Chapter e22: Pediatrics: Neonatal Critical Care

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 1, Pediatric Pharmacotherapy, Nutrition, and Neonatal Critical Care.

KEY CONCEPTS

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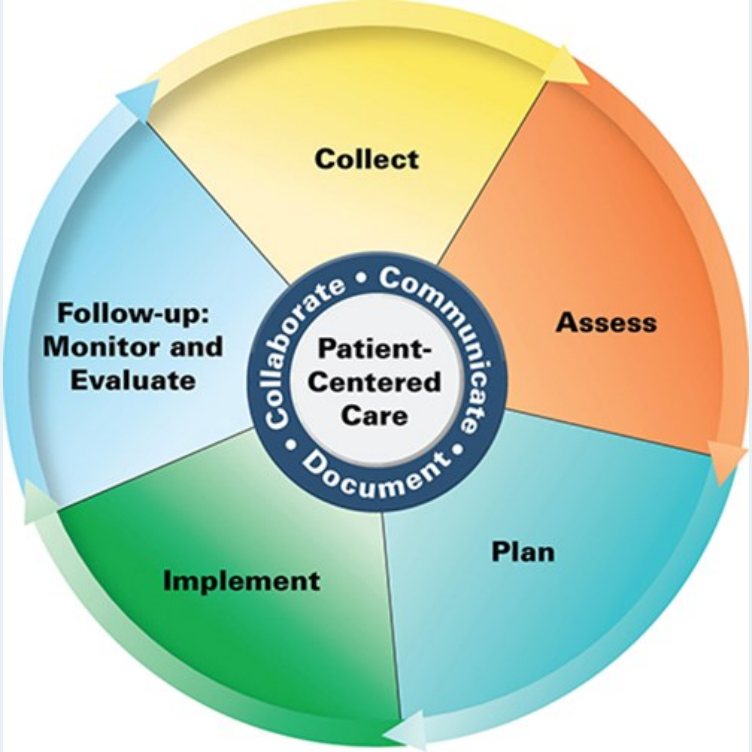
1. Pharmacokinetic parameters are altered across the age spectrum of the neonatal population (ie, preterm to term) because of developmental maturation and the effect of various disease states on these processes. Therefore, medication selection and monitoring is of utmost importance in this population.
2. Treatment guidelines for neonatal resuscitation have been extrapolated from studies in older children and adults, which may not be optimal because of differences in the pathophysiology of cardiopulmonary arrest among these populations.
3. Neonatal sepsis can be categorized as either early-onset sepsis (EOS) or late-onset sepsis (LOS). Pathogens associated with neonatal sepsis vary depending on the onset of sepsis (EOS vs LOS).
4. Empiric antibiotic therapy should be initiated in infants with suspected sepsis and should target the most common pathogens.
5. Patent ductus arteriosus occurs commonly in preterm neonates and, if hemodynamically significant, requires pharmacologic (with a cyclooxygenase inhibitor) or surgical closure.
6. In certain congenital heart defects (eg, tetralogy of Fallot, hypoplastic left heart syndrome, transposition of the great arteries), it is imperative that the ductus arteriosus remains patent. Prostaglandin E1 (alprostadil) is the drug of choice in these cases.
7. Neonatal hypotension can result in impaired cerebral perfusion and ischemic damage if left untreated. Since there is no clear consensus on the definition of neonatal hypotension, diagnosis and treatment are guided by clinical judgment, and review of the physiological parameters of the infant.
8. Pharmacologic therapy should be selected based on the etiology of hemodynamic instability and may include fluid bolus, vasopressors (eg, dopamine, dobutamine, epinephrine, norepinephrine), hydrocortisone, and vasopressin. Dopamine is the preferred initial vasopressor agent for hemodynamic support in neonates with hypotension.
9. Assessment of the degree of pain and sedation in the preverbal neonatal population is difficult. When using assessment tools, recognize the population and pain type for which each tool has been validated.
10. Opioids and benzodiazepines are commonly used to provide analgesia and sedation for critically ill neonates; however, there are concerns about their effects on long-term neurodevelopment.

Patient Care Process* for Neonatal Critical Care



Collect

- Patient characteristics (eg, gestational age, postnatal age [PNA]; see Table e22-1)
- Birth history (eg, ultrasound findings, timing of rupture of membranes, presence of maternal fever, Apgar scores, prenatal betamethasone, antibiotic therapy)
- Maternal history (eg, disease states, medications during pregnancy including substances of misuse)
- Current medications including surfactant, antibiotics, intravenous (IV) fluids, and parenteral nutrition (PN) orders
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), length, weight, oxygen saturation
  - Labs including electrolytes, blood urea nitrogen (BUN), serum creatinine (SCr), C-reactive protein (CRP), white blood cell count (WBC) and differential, cultures
  - Maternal serologies (eg, Group B streptococcus, hepatitis B, syphilis, HIV)

Assess

- Hemodynamic stability (see Table e22-5), evidence of peripheral perfusion (eg, capillary refill, peripheral pulses)
- Respiratory status (eg, grunting, flaring, retractions, need for respiratory support)
- Kidney function (eg, urine output, BUN, SCr)
- Pain (see Table e22-7)

Plan*

- Pharmacotherapeutic regimen including specific medication(s), route, dose, and frequency based on developmental pharmacokinetics
- Monitoring parameters using age-specific normal ranges
- Patient caregiver education (eg, purpose of treatment, medication administration/oral syringe technique, poison prevention principles)

Implement*

- Provide patient caregiver education regarding all elements of treatment plan
- Utilize technology (eg, "smart" IV pumps, computer order entry and dose range checking) to minimize medication errors

Follow-up: Monitor and Evaluate

- Re-evaluate weight-based and age-based medication dosing at least weekly
- Presence of adverse medication reactions

**** Collaborate with patient's caregivers and other health professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video titled "Healthcare Heroes-NICU episode" at https://www.youtube.com/watch?v=DEheE4rr1GU. This 8-minute video provides a brief overview of the initial assessment and treatment of a critically ill neonate admitted to the neonatal intensive care unit (NICU). The video will enhance the student's understanding of the role of an interprofessional team in the complex care of an NICU patient. After watching the video, the student's reflection should include identification of the roles various healthcare providers (eg, pharmacist, nurse, nurse practitioner, respiratory therapist) can play in the management of an unstable neonate. The ASSESS and PLAN steps of the patient care process will be developed through this exercise.

INTRODUCTION

Healthcare providers working in the neonatal intensive care unit (NICU) care for a wide range of patients—from those born prematurely to term newborns, newly born infants to infants who have spent months to years in the NICU, those with acute illnesses to those with chronic morbidities associated with prematurity. A large proportion of NICU patients are born prematurely. In the United States, almost 1 in 10 births is premature.[1] Preterm birth occurs when a neonate is born before 37 completed weeks of gestation.[2] Prematurity can be further categorized as late preterm (ie, 34-37 weeks), moderate preterm (ie, 32-34 weeks), very preterm (ie, 28-32 weeks), and extremely preterm (ie, less than 28 weeks).[2] Neonates born prematurely can have multiple complications including respiratory distress syndrome, intraventricular hemorrhage (IVH), seizures, necrotizing enterocolitis (NEC), and sepsis, among others. Survivors of preterm birth often have morbidities such as bronchopulmonary dysplasia (BPD), neurodevelopmental delay, and cerebral palsy.[1,3] Despite medical advances, mortality in this population, especially those born extremely premature, remains high (30%-50%).[3]

