Dear Reader,

Errata have been identified in the first printing of Questions From NeoReviews: A Study Guide for Neonatal-Perinatal Medicine on pages 120, 322, 391, 564, 635, and 636. (Please note: The change to page 391 caused text to reflow on pages 392 through 394.) The changes are as follows:

- **Page 120 (Genetics and Inborn Errors of Metabolism)**
  - **Question 39:** The third and final sentence in the question should be changed from “Of the following, paternal UPD for chromosome 15 is most characteristic of:” to “Of the following, maternal UPD for chromosome 15 is most characteristic of:”

- **Page 322 (Statistics, Research, Health Services, Ethics)**
  - **Question 26:** In the final question, “Of the following, the likelihood ratio for a negative result of the diagnostic test is closest to:” answer A should be changed from “0.3” to “0.5”

- **Page 391 (Fluids, Electrolytes, Nutrition)**
  - **Answer 64:** The answer and explanation should be changed from E. Vitamin D
    The primary factor in the development of bone disease of prematurity is vitamin D deficiency. Severe vitamin D deficiency in preterm neonates can be evident by severe bone abnormalities, seizures in the setting of hypocalcemia, failure to thrive, neurological abnormalities, and an increased number of respiratory infections.
    
    to the following:

    D. Phosphorus
    The complication of metabolic bone disease in prematurity is caused by multiple factors. However, the limitations in postnatal phosphorus delivery via parenteral nutrition and delays in fortification of phosphorus-depleted human milk feedings appear to be the primary factors in disease progression.1–3

References

- **Page 564 (Neurology)**
  - Answer 94: The answer *should be changed* from “B. Cervical nerve root 6” to “E. Thoracic nerve root 1”

- **Pages 635 and 636 (Statistics, Research, Health Services, Ethics)**
  - Question 26: The final answer on page 635 *should be changed* from “Likelihood ratio for a negative result: E. 2.2” to “Likelihood ratio for a negative result: A. 0.5”; the final question 26 answer explanation on page 636 *should be changed* from “Likelihood ratio for negative result = specificity / (1 – sensitivity) = 0.66 / (1 – 0.7) = 2.2” to “Likelihood ratio for negative result = 1 – sensitivity / specificity = (1 – 0.7) / 0.66 = 0.45”

Please contact AAP Member and Customer Care at mcc@aap.org if you have any questions.

Thank you,

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36. A neonate born at 38-weeks’ gestational age is being cared for in the postpartum unit and has lethargy and encephalopathy. After transfer to the neonatal intensive care unit, an evaluation includes laboratory testing for an inborn error of metabolism, and a lactate level is elevated at 15 mmol/L. Which of the following statements regarding an inborn errors and lactate elevation is correct?

A. In organic acidopathies such as methylmalonic acidemia, the acidosis will likely be out of proportion to the lacticemia.
B. In organic acidopathies, the lactate level is not a good indicator of metabolic control in the acute onset of catabolism but may be a good marker for improving status because the lactate level will always show decrease to normal levels before signs of clinical improvement.
C. In neonatal long-chain fatty acid oxidation defects, lacticemia will never be the only abnormality manifesting because there will also be other laboratory derangements, such as abnormal electrolyte and ammonia levels.
D. If a long-chain fatty acid oxidation defect is suspected in the setting of lacticemia, an acylcarnitine profile should be obtained for diagnostic purposes only after good metabolic control has already been established.
E. In the setting of an inborn error of metabolism, very high glucose infusion rates in neonates usually lead to falsely low lactate levels and may mask a catabolic state.


37. A neonate with skeletal abnormalities undergoes genetic testing and has this pathogenic variant: c.1138G>A (p.Gly380Arg). Which of the following is a correct characterization of this variant?

A. A shorter version of this could be represented as p.A1138-380.
B. The c stands for cytosine.
C. This is a situation in which the 1138 gene has greater numbers of polymorphisms than does the 380A gene.
D. The p stands for pathogenic variant.
E. This is a missense variant in which an arginine has substituted a glycine.


