during the first week of life. Phenobarbital may be administered prenatally in the mother or postnatally in the infant.

In populations in which the incidence of neonatal jaundice or kernicterus is high, this type of pharmacologic treatment may warrant consideration. However, concerns surround the long-term effects of phenobarbital on these children. Therefore, this treatment is probably not justified in populations with a low incidence of severe neonatal jaundice. Other drugs can induce bilirubin metabolism, but lack of adequate safety data prevents their use outside research protocols. Intravenous immunoglobulin at 500 mg/kg has been shown to significantly reduce the need for exchange transfusions in infants with isoimmune hemolytic disease. The mechanism is unknown but may be related to the way the immune system handles red cells that have been coated by antibodies. Published experience is still somewhat limited, but administration of Ig does not appear to be likely associated with greater risks for the infant than an exchange transfusion.

Physiologic jaundice usually is not clinically significant and resolves within 1 week. Frequent formula feedings can reduce the incidence and severity of hyperbilirubinemia by increasing GI motility and frequency of stools, thereby minimizing the enterohepatic circulation of bilirubin. The type of formula does not seem important in increasing bilirubin excretion.

Breastfeeding jaundice may be prevented or reduced by increasing the frequency of feedings. If the bilirubin level continues to increase > 18 mg/dL in a term infant with early breastfeeding jaundice, a temporary change from breast milk to formula may be appropriate; phototherapy also may be indicated at higher levels. Stopping breastfeeding is necessary for only 1 or 2 days, and the mother should be encouraged to continue expressing breast milk regularly so she can resume nursing as soon as the infant's bilirubin level starts to decline. She also should be assured that she may safely resume breastfeeding. It is not advisable to supplement with water or dextrose because that may disrupt the mother's production of milk.

Definitive treatment

1- Phototherapy

This treatment remains the standard of care, most commonly using fluorescent white light. Phototherapy is the use of light to photoisomerize unconjugated bilirubin into forms that are more water-soluble and can be excreted rapidly by the liver and kidney without glucuronidation. It provides definitive treatment of neonatal hyperbilirubinemia and prevention of kernicterus.

For neonates born at ≥ 35 wk gestation, phototherapy is an option when unconjugated bilirubin is >12 mg/dL (> 205.2 µmol/L) and may be indicated when unconjugated bilirubin is > 15 mg/dL at 25 to 48 h, 18 mg/dL at 49 to 72 h, and 20 mg/dL at> 72 h. Phototherapy is not indicated for conjugated hyperbilirubinemia.

For neonates born at < 35 wk gestation, threshold bilirubin levels for treatment are lower because premature infants are at a greater risk of neurotoxicity. The more preterm the infant, the lower the threshold.

Because visible jaundice may disappear during phototherapy even though serum bilirubin remains elevated, skin color cannot be used to evaluate jaundice severity. Blood taken for bilirubin determinations should be shielded from bright light, because bilirubin in the collection tubes may rapidly photo-oxidize.

Suggested Thresholds* for Starting Phototherapy or Exchange Transfusion in Infants < 35 wk Gestation

Gestational Age (wk)	Phototherapy (total serum bilirubin, mg/dL)	Exchange Transfusion (total serum bilirubin, mg/dL)
< 28	5–6	11–14
28 to < 30	6–8	12–14
30 to < 32	8–10	13–16
32 to < 34	10–12	15–18
34 to < 35	12–14	17–19

***Consensus-based recommendations adapted from Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK: An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. Journal of Perinatology 32:660–664, 2012.**

2- Exchange transfusion

This treatment can rapidly remove bilirubin from circulation and is indicated for severe hyperbilirubinemia, which most often occurs with immune-mediated hemolysis. Small amounts of blood are withdrawn and replaced through an umbilical vein catheter to remove partially hemolyzed and antibody-coated RBCs as well as circulating Igs. Only unconjugated hyperbilirubinemia can cause kernicterus, so if conjugated bilirubin is elevated, the level of unconjugated rather than total bilirubin is used to determine the need for exchange

transfusion. For term infants, specific indications are serum bilirubin ≥ 20 mg/dL at 24 to 48 h or ≥25 mg/dL at > 48 h and failure of phototherapy to result in a 1 to 2 mg/dL decrease within 4 to 6 h of initiation or at the first clinical signs of kernicterus regardless of bilirubin levels. If the serum bilirubin level is > 25 mg/dL when the neonate is initially examined, preparation for an exchange transfusion should be made in case intensive phototherapy fails to lower the bilirubin level.

Thresholds have been suggested for neonates born at < 35 wk gestation as shown in the table. Previously, some clinicians used criteria based solely on patient weight, but these criteria have been replaced by the more specific guidelines. The goal is to reduce bilirubin by nearly 50%, with the knowledge that hyperbilirubinemia may rebound to about 60% of pretransfusion level within 1 to 2 h. It is also customary to lower the target level by 1 to 2 mg/dL in conditions that increase the risk of kernicterus. Exchange transfusions may need to be repeated if bilirubin levels remain high. Finally, there are risks and complications with the procedure, and the success of phototherapy has reduced the frequency of exchange transfusion.