1 Opportunities abound to participate in the care of this heterogeneous NICU patient population. As such, there is terminology unique to the neonatal population that must be understood (Table e22-1). As a member of the interprofessional NICU team, the pharmacist has a key role in selection, dosing, and monitoring of medication therapy which is complicated by developmental pharmacokinetic changes that occur as a neonate ages from extreme prematurity to term (see Chapter e20). Neonates are rarely subjects in large, randomized, placebo-controlled clinical trials. Thus,

only slightly more than 30% of the medications most commonly used in the NICU have an FDA-approved indication in neonates.[4] Because of differences in physiology and pharmacokinetics, as well as the developmental changes that occur in both of these over time, it is difficult and often inappropriate to extrapolate data from studies conducted in other patient populations to the care of a NICU patient. Clinical decisions are made based on small, retrospective studies; case reports; or past experience. Study enrollment may be limited by institutional review board (IRB) regulations for conducting research in this vulnerable population as well as parents' reluctance to enroll their newborn in a clinical trial.[5,6]

TABLE e22-1

Neonatal Terminology

Term	Definition
Gestational age (GA)	Time between first day of mother's last menstrual period to the day of birth; reported as weeks plus days (eg, 32 4/7 weeks means the neonate was born at 32 weeks plus 4 days)
Postnatal age (PNA) or chronological age	Time since birth; reported as days (PNA), weeks, months, or years
Postmenstrual age (PMA)	GA plus chronological age (eg, if 16-day-old infant was born at 28 2/7 weeks then PMA is 30 4/7 weeks)
Very low birth weight (VLBW)	Birth weight (BW) less than or equal to 1,500 g
Extremely low birth weight (ELBW)	BW less than or equal to 1,000 g

Data from Reference 7.

Healthcare providers must prevent and identify medication errors because neonates represent a very high-risk population.[8] Medication errors occur most commonly in the neonatal population for various reasons, including developmental changes; a neonate's inability to communicate with the healthcare team; complex calculations required to determine doses; a lack of commercially available, age-appropriate dosage forms; and a paucity of robust, published drug information related to medication use in this population.[9]

NEONATAL CARDIOPULMONARY RESUSCITATION

2 Resuscitation of a newborn in the delivery room may be necessary for various reasons including respiratory failure due to prematurity, a hypoxic-ischemic *in utero* event, and medication-induced respiratory depression. During the first minute after birth, the neonate's tone, RR (eg, presence of apnea) and pattern (eg, gasping, labored), cry, and HR are assessed. If any abnormalities are noted, positive pressure ventilation is initiated. The basis of neonatal resuscitation is inflation and ventilation of the lungs; unlike in adults, cardiopulmonary collapse is rarely caused by nonperfusing rhythms such as ventricular fibrillation.[10,11] If after 30 seconds of adequate ventilation and corrective measures (eg, positioning airway, clearing secretions, intubation) the HR remains or falls below 60 bpm, chest compressions are initiated in the neonate.[12,13] This is different than adult life support during which chest compressions begin when a pulse cannot be detected.[14] If the newborn's HR remains below 60 bpm after 30 seconds of effective chest compressions, epinephrine is indicated.[12,13] The majority of newborns will not require epinephrine administration; less than 0.1% receive epinephrine despite requiring cardiorespiratory support in the delivery room.[15]

If epinephrine is indicated, it is preferred to be given by the IV route.[12] A catheter is often placed in the umbilical vein to establish IV access during newborn resuscitation.[11,16] The optimal dose of epinephrine during resuscitation has not been studied in neonates so the recommended dose, 0.01 to 0.03 mg/kg/dose, has been extrapolated from adult data.[12,17] If IV access cannot be established, epinephrine can be administered by an endotracheal

tube (0.05-0.1 mg/kg/dose).[12] Although epinephrine administration by the endotracheal tube is often done because the route is readily accessible, the efficacy is less than when administered intravenously.[16] The difference in efficacy may be because endotracheal administration results in lower peak and overall plasma concentrations of epinephrine compared to IV administration despite higher doses.[18–20] The difference in efficacy may be further magnified in newborns because of medication dilution in retained fetal lung fluid immediately after birth.[11] Systemic absorption of epinephrine from the lungs may also be decreased in the newborn because of right-to-left shunting of blood (ie, from the pulmonary artery to the aorta) through the patent ductus arteriosus (PDA) resulting in reduced blood flow to the pulmonary circulation.[11] The intraosseous (IO) route, which is a preferred route in pediatric advanced life support (PALS), is also an alternative if IV access cannot be established in a newborn, although establishing this form of access is not generally done in preterm neonates.[21,22]

Alternatives to standard-dose epinephrine have been evaluated. Higher dose IV epinephrine (0.05-0.2 mg/kg) does not appreciably improve outcomes and in cases of arrest precipitated by asphyxia, survival is worse when high-dose epinephrine is used.[23–26] This finding is relevant because most newborn cases are associated with hypoxia and asphyxia. Another concern related to the use of high-dose epinephrine is abrupt rebound hypertension. This acute fluctuation in BP could increase the risk of IVH particularly in premature neonates undergoing cardiopulmonary resuscitation (CPR).[10,21,27] Vasopressin is another alternative to epinephrine and provides the advantage of not increasing myocardial oxygen demand, but there is no evidence to support its use in pediatric or neonatal resuscitation.[10,21,28]

Sodium bicarbonate was routinely administered during neonatal resuscitation to treat the mixed respiratory and metabolic acidosis that results from failure of the cardiopulmonary system. This practice has fallen out of favor because of concerns about the potential to worsen myocardial function and respiratory acidosis because of carbon dioxide production and increase the risk of IVH because of its hyperosmolarity. Additionally, sodium bicarbonate use does not improve neurodevelopmental outcomes or survival following resuscitation. Administration of sodium bicarbonate may still be considered during prolonged resuscitation efforts if metabolic acidosis persists despite adequate ventilation and perfusion.[27]

Historically, naloxone was given to newborns experiencing respiratory depression in the delivery room because of maternal opioid exposure during labor. However, naloxone administration does not decrease the need for assisted ventilation in the delivery room or admissions to the NICU.[29] Withdrawal symptoms have been precipitated by naloxone administration in neonates born to mothers with opioid use disorder.[30] Because of lack of evidence for benefit and the potential for harm, naloxone use is not recommended in cases of neonatal respiratory depression immediately after birth in the setting of maternal opioid administration; instead the newborn should be supported with positive pressure ventilation.[13]

Mortality following newborn resuscitation is between 10% and 30%.[31] Extremely low-birth-weight neonates who receive CPR in the delivery room have a higher mortality rate (70%) and survivors are more likely to develop severe IVH and BPD. Additionally, the incidence (50%-90%) of neurodevelopmental impairment (eg, cerebral palsy, deafness) and death is higher in these patients than those who do not require resuscitation.[28,32,33]

NEONATAL SEPSIS AND MENINGITIS

Epidemiology

Neonatal sepsis and meningitis contribute to neonatal morbidity and mortality. Neonatal sepsis can be categorized as either early-onset sepsis (EOS) or late-onset sepsis (LOS), depending on the age at onset of signs and symptoms. Early-onset sepsis is defined as a positive blood or cerebrospinal fluid (CSF) bacterial culture within 72 hours of life compared to greater than 72 hours of life for LOS. The overall incidence of EOS is about 1.08 cases per 1,000 live births in the United States and is inversely proportional to birth weight (BW) and gestational age (GA).[34] The incidence of EOS is about 18.5 cases per 1,000 infants born at 22 to 28 weeks' gestation; 6.2 per 1,000 infants born at 29 to 33 weeks' gestation; 0.73 per 1,000 infants born at 34 to 36 34 weeks' gestation; and 0.56 per 1,000 infants born at 37 weeks' gestation or greater.[34,35] Similar to EOS, the incidence of LOS is also inversely related to BW and GA, with an incidence of 51% in those with BW 501 to 750 g compared to 16.3% in those with BW 1,001 to 1,250 g and 7.5% in those with BW 1,251 to 1,500 g.[36] Risk factors for neonatal sepsis include prematurity, male sex, African-American descent, and predisposing maternal conditions such as chorioamnionitis, prolonged rupture of membrane, and urinary tract infection.[37] Premature infants have a 3 to 10 times higher incidence of neonatal sepsis than full-term infants due to their lower immunoglobulin concentrations and decreased neutrophil function. The

incidence of mortality from neonatal sepsis is also inversely related to GA: 50% in those born at 22 to 24 weeks' gestation compared to 30% at 25 to 28 weeks' gestation, 12% at 29 to 33 weeks' gestation, and 1.6% at ≥ 37 weeks' gestation.[35,37]