38. Most cytogenetic anomalies are aneuploidies, abnormal numbers of chromosomes, which often result from nondisjunction events in meiosis correlated with advanced maternal age. Of the following, the most common autosomal trisomy is:

A. Trisomy 8
B. Trisomy 13
C. Trisomy 16
D. Trisomy 18
E. Trisomy 21


39. Genomic imprinting indicates differential expression of a gene, depending on whether the gene is inherited from the mother or the father. Uniparental disomy (UPD) is the inheritance of both chromosomes in a pair from the same parent rather than 1 from each parent. Of the following, maternal UPD for chromosome 15 is most characteristic of:

A. Albright hereditary osteodystrophy
B. Angelman syndrome
C. Beckwith-Wiedemann syndrome
D. Prader-Willi syndrome
E. Silver-Russell syndrome

26. You are performing an observational study to determine the diagnostic value of measuring brain natriuretic peptide (BNP) in serum as a biomarker for symptomatic patent ductus arteriosus (sPDA) in a cohort of 200 preterm neonates. You choose a threshold value for BNP to represent a positive result (positive for sPDA) and use echocardiography as a gold standard for confirmation of sPDA. The results (fictitious in this example) are tabulated in the following contingency table:

<table>
<thead>
<tr>
<th>BNP Test</th>
<th>sPDA Present</th>
<th>sPDA Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (n = 100)</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td>Negative (n = 100)</td>
<td>26</td>
<td>74</td>
</tr>
</tbody>
</table>

Of the following, the sensitivity of this diagnostic test is closest to:
A. 40%
B. 50%
C. 60%
D. 70%
E. 80%

Of the following, the specificity of the diagnostic test is closest to:
A. 55%
B. 66%
C. 77%
D. 88%
E. 99%

Of the following, the positive predictive value of the diagnostic test is closest to:
A. 52%
B. 62%
C. 72%
D. 82%
E. 92%

Of the following, the negative predictive value of the diagnostic test is closest to:
A. 44%
B. 54%
C. 64%
D. 74%
E. 84%

Of the following, the likelihood ratio for a positive result of the diagnostic test is closest to:
A. 2.0
B. 2.5
C. 3.0
D. 3.5
E. 4.0

Of the following, the likelihood ratio for a negative result of the diagnostic test is closest to:
A. 0.5
B. 0.8
C. 1.3
D. 1.8
E. 2.2

However, the precise concentration of LCPUFAs needed to achieve this effect is not known. Multiple trials have examined the effect of LCPUFA-enriched formulas and have not found an alteration in the incidence of sepsis, necrotizing enterocolitis, or bronchopulmonary dysplasia in preterm neonates.\textsuperscript{2–6} Fewer studies have examined the effect on intraventricular hemorrhage, but none have found a difference with LCPUFA-enriched formulas.\textsuperscript{3–5}

### References

### 61. E. Toll-like receptors
Ingestion of human milk promotes growth of commensal bacteria. These organisms attach to toll-like receptors, preventing pathogenic bacteria from binding. The binding of commensal organisms to these receptors leads to a decrease in nuclear factor κB activation, which prevents neutrophil entry into the intestines.\textsuperscript{1} In contrast, ingestion of formula increases pathogenic intestinal bacteria, which is associated with enhanced intestinal inflammation.