References:

1) Lantzy A. *Neonatal Hyperbilirubinemia* [Internet]; Aug 2015 [cited Dec 4 2017]. Available from: www.msdmanuals.com/professional/pediatrics/metabolic,-electrolyte,-and-toxic-disorders-in-neonates/neonatal-hyperbilirubinemia
2) Hansen T. *Neonatal Jaundice*. [Internet]; Mar 2016 [cited Dec 4 2017]. Available from: https://emedicine.medscape.com/article/974786-overview

OTC Medicines Corner

Unique dosing regimen may result in better iron absorption

Administration of iron on alternative days compared with consecutive days resulted in better iron absorption, and once-daily dosing resulted in similar iron absorption compared with twice-daily dosing, according to results of two open-label, randomized controlled trials published in *Lancet Haematology*.

Source: www.aphanet.org/otc-medicines-corner/unique-dosing-regimen-may-result-better-iron-absorption

Health Benefits of

Garden Cress (*Lepidium sativum*) Seeds

Medical applications of *Lepidium sativum* have been revealed from a review of its uses in different communities. These medical usages of *Lepidium sativum* have been reported in folk medicine since time immemorial. Recently, medical applications and efficacy have been observed in research, including effects on fracture healing, a role in diabetes as a blood glucose lowering agent, a role in bronchial asthma, and its activity as an antihypertensive and as an oral contraceptive.

Lepidium sativum seed extracts are used as an antirheumatic, diuretic, and febrifuge, in abdominal discomfort, in fracture healing, and in the treatment of gout. These medicinal uses of LSS are practiced routinely in Ayurveda. Kasturyadi (Vayu) gutika is an important formulation containing LSS extract which is prescribed by Ayurvedic practitioners for dysentery, hiccoughs, and gout. Some practitioners are using roasted LSS for its anti-inflammatory effect.

Adverse Effects and Reactions

Although garden cress seeds have many benefits and usages, it can be harmful by causing allergy or toxicity in moderate or high doses. It should be consumed in moderation, since

digestive problems can arise due to its content of mustard oil. Significant gain in body weight of mice was reported after the administration of methanolic extract for a prolonged duration (90 days) at 100 mg/kg per day. Similar effects have been reported in rats.

Sources: 1) Juma A and Martin C. Garden Cress (*Lepidium sativum*) Seeds in Fracture-induced Healing. In: Preedy V, Watson R and Patel V. Nuts & Seeds in Health and Disease Prevention. London: Academic press; 2011.
2) Ghante M, Badole S and Bodhankar S. Health Benefits of Garden Cress (*Lepidium sativum* Linn.) Seed Extracts. In: Preedy V, Watson R and Patel V. Nuts & Seeds in Health and Disease Prevention. London: Academic press; 2011.

1. Vitamin K promotes the hepatic biosynthesis of following blood clotting factor?

(A) Factor I (B) Factor II (C) Factor VIII (D) All of the previous

2. Which local anesthetic should be used to treat symptoms of pain, itching, burning, and discomfort in patients with an established lidocaine allergy?

(A) tetracaine (B) dibucaine (C) pramoxine (D) benzocaine

3. Commercial parenteral nutrition (PN) formulations for hypermetabolic critically ill patients:

(A) are enriched in branched-chain amino acids and contain low concentrations of aromatic amino acids.
(B) contain primarily essential amino acids.
(C) have not demonstrated a positive clinical outcome benefit in this patient population.
(D) are the preferred PN formulation used in this clinical setting.
(E) are enriched with arginine to enhance immune function.

Real Enquiries

At the "Drug Information Center", we respond to enquiries from the professional healthteam as well as from others. Here's one of the enquiries received at the center:

Enquiry received from: J. M.- Women's Health Center- Assiut University
Enquiry: What is the maximum treatment duration with ketorolac injection?
Summary of the answer: Before initiating treatment with ketorolac tromethamine injection, the potential benefits and risks of therapy should be weighed and other treatment options should be considered. Use the lowest effective dose for the shortest duration consistent with patient treatment goals.

The maximum duration of ketorolac tromethamine therapy is 5 days. If breakthrough pain relief is needed, do NOT increase the ketorolac tromethamine dose or dosing frequency. Instead consider low-doses of supplemental opioids. Administer the lowest effective dose of ketorolac tromethamine for the shortest duration.

Ketorolac has been removed from the market in France and Germany. The primary reason for withdrawal was an increased incidence of adverse effects (gastrointestinal tract and postoperative hemorrhage, acute renal insufficiency, anaphylactic reactions). About 100 deaths, out of a total of 31 million patients, have occurred worldwide. In the United Kingdom, the Committee on Safety of Medicines recommends that parenteral ketorolac use be limited to 2 days. The dosage for younger patients should not exceed 90 mg/day or 60 mg/day for elderly patients.

References: 1) Keterolac Tromethamine. In: DRUGDEX [Internet] Greenwood Village (CO): Truven Health Analytics; 2017 [cited Dec 4 2017]. Available from: www.micromedexsolutions.com
2) McEvoy G K. *AHFS Drug Information Essentials*. Bethesda: American Society of Health-System Pharmacists; 2011.