Common Pathogens

Early-Onset Sepsis

Early-onset sepsis occurs in utero and is acquired either transplacentally or via ascending bacteria entering the uterus from the vaginal environment following a ruptured amniotic membrane. Once the membranes are ruptured, the infant may be at risk for colonization of microorganisms from the maternal genital tract. It can also occur when infants are exposed to pathogenic bacteria, viruses, or fungi while passing through the birth canal. Risk factors for EOS include the presence of chorioamnionitis, prolonged rupture of membranes, vaginal colonization with group B *Streptococcus* (GBS), GBS bacteriuria, and prematurity. The most common pathogens for EOS are *Escherichia coli* (36.6%) and GBS, also known as *Streptococcus agalactiae* (30.2%).[34] Other pathogens include *Listeria monocytogenes*, other streptococci (most commonly viridans group streptococci), *Enterococcus* species, nontypeable *Haemophilus influenzae*, and *Candida* species. GBS infections usually occur in term infants, whereas *E. coli* is more common among preterm infants, both at 52%.[34] *Listeria* is usually acquired via maternal consumption of contaminated meats, poultry, and dairy products.

Late-Onset Sepsis

Late-onset infections are acquired after delivery or beyond 3 to 7 days of age and are attributed to organisms acquired from the hospital or community environment. Neonates with central venous catheters are at higher risk for LOS. Other risk factors include prematurity, low BW, PN, prolonged hospitalization, prior antibiotic use, use of histamine (H_2)-receptor blockers, and NEC. Late-onset sepsis is usually caused by the same organisms as for EOS or by nosocomial pathogens. Gram-positive organisms constitute 79%, with coagulase-negative staphylococci (CONS; specifically, *Staphylococcus epidermidis*) occurring in 57% of the total and *S. aureus* in 12%. Gram-negative organisms such as *Enterobacteriaceae* and *Pseudomonas* species constitute 19% of the total, with *E. Coli* being the most predominant (7% of total).[38] Although CONS are the most commonly isolated pathogens in neonates with LOS, especially among those with central venous catheters, it is important to distinguish whether the presence of CONS is the result of colonization of IV catheters or represents a true bacteremia.

Viral infections, such as herpes simplex virus (HSV) and enteroviruses, can also cause EOS and meningitis, but are more common in LOS. About 5% of neonatal HSV infections are acquired in utero, 85% are peripartum, and 10% are postnatally.[39] HSV infections are associated with high morbidity and mortality and are usually due to HSV-1 infection. In addition to bacterial and viral infections, fungal pathogens can cause neonatal sepsis (more commonly associated with LOS) and are inversely related to GA and BW. The incidence of invasive candidiasis varies but can be as high as 10% to 16% in ELBW infants compared to 2% to 8% in VLBW infants.[40] In addition, *Candida* species colonization can be as high as 60% in VLBW with up to 20% progressing to invasive fungal infections.[40] Risk factors include extreme prematurity, abdominal surgery, central venous catheters, prolonged use or broad-spectrum antibiotics, steroids and H_2 blockers, and prolonged duration of mechanical ventilation.

Meningitis should always be considered in infants with neonatal sepsis. Although the incidence of neonatal meningitis is low, it remains a devastating infection with high morbidity and mortality. The pathogens causing neonatal meningitis are the same as for neonatal sepsis. Neonatal meningitis is often caused by GBS (50%) followed by *E. Coli* (20%). *Citrobacter* species and *Cronobacter sakasakii*, although uncommon (~5% in VLBW infants), are important pathogens due to their association with meningitis from brain abscesses.[34,41] Most cases of meningitis are late-onset infections resulting from hematogenous spread.

Clinical Presentation

The clinical signs and symptoms of neonatal sepsis and meningitis vary by GA and severity of infection, ranging from nonspecific to multiorgan failure. Initially, infants with neonatal sepsis may have poor feeding, irritability, lethargy, and hypothermia. Fever is uncommon unless the infants are born to a febrile mother and have a fever immediately after delivery. In addition, infants with neonatal sepsis can have respiratory (eg, apnea, tachypnea, grunting, nasal flaring) or cardiac symptoms (eg, cyanosis, desaturation, bradycardia, poor perfusion, metabolic acidosis, hypotension). Premature infants usually present with apnea, bradycardia, cyanosis, and lethargy while term infants will present with respiratory distress. Late complications of neonatal infection include jaundice, hepatosplenomegaly, respiratory failure, severe metabolic acidosis, bone marrow dysfunction (eg, neutropenia,

thrombocytopenia), and disseminated intravascular coagulation.[37] Most infants with EOS will present within the first 24 to 48 hours of life, and those with gram-negative and fungal infections will have more severe symptoms than those with gram-positive infections. It is important to perform a thorough review of antenatal risk factors when evaluating an infant for suspected sepsis and meningitis. The presence of rash, seizures, or liver dysfunction should lead to suspicion of a viral infection such as HSV.[39]

Diagnostic and Laboratory Findings

A complete sepsis workup for neonatal sepsis includes a blood culture, complete white blood cell count (WBC) with differential, a urine culture (for LOS only), and a lumbar puncture (LP) for cell count and culture. The gold standard for diagnosis of neonatal sepsis is the isolation of an organism in blood culture. A minimum of 1 mL of blood, collected from a peripheral vein, is recommended for blood cultures for EOS.[42] For LOS, two different venipunctures (1 mL of blood) from two separate sites for blood cultures are required. This is particularly important for those with central venous catheters, since a true pathogen is more likely to be present in both culture specimens. This will identify those with a true bacterial infection versus those with colonization. Because of a decreased detection of organisms due to the small amount of blood obtained for blood cultures, neonatal sepsis cannot be excluded when blood cultures show no growth. WBC with differential and the ratio of immature to total neutrophils (I/T) are commonly used as screening tests for neonatal sepsis. An I/T ratio is defined as immature (bands plus earlier cell lines) to total neutrophils (neutrophils plus immature cells); a ratio of less than 0.2 is considered normal. Unfortunately, none of these tests are absolutely indicative of neonatal sepsis as they have poor sensitivity and specificity. Neutropenia has a greater specificity and can be a sign of WBC depletion from bone marrow owing to overwhelming sepsis. An elevated WBC can also indicate bacterial infection but may be less specific. In contrast, those with viral infections, including HSV, usually have normal WBC. Leukopenia, neutropenia, and elevated I/T ratio were associated with increased odds of infection, with high specificity and negative predictive value and low sensitivity.[43]

Generally, a urine culture is not needed for neonates suspected of EOS since most urinary tract infections in neonates are secondary to seeding of bacteria in the kidney. However, urine culture is routinely performed in neonates suspected with LOS. Specimens should be obtained only by suprapubic aspiration or urethral catheterization since there is a higher risk of bacterial contamination with bag urine specimens and neonates are unable to provide a clean catch urine. A LP should be performed in neonates with a positive blood culture, abnormal neurologic signs, or elevated WBC or left shift. CSF cultures may be falsely negative in those who are receiving antibiotic therapy prior to an LP. Therefore, it is important to not only send CSF fluid for culture but for cell counts with differential, glucose, and protein concentrations. Although a CSF WBC count < 20 cells/mm^3 (0.02 x 10^9/L) is considered normal in most infants, the levels are age-dependent, with the highest levels occurring in the first week of life.