### References

### 62. D. Initial infusion rate, 4 to 6 mg/kg/min; daily increment, 1 to 2 mg/kg/min; maximal rate, 12 mg/kg/min
Preterm neonates require sufficient glucose supplementation because this carbohydrate is the primary source of energy for the brain. Preterm neonates have poor glucose production as a result of limited glycogen stores and have high glucose requirements because of highly metabolic organs.\textsuperscript{1} In preterm neonates receiving parenteral nutrition, the most appropriate initial rate of glucose is 4 to 6 mg/kg/min (sometimes limited to 4 mg/kg/min in extremely low-birth-weight neonates) with a daily rate of increase of 1 to 2 mg/kg/min, up to a maximal rate of 12 mg/kg/min.\textsuperscript{2}

### References

### 63. C. Docosahexaenoic acid (22:6, n-3)
The newly identified anti-inflammatory mediators resolvin D1 and protectin D1 are most likely to be derived from docosahexaenoic acid (22:6, n-3).

### 64. D. Phosphorus
The complication of metabolic bone disease in prematurity is caused by multiple factors. However, the limitations in postnatal phosphorus delivery via parenteral nutrition and delays in fortification of phosphorus-depleted human milk feedings appear to be the primary factors in disease progression.\textsuperscript{1–3}

### References

### 65. C. 1,000 mOsm/L
Peripherally infused parenteral nutrition solutions have an osmolarity tolerance that ranges from 700 to 1,000 mOsm/L. Osmolarity depends on the amino acid, glucose, sodium, and phosphorus concentrations.
It is calculated by using the following equation:\(^1\):

\[
\text{Osmolarity} = (\text{amino acid} \times 8) + (\text{glucose} \times 7) + (\text{sodium} \times 2) + (\text{phosphorus} \times 0.2) - 50
\]

Amino acid concentration is in grams per liter (g/L), glucose concentration is in grams per liter (g/L), sodium is in milliequivalents per liter (mEq/L), and phosphorus is in milligrams per liter (mg/L).

References

66. A. Adipose tissue

Lipoprotein lipase is a glycoprotein found mostly in adipose tissue. It is also found in muscle, adrenal glands, kidneys, intestines, and the liver. The activity of this enzyme is decreased in preterm neonates born younger than 28-weeks’ gestational age.

67. A. Ascorbic acid

The amount of copper absorption in neonates is unknown but may be as high as 75% in those receiving breast milk.\(^1\) Copper absorption is increased by the enteral intake of glutathione, cysteine, lactose, starch, and glucose,\(^2\) whereas copper absorption is impaired by the enteral intake of ascorbic acid, iron, and zinc,\(^3\) as well as by glucocorticoid treatment.\(^4\)

References

68. E. Rash

Clinical zinc deficiency has been found in breastfeeding neonates.\(^1,2\) The most common clinical manifestation of zinc deficiency in neonates is a rash.\(^3\) The rash is typically located in the anogenital area and on the face, fingers, and trunk.\(^3\) Affected neonates are also at risk for alopecia, failure to thrive, oral candidiasis, and irritability, although these are less common findings.\(^1,3\)

References

69. C. Linoleic acid

Although Holder pasteurization is effective at eliminating bacterial and viral pathogens in donor human milk, this process also affects the nutritional content of the milk. Freezing and pasteurization eliminates all immunoglobulin M, lipoprotein lipase, and bile salt–activated lipase.\(^1\) In contrast, freezing and pasteurization do not affect the levels of linoleic acid, free fatty acids, or monoglycerides.\(^1\) Immunoglobulin A and G levels are decreased slightly. After this process, lactoferrin levels are decreased by more than 50%, and lysozyme levels are decreased by 75% of the original amount.\(^1\)

References

70. D. Women not born in the United States often have higher breastfeeding rates than do women born in the United States.