Why Do Some Diets Fail?

- Many diets are *restrictive* and cut out certain food groups. For example, the low carb diet or Atkins diet restricts carbohydrates. This is not pleasant OR sustainable.
- Most diets *force a person to rely on the pill, supplement, shake or product for a certain amount of time*. Why is the failure rate so high for dieters? Why do people regain the weight? Putting a band-aid over a problem will help it temporarily, but it won't solve the problem. Once that weight loss aid is removed, the weight slowly creeps back. What happens when you go out to a party or out to eat with friends? The list goes on and on.
- Minimal or no focus on the mindset component. We are all going to have our stressful moments or times when we're invited to have dinner with friends. Having awareness and anticipating possible barriers or challenges can help you work through them.

What is the optimal way to lose weight? How do you know which "diet" is for you?

You need tools, or knowledge, to be able to lose weight. *There is no short cut. There are no magic pills.* We must make the process fun and learn the principles to be able to translate it into long-term, permanent, weight loss.

The problem with the word "diet" is that it is a temporary solution. Discovering what works best for your body may require support and knowledge about your specific medical history, food preferences, schedule and goals. When you discover what works for you, you will feel more confident, energetic, and happy that you made the choice to take care of your body.

Source: Tarantola C. Why do some diets fail? [Internet]; Nov 2017 [cited Dec 4 2017]. Available from: www.pharmacytimes.com/contributor/christina-tarantola/2017/11/why-some-diets-fail

What is Clenbuterol?

Clenbuterol is a steroid-like chemical that was initially developed to treat asthma in horses, working by relaxing the airways in the animals' lungs. The drug is both a decongestant and a bronchodilator. In some European and Latin American countries, clenbuterol is approved as an asthma drug for humans too. But, in the United States and in many countries, it is illegal to use clenbuterol in animals or humans.
In the U.S. in the past, clenbuterol has been used in animal rearing as well as by vets. In 1991, the U.S. Food Safety and Inspection Service found it had been fed to livestock, so the animals gained more muscle and less fat.

What does clenbuterol do?

Clenbuterol is a beta-2-agonist. It exerts effect on the catecholamine neurotransmitters. This includes dopamine, which is commonly known as the reward hormone. Dopamine is often thought to be the primary mover of addiction in general and as such, this makes Clenbuterol potentially *highly* addictive. Clenbuterol stimulates both the heart and central nervous system.

Why is clenbuterol used?

The drug is now controversial because of its use in bodybuilding and weight-loss programs. Clenbuterol can be used as a weight-loss aid because it can increase a person's metabolism. It also allows the user to retain both muscle mass and body strength at the same time.
Clenbuterol became known as a celebrity diet secret because of its apparent use by celebrities and famous athletes. One study reviewing data from two regional poison centers in the U.S. found that in 11 of the 13 reported cases of people taking clenbuterol, it had been used for weight loss reasons or as part of a bodybuilding regime.

The World Anti-Doping Agency has banned the use of clenbuterol at all times, both in and outside of competition.

Risks and side effects

Clenbuterol offers all the unwanted side effects of amphetamines, including anxiety, jitters, shakes, anxiousness, headaches and sweatiness. The most alarming danger of Clenbuterol is that it can potentially cause long term negative effects on the heart. Increased heart rate and dilation can lead to 'cardiac hypertrophy', which can potentially lead to heart attack and eventually death. In 1994, 140 people in Spain were hospitalized after eating meat tainted by clenbuterol. Similarly, in 2006, 336 people in China were poisoned after eating pork that contained it.

Outlook

The effects that clenbuterol can have on the heart and muscles will depend on how high a dose someone has been taking and for how long. The risks increase with the dose and duration. Those taking high doses can experience long-term side effects quickly, such as a decrease in the size, weight, strength, and activity of the heart.

Clenbuterol is illegal for human consumption in many countries for a good reason, and anyone buying the drug online should be extremely cautious. While some may choose to take the risk because of the less harmful side effects, they should always remember the potentially extreme side effects as well.

References: 1) Seymour T. What is clenbuterol? [Internet]; Nov 2017 [cited Dec 5 2017]. Available from: www.medicalnewstoday.com/articles/319927.php
2) Mae JR. What is clenbuterol? [Internet]; Nov 2017 [cited Dec 5 2017]. Available from: www.healthguidance.org/ entry/17508/1/What-Is-Clenbuterol.html

When Pharmacists Tell the Truth!

Answers:

1. B) Vitamin K promotes the hepatic biosynthesis of factor II (prothrombin) and also factors VII, IX and X. Vitamin K does not play important role in the biosynthesis of factors I and VIII.

2. C) Because of its chemically distinct structure, pramoxine exhibits less cross-sensitivity compared to the other anesthetics and should be used in patients with a lidocaine allergy.

3. C) PN formulations enriched in branched-chain amino acids have been made available with the rationale that, being t he preferred fuel source in this patient population, it would enhance protein synthesis, decrease protein catabolism, and improve the patient's clinical outcome. However, these more expensive formulations have not been shown to favorably influence clinical outcomes in critically ill patients.