C-reactive protein (CRP) and procalcitonin (PCT) are commonly evaluated acute-phase reactants in the diagnosis of neonatal sepsis. A CRP concentration of greater than 10 mcg/mL (mg/L) is frequently used as a cut-off for normal. CRP concentrations rise within 6 to 8 hours and peak at 36 to 48 hours. Due to the delayed response, CRP may not be useful for detection of EOS. It has a sensitivity of 30% to 80% and a specificity of 83% to 100% as a marker for bacterial infection.[43] Two or more normal CRP concentrations indicate that sepsis is unlikely and antibiotic therapy can be discontinued.[38,43] In contrast, elevated CRP concentrations do not always indicate bacterial infection since other clinical conditions such as chorioamnionitis, meconium aspiration syndrome, surfactant administration, viral infection, hemolysis, and ischemic tissue injuries can result in elevated CRP concentrations.[43] Therefore, serial CRP concentrations may be used to assess clinical improvement and guide duration of antibiotic therapy. Assays for CRP measurement are reliable, rapid, and inexpensive. CRP is most commonly evaluated in the diagnosis of neonatal sepsis, mainly because it is more studied for neonatal sepsis and reference ranges for neonates are established.

Procalcitonin, a precursor protein of calcitonin, is another acute-phase reactant protein that may be more useful for early detection of sepsis since it is released (3-4 hours) and peaks (6-24 hours) earlier than CRP in the presence of bacteria. It has a sensitivity of 92% and specificity of 97% for early diagnosis of EOS.[43] However, its use may be limited due to the lack of age-specific reference ranges; although in most cases, the normal concentration for neonates >72 hours of age is usually <0.1 mcg/mL (mg/L). In addition, PCT plasma concentrations may be influenced by prematurity, intracranial hemorrhage, birth depression, chorioamnionitis, prolonged rupture of membranes ≥ 18 hours, surfactant administration, and pre- and postnatal use of antibiotics.[43] Furthermore, the methods used to measure PCT concentrations are costly.

Because laboratory markers and clinical signs and symptoms are nonspecific in neonates, the Kaiser neonatal sepsis calculator was developed.[44] This calculator is used to assess the need for antibiotic therapy and laboratory monitoring for EOS in infants ≥ 34 weeks' gestation based on maternal risk factors as well as the infant's clinical examination. Use of the neonatal sepsis calculator reduces antibiotic use and hospitalization as well as the need

for blood culture evaluation; however, there is no difference in mortality, culture-positive EOS, and hospital readmissions.[45] This tool is not validated for use in preterm infants < 34 weeks' gestation and does not guide the duration of antibiotic therapy for EOS.

Treatment

Empiric Antibiotic Therapy for EOS

4 Empiric antibiotics should be initiated in infants with suspected sepsis once a blood culture is obtained and should target the most common pathogens. Delaying antibiotic initiation may result in high morbidity and mortality. The combination of ampicillin and an aminoglycoside (eg, gentamicin, tobramycin) is commonly initiated for EOS.[35] This combination covers *E. coli* and has synergistic activity against GBS and *L. monocytogenes*. In addition, these antibiotics are bactericidal against the common neonatal pathogens, penetrate into the CNS, and are generally effective and safe. Meningitic doses of ampicillin, which are higher than those used for other infections, should be used until meningitis is ruled out. Selection of a specific aminoglycoside should be determined by a NICU-specific antibiogram. Amikacin is generally reserved for gram-negative organisms resistant to gentamicin or tobramycin. When dosing aminoglycosides, it is important to select a dosing regimen that is safe and achieves therapeutic serum concentrations, with peak concentrations at least 8 to 10 times greater than the minimum inhibitory concentration (MIC) of the organism being treated and low trough concentrations (< 1 mcg/mL [mg/L]).

Traditional dosing of aminoglycosides was 2.5 mg/kg/dose every 8 hours. However, this dosing strategy resulted in subtherapeutic peak and supratherapeutic trough concentrations especially in preterm infants due to a higher volume of distribution and slower renal elimination of aminoglycosides, respectively. Most institutions utilize extended-interval dosing (EID) of aminoglycosides in neonates, where higher mg/kg doses (eg, 4-5 mg/kg/dose) are given at prolonged dosing intervals (eg, every 24, 36, or 48 hours, depending on PMA). EID of gentamicin achieves more therapeutic peak and trough concentrations without increasing nephrotoxicity and auditory toxicity compared with multiple daily dosing in both term and preterm neonates.[46,47] The rationale for EID dosing is to enhance bacterial killing by providing higher peak serum concentration to MIC ratio and minimizing postexposure microbial resistance by achieving a drug-free period at the end of the dosing interval.[46] For EID of aminoglycosides in neonates, peak concentrations are usually between 8 and 12 mcg/mL (mg/L) while trough concentrations are usually low but detectable. Routine peak and trough concentrations are needed for neonates as there is no nomogram available to guide dosing adjustment. EID of aminoglycosides in neonates should not be confused with EID of aminoglycosides in adults which involves different dosing frequency and concentration targets.

Cefotaxime, a third-generation cephalosporin, may be added or used in place of gentamicin in infants suspected with gram-negative meningitis due to its greater CNS penetration compared with aminoglycosides. Other advantages of cefotaxime are that it is less nephrotoxic and does not require serum concentration measurements. However, its use has been associated with the development of resistant gram-negative bacilli such as *Enterobacter cloacae* and increased risks for invasive candidiasis, NEC, and death.[42] Therefore, cefotaxime should be reserved for neonates with suspected meningitis or those with aminoglycoside-resistant gram-negative bacilli; for those where serum gentamicin concentrations are not available at their institutions; and for those with impaired kidney function. Ceftriaxone, a highly protein-bound antibiotic, should not be used in neonates due to its risk of kernicterus secondary to displacement of bilirubin from albumin. Furthermore, biliary sludging may occur in neonates receiving ceftriaxone. In addition, concomitant ceftriaxone and calcium infusions may result in neonatal death. Calcium-ceftriaxone precipitates have been found in the lungs and kidneys of infants given calcium-containing products and ceftriaxone within 48 hours from each other.[48]

Due to the shortage of cefotaxime, ceftazidime has been used as an alternative as it offers the same coverage and is approved by the Food and Drug Administration for all pediatric patients. Ceftazidime achieves therapeutic concentrations in all tissues, including the CSF. Unlike cefotaxime, ceftazidime has not been used extensively in neonates; therefore, neonates should be closely monitored for efficacy and toxicity. Furthermore, it is important to monitor for potential bacterial resistance, as well as other potential risks such as invasive candidiasis, NEC, and death, all of which have been associated with cefotaxime in neonates.