According to Massachusetts data from 2002, women not born in the United States often have higher breastfeeding rates than do women born in the United States, with Hispanic women not born in the United States having the highest rates.\(^1\) Not surprisingly, preterm neonates are less likely to receive human milk than are term neonates, with neonates of the youngest gestational age receiving the least amount of human milk.\(^1\) Women who are older and have private insurance are more likely to breastfeed.\(^1\)
71. E. Shift of potassium from intracellular to extracellular fluid
Hyperkalemia is a complication of preterm birth in up to one-half of neonates with a birth weight less than 1,000 g or birth gestational age younger than 28 weeks during the first 3 days after birth.1,2 This finding is independent of the neonate's exogenous potassium supplementation amount and the neonate's renal function.1,2 The pathophysiological mechanism of this hyperkalemia is explained by a shift of potassium from intracellular to extracellular fluid.3 This most likely is a developmentally regulated process because neonates with a birth gestational age older than 30 weeks do not have this finding.4

References

72. C. 400 mcg/d
In 1992, the US Public Health Service recommended daily folic acid intake of 400 mcg/d for all women of childbearing potential. However, surveys have shown that only approximately 30% of women aged 18 to 45 years adhere to this guideline. Furthermore, approximately one-half of primary care providers in the United States discuss the importance of folic acid supplementation with their patients of reproductive age. To address this lack of adherence, the US Food and Drug Administration mandated fortification of grain products with folic acid by 1998. Since this mandate, the incidence of neural tube defects has decreased.1 Concerns have been raised about the potential negative effects of fortification as a result of possible epigenetic changes that might have long-lasting effects, although there are no data to support this concern.

References

73. E. Preterm gestation
There is a misconception that mothers of very low-birth-weight or extremely low-birth-weight neonates are unable to provide adequate amounts of breast milk to their neonates. Although these women are at increased risk for a delay in lactogenesis and may have stress-related lactation issues, preterm birth itself does not cause insufficient milk volumes.1–3 The main reason for the association of preterm birth with insufficient milk volume is that mothers have inadequate information, equipment, and resources during the first 2 weeks after delivery.4

References

74. C. Postpartum depression decreases the duration of breastfeeding among mothers of term neonates
Multiple studies have found that mothers who have term neonates and who have postpartum depression experience a shorter period of breastfeeding.1,2 It is not known whether breastfeeding or use of a breast pump affects the risk of postpartum depression.

References
75. **C. Selenium**

Selenium interacts with glutathione peroxidase to reduce oxidative stress. Preterm neonates have decreased amounts of plasma selenium concentrations and, correspondingly, lower glutathione peroxidase activity. Further studies are needed to determine the precise effect of selenium deficiency on preterm-related diseases.

References

76. **B. Cue-based feeding**

There are different interventions or feeding strategies that can be used when transitioning a preterm neonate from gastric to oral feedings. If a neonate has clinical instability during feedings, interventions such as cue-based feedings, slow-flow nipples, and pacing may help to establish more stable feedings. For neonates with difficulty latching or maintaining a seal, a nipple shield, proper head support, and proper positioning are helpful. Neonates with a disorganized sucking, swallowing, and breathing sequence may benefit from swaddling to assist with state regulation, cue-based feedings, and pacing. Strategies to assist neonates who have poor endurance during feeding include limiting the length of feedings, providing cue-based feeding, and pacing.

References

77. **B. 2 weeks**

Initiation of iron supplementation at 2.0 mg/kg/d in low-birth-weight neonates at 2 weeks of age leads to improved iron status at 3 to 6 months of age compared with results in neonates who received iron supplementation only if they developed an iron deficiency. When iron supplementation was initiated at 2 weeks of age instead of 4 weeks of age, neonates had improved iron status at 1 and 2 months of age.

References

78. **B. 0.5 to 1.0 g/kg/d**

To prevent essential fatty acid deficiency, preterm neonates receiving total parenteral nutrition require at least 0.5 to 1.0 g/kg/d of lipids. Neonates who do not receive this minimum lipid amount can present with poor growth, scaly skin lesions, visual abnormalities, and neurological deficits after several weeks.