Empiric Antibiotic Therapy for LOS

Initial empiric antibiotic therapy for LOS or meningitis should be directed toward common nosocomial pathogens as well as the primary pathogens for EOS. For many years, empiric antibiotic therapy included a combination of gentamicin and vancomycin since CONS is the most common causative organism. However, due to an increased emergence of vancomycin-resistant *Enterococcus* and *S. aureus*, the Centers for Disease Control and Prevention have recommended against using vancomycin empirically. Vancomycin should be used selectively in infants with proven CONS or

methicillin-resistant *S. aureus* (MRSA) bacteremia. Institutional NICU guidelines should be implemented to guide selective use of vancomycin based on individual NICU's nosocomial pathogens and susceptibility patterns as well as patient risk factors, clinical condition, and previous antibiotic usage. Many neonatal centers are now using nafcillin or oxacillin in place of vancomycin to decrease vancomycin use and decrease vancomycin-resistant organisms. Patients with suspected HSV infection should be initiated with IV acyclovir. Treatment with IV acyclovir decreases mortality and morbidity in infants with CNS and disseminated disease. In those with skin, eye, and oral mucosal disease, IV acyclovir may also prevent progression to disseminated or CNS disease.[39] Antimicrobial dosing regimens for EOS and LOS are given in Tables e22-2 and e22-3.

TABLE e22-2

Antimicrobial Dosage Regimens for Neonates

	Chronologic Age ≤ 28 days				Chronologic Age > 28 days
	Dosage expressed in mg/kg/dose				
	Weight ≤ 2,000 g		Weight > 2,000 g		All Weights
Medication	**PNA 0-7 days[a]**	**PNA 8-28 days[a]**	**PNA 0-7 days[a]**	**PNA 8-28 days[a]**	**PNA 29-60 days[a]**
Antibiotics					
Ampicillin	50 Q 12 hr	75 Q 12 hr	50 Q 8 hr	50 Q 8 hr	50 Q 6 hr
Ampicillin *(GBS meningitis)*	100 Q 8 hr	75 Q 6 hr	100 Q 8 hr	75 Q 6 hr	75 Q 6 hr
Cefazolin	25 Q 12 hr	25 Q 12 hr	25 Q 8 hr	25 Q 8 hr	25 Q 8 hr
Cefepime	30 Q 12 hr	30 Q 12 hr	50 Q 12 hr	50 Q 12 hr	50 Q 8 hr
Cefotaxime	50 Q 12 hr	50 Q 8 hr	50 Q 12 hr	37.5 Q 6 hr	50 Q 6 hr
Ceftazidime	50 Q 12 hr	50 Q 8 hr	50 Q 12 hr	50 Q 8 hr	50 Q 8 hr
Clindamycin	5 Q 8 hr	5 Q 8 hr	7 Q 8 hr	9 Q 8 hr	10 Q 8 hr
Meropenem[b]	20 Q 12 hr	20 Q 8 hr	20 Q 8 hr	30 Q 8 hr[c]	30 Q 8 hr
Metronidazole	7.5 Q 12 hr	7.5 Q 12 hr	7.5 Q 8 hr	10 Q 8 hr	10 Q 8 hr
Nafcillin/Oxacillin	25 Q 12 hr	25 Q 8 hr	25 Q 8 hr	25 Q 6 hr	37.5 Q 6 hr
Penicillin G *(GBS meningitis)*	150,000 Units	125,000 Units	150,000 Units	125,000 Units	125,000 Units
	Q 8 hr	Q 6 hr	Q 8 hr	Q 6 hr	Q 6 hr
Penicillin G *(Congenital syphilis)*	50,000 Units	50,000 Units	50,000 Units	50,000 Units	50,000 Units
	Q 12 hr	Q 8 hr	Q 12 hr	Q 8 hr	Q 6 hr
Piperacillin/Tazobactam	100 Q8 hr	80 Q 6 hr[d]	80 Q 6 hr	80 Q 6 hr	80 Q 6 hr

Vancomycin	15 Q 12-18 hr	15 Q 8-12 hr	15 Q 8-12 hr	15 Q 6-8 hr	15 Q 6-8 hr
Antiviral					
Acyclovir	20 Q 12 hr	20 Q 8 hr	20 Q 8 hr	20 Q 8 hr	20 Q 8 hr
Antifungals					
Amphotericin B Deoxycholate	1 Q 24 hr	1 Q 24 hr	1 Q 24 hr	1 Q 24 hr	1 Q 24 hr
Liposomal/Lipid Complex Amphotericin B	5 Q 24 hr	5 Q 24 hr	5 Q 24 hr	5 Q 24 hr	5 Q 24 hr
Fluconazole[e]	12 Q 24 hr	12 Q 24 hr	12 Q 24 hr	12 Q 24 hr	12 Q 24 hr

Data from References 49,50.

[a]PNA (postnatal age).

[b]Higher dosage may be required for meningitis.

[c]Adjust dosage after 14 days of age instead of 7 days of age.

[d]When postmenstrual age reaches 30 weeks.

[e]Load with 25 mg/kg/dose followed maintenance dose 24 hr later; adjust for renal dosing if serum creatinine ≥ 1.3 mg/dL (115 µmol/L).

TABLE e22-3

Extended-Interval Dosing of Gentamicin for Neonates

Gestational Age (Weeks)	Postnatal Age (Days)	Dosing Regimen[a]
<30	≤14	5 mg/kg/dose Q 48 hr
	≥15	5 mg/kg/dose Q 36 hr
30-34	≤10	5 mg/kg/dose Q 36 hr
	≥11	5 mg/kg/dose Q 24 hr
≥35	≤7	4 mg/kg/dose Q 24 hr
	≥8	5 mg/kg/dose Q 24 hr

Data from References 49-51.

[a]Some institutions empirically adjust dosing interval based on clinical factors that may affect renal medication clearance (eg, birth depression, hypotension requiring vasopressor support, congenital heart defects resulting in decreased peripheral perfusion).

Based on Infectious Diseases Society of America guidelines, NICUs with high rates (> 10%) of invasive candidiasis should provide prophylactic fluconazole, given orally or intravenously, at a dose of 3 to 6 mg/kg/dose twice weekly for 6 weeks to all ELBW infants.[52] If fluconazole is not available or if there are concerns for resistance, oral nystatin at a dose of 100,000 units three times a day for 6 weeks can be used as an alternative in VLBW infants. Prophylactic fluconazole decreases invasive candidiasis, fungal colonization rate, and mortality in ELBW and VLBW infants. In addition, short-term use of prophylactic fluconazole does not result in the development of fungal resistance or significant adverse medication reactions.[40] Despite the benefits of prophylactic fluconazole, there is also a concern for the potential development of resistant pathogens as well as the adverse medication reactions of long-term use of fluconazole. Infants should be monitored for potential short- and long-term adverse medication reactions associated with fluconazole.

For systemic neonatal fungal infections, conventional amphotericin B deoxycholate is considered the empiric treatment of choice. Fluconazole may be considered as initial treatment in infants who have not received prophylactic fluconazole.[42] Liposomal amphotericin B may also be used as an alternative but not for the treatment of urinary tract infections due to its inadequate penetration in the kidneys. There is an increased rate of mortality associated with liposomal amphotericin treatment when compared to conventional amphotericin B or fluconazole.[53] Therefore, conventional amphotericin B and fluconazole remain the medications of choice for empiric therapy.

For both EOS and LOS, once a pathogen is isolated and antimicrobial susceptibilities are available, antibiotic therapy should be tailored accordingly. Blood, CSF, and/or urine cultures should be repeated after 24 to 48 hours of appropriate therapy to ensure bacterial elimination.

Duration of Therapy

Treatment duration for culture-proven sepsis varies from 10 to 14 days. For those with meningitis, the duration of therapy varies depending on the organisms. For gram-positive pathogens, infants should receive at least 14 days of therapy and 21 days for gram-negative pathogens. In general, antibiotic therapy should be continued for a minimum of 14 days after the repeat CSF culture is negative. Infants with abscesses, osteomyelitis, or endocarditis may require longer durations of therapy. Oftentimes, clinicians opt to continue antibiotic therapy up to 7 to 10 days in infants with culture-negative sepsis who is clinically septic or who may have abnormal laboratory tests. Cardiorespiratory instability in VLBW infants is common and should not justify the need for prolonged antibiotic therapy. Unnecessary and prolonged antibiotic therapy can lead to long-term complications. VLBW neonates exposed to prolonged antibiotic therapy within the 14 days of life are at an increased risk of the compositive outcome of LOS, NEC, or death.[54] This may be because antibiotic therapy may promote dysbiosis of the gut, skin, and respiratory tract. Therefore, for those with negative cultures, antibiotic therapy should be discontinued by 36 to 48 hours.[35] Furthermore, abnormal laboratory tests should not be used solely to continue antibiotic therapy.[35] Clinicians should weigh the risk/benefit of continuing antibiotic therapy in those with culture-negative sepsis and discontinue therapy as soon as the patients are clinically improving, and laboratory markers are returning to normal.

Therapeutic Drug Monitoring

Aminoglycosides exert a concentration-dependent killing effect and may cause nephrotoxicity and ototoxicity. Therefore, therapeutic drug monitoring (TDM) is important to maximize efficacy while reducing toxicity. Most infants with suspected sepsis will be treated with gentamicin for 48 hours and, therefore, TDM of gentamicin is not necessary, especially if EID is utilized. However, if treatment is beyond 72 hours, gentamicin peak and trough concentrations should be obtained at steady-state conditions, prior to the second (if receiving every 36- to 48-hour dosing) or third (if receiving every 24 hour dosing) dose. In those with unstable kidney function, gentamicin concentrations should be obtained immediately, regardless of the number of doses administered. Serum trough concentrations should be obtained at least 30 minutes or immediately before the dose; serum peak concentrations should be obtained at least 30 to 60 minutes after the end of a 30-minute infusion. Therapeutic peak concentrations of 8 to 10 mcg/mL (mg/L; 16.7-20.9 µmol/L) (for MIC ≤ 1) are generally targeted with trough concentrations < 1 mcg/mL (mg/L; 2.1 µmol/L). Similar to gentamicin, vancomycin can also cause nephrotoxicity but exert a time-dependent killing. Therapeutic monitoring of vancomycin is warranted if treatment is beyond 48 hours. Due to increased risk of nephrotoxicity associated with vancomycin trough concentrations of 15 to 20 mcg/mL (mg/L; 10.4-13.8 µmol/L), trough-only monitoring is no longer recommended in adult patients with serious infections (eg, bacteremia, endocarditis, osteomyelitis, meningitis, and pneumonia due to MRSA). An AUC/MIC of 400 to 600 mg·L/hr (MIC ≤ 1) is now recommended, as this achieves clinical efficacy while reducing nephrotoxicity in adult and pediatric patients, including neonates.[55] For pediatric and neonates, vancomycin exposure should be maintained below an AUC of 800 mg·L/hr and trough concentrations ≤ 15 mcg/mL (mg/L; 10.4 µmol/L)(at least 30 minutes or immediately before the third or fourth dose) to minimize the risk for nephrotoxicity. Monitoring of peak vancomycin concentrations is not recommended. Obtaining targeted vancomycin trough

concentrations in neonates remains controversial. Vancomycin trough concentrations as low as 7 mcg/mL (mg/L; 4.8 µmol/L) can still achieve targeted AUC/MIC ≥400 mg·L/hr in neonates due to slower clearance.[55]

CONGENITAL HEART DEFECTS

Nearly 1% of all babies born in the United States each year have a congenital heart defect (CHD). These defects have a wide range of severity and are generally classified as cyanotic or acyanotic. They can also be classified as critical (ie, requiring surgery within the first year after birth) or noncritical. About 25% of CHDs are considered critical. Most children with noncritical CHD survive into adulthood, but only about 69% of those with critical CHD survive. More than half of the survivors of critical CHD will have developmental disabilities or delays.[56,57]

Acyanotic Heart Defects

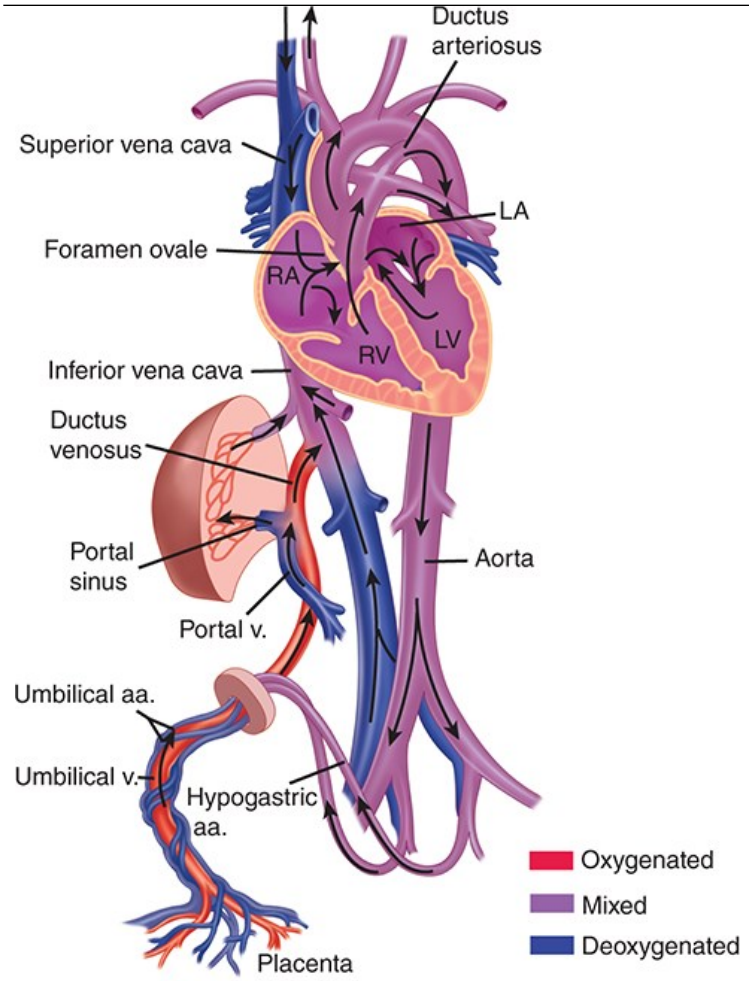
Most acyanotic CHDs (eg, atrial septal defect, ventricular septal defect) do not require pharmacologic treatment in the immediate postnatal period. Depending on the size of the defect, some infants eventually will require treatment for heart failure symptoms, most commonly with diuretics, angiotensin-converting enzyme inhibitors, and digoxin, before surgical closure of the defect.[57] However, PDA is an acyanotic defect that frequently requires pharmacologic management in the NICU.