References
References

94. E. Thoracic nerve root 1
Perinatal brachial plexus palsy (PBPP) is classified according to the location of the nerve injury as follows:
- Upper lesion (C5, C6, and ±C7), characterized by poor shoulder function and variable hand function. Erb palsy is an upper trunk lesion (C5 and C6) resulting in the “waiter’s tip” posture, with shoulder adduction and internal rotation, elbow extension, forearm pronation, and wrist flexion.
- Lower lesion (C8 and T1), characterized by good shoulder function and poor hand function. Klumpke palsy is a lower trunk lesion (C8 and T1) affecting wrist and finger flexors as well as intrinsic hand muscles. Horner syndrome occurs alongside lower lesions when the sympathetic fibers of T1 are injured.
- Total lesion (C5–T1), characterized by poor function in the entire arm and accounting for 18% of all PBPP cases.1,2

References

95. E. EDS type VII (arthrochalasis)
Ehlers-Danlos syndrome (EDS) represents a heterogeneous group of disorders characterized by joint laxity, skin abnormalities, and skeletal changes, as well as cardiovascular and ophthalmologic abnormalities. Among EDS, types VIIA and VIIB (arthrochalasis) are the most likely to be recognized in the newborn period.

Affected newborns may present with
- Bilateral hip dislocations
- Congenital patellar dislocations with hyperextension of the knees
- Hypotonia secondary to excessive joint laxity

A history of breech in presentation may also be present.

EDS types VIIA and VIIB are autosomal dominant disorders caused by mutations in exon 6 of the COL1A1 or COL1A2 gene.1

References

96. C. Fatty acid ethyl ester
The early recognition of fetal alcohol syndrome is important to improve the long-term outcomes of children with gestational alcohol exposure. However, because of maternal underreporting, affected children may have significant delays in diagnosis. As such, methods to detect fetal alcohol exposure are actively being investigated. Among those, the most promising is the detection of fatty acid ethyl esters (FAEEs). While they are present in the meconium of neonates born to mothers who abstain or mothers with poorly controlled diabetes and glycosuria, FAEEs are more prevalent among the meconium of neonates born to mothers with problematic drinking. In addition, a FAEE value greater 600 ng has a sensitivity of 100% and a specificity of 98.4% for exogenous alcohol exposure in utero.1–3

References
22. **C. Study design**

Studies considered in a given systematic review often have differences. This variability among studies in a systematic review is termed *heterogeneity*. Clinical heterogeneity refers to variability in the participants, interventions, and outcomes considered. Methodological heterogeneity refers to variability in the study design. Clinical or methodological heterogeneity may contribute to measurable statistical heterogeneity. Methods have been developed for quantifying inconsistency across studies that move the focus away from testing whether heterogeneity is present (which is almost inevitable) to assessing the effect of heterogeneity on the meta-analysis. The $I^2$ statistic is used to evaluate whether substantial heterogeneity is present in a meta-analysis and may influence its interpretation.\footnote{Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. Oxford, United Kingdom: The Cochrane Collaboration; 2009}

**References**


23. **D. Presymptomatic state: this screening is a form of secondary prevention, allowing for detection of the condition at an earlier point in the natural history of the disease**

The rationale for implementing a screening test depends on several factors:

- **Prevalence**: The prevalence of the detectable preclinical phase of the disease should be reasonably high among the population screened.
- **Accuracy**: The test should have a high ability to detect true disease and to distinguish between who has a disease and who does not. A screening test ideally should be highly sensitive and reasonably specific to detect disease but also not lead to too many false-positive results.
- **Risk-benefit ratio**: The costs, benefits, and risks should be considered for both those affected by the disease and those who may have positive results even though they do not have the disease.
- **Presymptomatic state**: The test should be available to detect the condition before the onset of symptoms or at least early in the disease course. Once a patient has symptoms, the natural history of a disease may continue to progress to a critical point beyond which an appropriate treatment is less effective or more difficult to administer.