Patent Ductus Arteriosus

5 The ductus arteriosus is an essential fetal vessel that connects the pulmonary artery and descending aorta allowing oxygenated blood from the placental circulation to enter the fetal systemic circulation (Figure e22-1). In the fetus, pulmonary vascular resistance (PVR) is elevated causing blood to flow from the pulmonary artery to the aorta (ie, right-to-left shunt). The fetal ductus arteriosus remains patent due in part to high circulating concentrations of prostaglandins. After a full-term birth, a large drop in prostaglandin concentration occurs, which results in functional closure of the ductus arteriosus by about 24 hours after birth. In preterm neonates, several factors including (1) incomplete prostaglandin metabolism, (2) increased sensitivity to prostaglandins, (3) lower ductal tone, and (4) decreased muscle fibers within the ductus arteriosus contribute to the vessel remaining patent.[58,59] Approximately half of neonates born younger than 29 weeks' gestation will have a PDA.[59]

FIGURE e22-1

In normal fetal circulation, gas exchange occurs in the placenta from which oxygenated blood travels through the umbilical vein to the inferior vena cava. After entering the right atrium, a large portion of the blood is shunted across the foramen ovale to the left atrium where it is subsequently pumped into the systemic circulation via the left ventricle and aorta. Blood that enters the right ventricle is pumped into the pulmonary artery from which a large volume is shunted across the ductus arteriosus to the aorta and systemic circulation. The fetal lungs do not play a role in oxygenating blood.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Neonates with a PDA may be asymptomatic or have hemodynamic alterations depending on the size of the ductal lumen and the degree and direction of blood shunting across the PDA. After birth, PVR decreases and systemic vascular resistance (SVR) increases. This can result in blood flow from the aorta to the pulmonary artery (ie, left-to-right shunt). If the PDA is hemodynamically significant, the left-to-right shunt can cause decreased kidney, intestinal, and cerebral perfusion. Complications associated with altered systemic blood flow because of a PDA include acute kidney injury (AKI), NEC, and IVH. Additionally, overcirculation of pulmonary blood flow can result in pulmonary edema, pulmonary hemorrhage, BPD, and right heart failure.[59]

Controversy exists about what the optimal timing for PDA closure is and whether or not all patients with a PDA require medical closure (ie, pharmacological or surgical). If pharmacologic closure is planned, the preferred agents are the cyclooxygenase inhibitors (ie, indomethacin or ibuprofen). Three pharmacologic approaches have been assessed: prophylaxis (administered within 24 hours of birth), early (administered within 6 days after birth), or late symptomatic (administered 6 days or later after birth) treatment. Prophylaxis reduces hemodynamically significant PDA, need for surgical ligation, and IVH (specifically if indomethacin is used) without increasing bleeding or spontaneous intestinal perforation. The use of prophylactic indomethacin may decrease urine output. Because this approach has not improved neurodevelopmental outcomes or reduced BPD and it exposes neonates who may have spontaneous ductal closure to potential adverse medication reactions, routine prophylaxis is no longer common practice. Early treatment does not reduce BPD and also may treat neonates who would otherwise have spontaneous closure of their PDA. This approach is only recommended for neonates born before 28 weeks' gestation with a significant left-to-right shunt who require more than minimal respiratory support. Conservative management with fluid restriction and "watchful waiting" is recommended for those without hemodynamic alterations, with late treatment recommended if the PDA becomes hemodynamically significant.[58,59]

There is also controversy about the medication of choice for PDA closure (indomethacin vs ibuprofen). Indomethacin and ibuprofen have similar efficacy in closing the PDA (~70%-80%), but their dosing regimens differ. Indomethacin dosing is based on PNA (Table e22-4). Indomethacin decreases

mesenteric blood flow to a greater degree than ibuprofen, so the risk of NEC and AKI is higher with indomethacin. However, more neonates exposed to ibuprofen develop BPD and, because ibuprofen is highly protein bound, the risk of kernicterus because of displacement of bilirubin from albumin binding sites in neonates with hyperbilirubinemia is a concern.[58,59] Because of its overall favorable safety profile, ibuprofen is often considered the medication of choice.[59]

TABLE e22-4

Medications Used for PDA Closure

Medication	Dosing Regimen	Monitoring Parameters
Indomethacin	• **IV, intermittent:** • PNA <48 hours: 0.1 mg/kg/dose Q 12-24 hours × 3 doses • PNA 2-7 days: 0.2 mg/kg/dose Q 12-24 hours × 3 doses • PNA >7 days: 0.25 mg/kg/dose Q 12-24 hours × 3 doses	• Urine output (hold dose if <0.6 mL/kg/hr), SCr (hold dose if >1.6 mg/dL [141 µmol/L]), platelets, signs of bleeding • BP, murmur, respiratory status, echocardiogram
Ibuprofen	• **IV, intermittent:** • "Standard-dose": 10 mg/kg/dose x 1 dose followed by 5 mg/kg/dose Q 24 hours × 2 doses • "High-dose": 20 mg/kg/dose × 1 dose followed by 10 mg/kg/dose Q 24 hours × 2 doses • *High-dose regimen found to have higher closure rates compared to standard-dose without more frequent adverse medication reactions	• Urine output (hold dose if <0.6 mL/kg/hr), serum creatinine, platelets, signs of bleeding • BP, murmur, respiratory status, echocardiogram
Acetaminophen	• **IV, intermittent:** • 15 mg/kg/dose Q 6 hours × 3-7 days	• Liver function tests • BP, murmur, respiratory status, echocardiogram

Data from Reference 49.

BP, blood pressure; IV, intravenous; PDA, patent ductus arteriosus; PNA, postnatal age; SCr, serum creatinine.

There has been interest in using acetaminophen for PDA closure. Acetaminophen has a different mechanism of action than indomethacin and ibuprofen; reducing prostaglandin concentrations by inhibiting the peroxidase component of prostaglandin synthase. While acetaminophen has minimal to no adverse medication reactions, it is less effective for PDA closure than indomethacin in preterm infants.[58,59] A number of questions still remain regarding the use of acetaminophen for PDA closure including an examination of long-term outcomes; therefore, if used in clinical practice, it is generally reserved for patients who have failed indomethacin or ibuprofen or who have contraindications to these agents (eg, thrombocytopenia, impaired kidney function, and bleeding).[58,59]

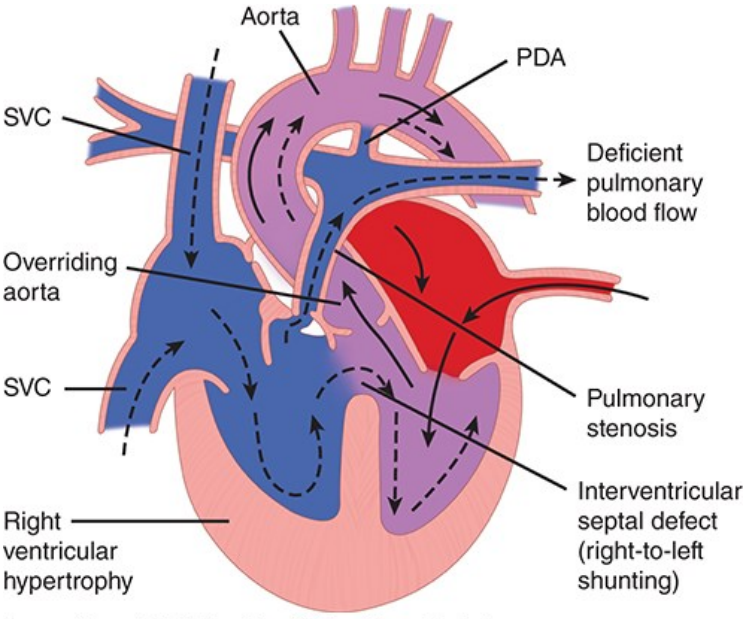
Cyanotic Heart Defects

6 The underlying physiology of cyanotic heart defects prevents blood from entering the pulmonary circulation to be oxygenated (eg, Tetralogy of Fallot; Figure e22-2), prevents oxygenated blood from entering the systemic circulation (eg, hypoplastic left heart syndrome; Figure e22-3), or both (eg, transposition of the great arteries; Figure e22-4). These defects can be diagnosed by prenatal ultrasound or, after a neonate remains cyanotic despite provision of 100% oxygen, by a postnatal echocardiogram. In these cases, interventions are required to maintain patency of the ductus arteriosus.[57] Prostaglandin E1 (ie, alprostadil) should be administered by continuous IV infusion at a dose of 0.05 to 0.1 mcg/kg/min. Oxygen saturation, peripheral perfusion, and ductal patency as seen on echocardiogram are monitored for efficacy. Apnea and fever are common adverse medication reactions.[57] Ultimately, these patients require complex surgical repairs to correct the underlying defect and restore adequate blood flow to the pulmonary and

systemic circulations.[57]