The rationale for pulse oximetry for congenital heart disease screening has been established based on these factors.\footnote{Mahle W, Koppel R. Screening with pulse oximetry for congenital heart disease. Lancet. 2011;378(9793):749–750} \footnote{Mahle WT, Martin GR, Beekman RH III, et al; Section on Cardiology and Cardiac Surgery Executive Committee. Endorsement of Health and Human Services recommendation for pulse oximetry screening for critical congenital heart disease. Pediatrics. 2012;129(1):190–192}

**References**


24. **E. Stratification**

Various strategies in study design can be implemented to manage the potential for confounding variables. Stratification segregates individuals into subgroups by analyzing the study question in more than 1 group. In this example, the potential confounding factor of human milk receipt will be removed by stratifying the study group into those who did and those who did not receive human milk.\footnote{Norman GR, Streiner DL. Biostatistics: The Bare Essentials. Hamilton, ON: B.C. Decker; 2008}

**References**


25. **C. The risk-benefit profile is at least as favorable as the existing alternatives to research participation.**

According to the Code of Federal Regulations, title 45, part 46, a study that is not considered minimal risk should hold out potential direct benefit. To meet this requirement, the risk of the research protocol must be justified by the anticipated benefits. Furthermore, the risk-benefit profile must be at least as favorable as the existing alternatives to research participation.\footnote{The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. Washington, DC: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; 1979}

**References**


26. **Sensitivity: D. 70%**
   **Specificity: B. 66%**
   **Positive predictive value: B. 62%**
   **Negative predictive value: D. 74%**
   **Likelihood ratio for a positive result: A. 2.0**
   **Likelihood ratio for a negative result: A. 0.5**
Sensitivity = true positive / (true positive + false negative) = 62 / (62 + 26) = 70%
Specificity = true negative / (false positive + true negative) = 74 / (38 + 74) = 66%
Positive predictive value = true positive / (true positive + false positive) = 62 / (62 + 38) = 62%
Negative predictive value = true negative / (true negative + false negative) = 74 / (74 + 26) = 74%
Likelihood ratio for positive result = sensitivity / (1 − specificity) = 0.7 / (1 − 0.66) = 2.06
Likelihood ratio for negative result = 1 − sensitivity / specificity = (1 − 0.7) / 0.66 = 0.451.2

References

27. C. 4
The number needed to treat is the reciprocal of absolute risk reduction.1 It is calculated for this example as follows:
1 / [(250 / 500) − (125 / 500)] = 1 / (0.25) = 4

References

28. D. Physician
A multidisciplinary team is essential to providing compassionate and comprehensive care to a family facing challenging circumstances, such as in extremely preterm birth. In that setting, physicians should exercise responsive leadership in making ethically and legally sound decisions and also in facilitating avenues for discussion and opportunities for any disagreement or discomfort to be voiced. In the current standard of joint decision-making in neonatal intensive care unit care, parents are accorded primary, but not absolute, decision-making authority; physicians bear the ultimate responsibility for care.1

References

29. A. Application and dissemination of evidence-based treatments to promote individual patient and public health outcomes
One categorization of translational research in medicine is as follows1:
- T1: translating biomedical science to clinical efficacy knowledge
- T2: translating clinical efficacy knowledge to clinical effectiveness knowledge
- T3: translating clinical effectiveness knowledge to improved health care quality and value and public health1
This last step of T3 translational research aims to study how evidence-based treatments can be best disseminated and applied in a broad spectrum of clinical settings to improve individual patient outcomes and public health.

References

30. D. Justice: the burdens and benefits of research should be equitably distributed such that potential subjects are not targeted disproportionately to bear the brunt of the risk
The ethical principles in The Belmont Report include the following1:
- Respect for persons: individuals should be treated as autonomous agents; persons with diminished autonomy are entitled to protection
- Beneficence: do no harm; maximize possible benefits and minimize possible harm; consider the risks and benefits to society or particular populations, as well as to the individual subject
- Justice: distribute the burdens and benefits of research equitably such that potential subjects (or populations) are not targeted disproportionately to bear the brunt of the risk or excluded when they benefit from participation

References