FIGURE e22-2

Tetralogy of Fallot is a cyanotic heart defect that consists of four anatomic abnormalities: ventricular septal defect (VSD), overriding aorta, pulmonary stenosis, and right ventricular hypertrophy. Pulmonary stenosis limits the amount of blood delivered to the lungs to be oxygenated; therefore, the patency of the ductus arteriosus is maintained by administration of prostaglandin E1 after birth. The patent ductus arteriosus allows some blood flow from the higher pressure systemic circulation (ie, aorta) to the lower pressure pulmonary circulation (ie, pulmonary artery) so that blood is delivered to the lungs to be oxygenated. Oxygenated blood returns from the lungs via the pulmonary veins to the left atrium and mixes in the left ventricle with deoxygenated blood that crossed the VSD before it is pumped to the systemic circulation. This defect requires surgical repair.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

FIGURE e22-3

Hypoplastic left heart syndrome is a cyanotic heart defect that consists of a left ventricle that is too small to support systemic circulation. Patency of the ductus arteriosus is maintained by administration of prostaglandin E1 after birth. The patent ductus arteriosus allows some blood flow from the pulmonary circulation (ie, pulmonary artery) to shunt into the aorta providing mixed oxygenated blood to the systemic circulation. This defect requires a complex, stepwise surgical repair.

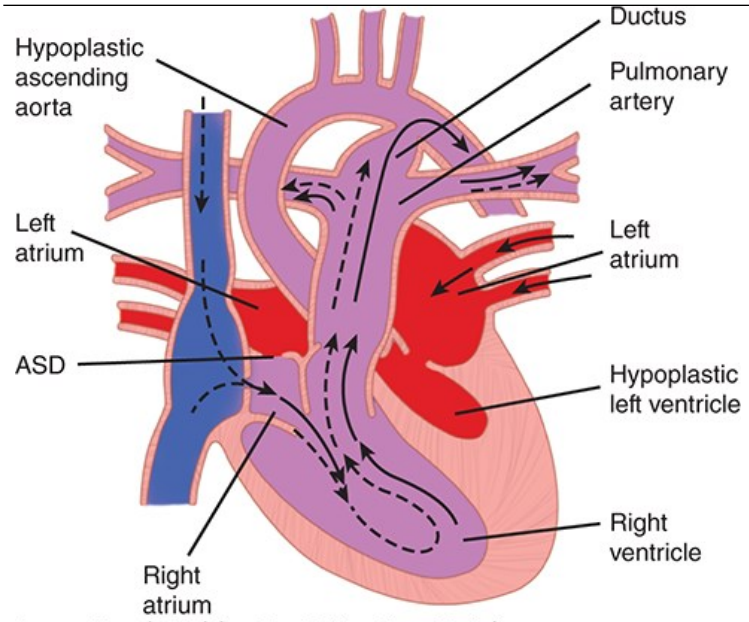
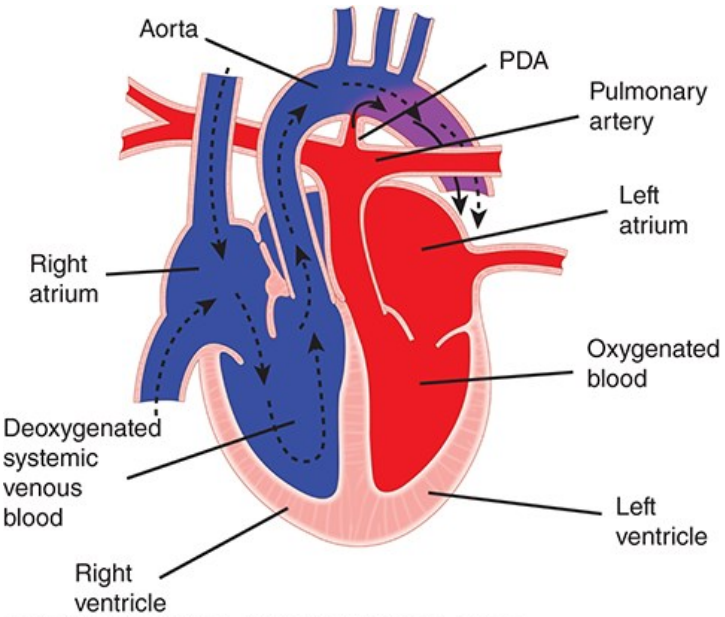


FIGURE e22-4

Transposition of the great arteries is a cyanotic heart defect that consists of malposition of the pulmonary artery and aorta resulting in parallel circuits of blood flow. Patency of the ductus arteriosus is maintained by administration of prostaglandin E1 after birth. Mixing of oxygenated and deoxygenated blood across the patent ductus arteriosus allows for some oxygen delivery to the systemic circulation. Emergent catheterization with balloon atrial septostomy to open the atrial septum and allow mixing of oxygenated and deoxygenated blood between the left and right atria is typically performed shortly after birth. Eventually, neonates with this defect require definitive surgical repair.



NEONATAL HYPOTENSION

Neonatal hypotension remains one of the most commonly encountered problems in NICU, especially in preterm infants. The prevalence is up to 50% in VLBW infants.[60] Neonatal hypotension is also associated with high morbidity and mortality. The biggest challenge with its management is that the normal physiological BP of neonates is unknown and differs by gestational and PNA. Therefore, definitions of hypotension in neonates used in clinical practice are variable. One definition of neonatal hypotension is any BP value that falls below the 5th or 10th percentile of population-based normative BP values. Using this definition, hypotension occurs in about 50% of infants.[61] Another definition of hypotension in VLBW infants is any systolic BP at which there is loss of autoregulation of organ blood flow that can cause tissue ischemia and organ damage.[62] The rationale for using this definition is that it allows clinicians to measure clinical indicators of hypotension rather than relying on numerical BP values. Most clinicians and researchers define neonatal hypotension as a mean arterial pressure (MAP) below the numerical value of the GA of the infant, as it is the easiest to use.[60] However, since BP increases with increasing PNA, this definition needs to be used with caution beyond the first several days of life. Since there is no clear consensus on the definition of neonatal hypotension, diagnosis and treatment are guided by clinical judgement and careful review of the physiological parameters of the infant.

Pathophysiology

The etiology of hemodynamic instability during the neonatal period is multifactorial. Assessment of clinical risk factors as well as physical examination can help identify the cause. BP is the product of cardiac output (CO) and SVR. Adequate organ perfusion is dependent on CO and SVR. CO is determined by HR and stroke volume (SV). Neonates often lack the ability to increase SV (in the face of low CO); therefore, they rely primarily on increased HR to compensate.

There are several causes of neonatal hypotension. Hypotension and low systemic blood flow can occur during the first days of life, due to delayed circulatory transition from intrauterine to extrauterine life; this effect is more prominent in preterm infants. In addition, the immature myocardium of preterm infants may impact their ability to adapt to the stress during circulatory transition, resulting in a decreased systemic BP in the first few days of life. By 48 hours of life, hypotension generally resolves due to increasing SVR and improved cardiac contractility.[63] Other causes of hypotension include PDA, chorioamnionitis, perinatal depression/asphyxia, immature hypothalamic-pituitary-adrenal (HPA) axis system/adrenal insufficiency, sepsis/septic shock, NEC, hypovolemia, and medications. A hemodynamically significant PDA in a VLBW infant can also cause systemic hypotension as well as decreased perfusion to the organs. Infants born to mothers with chorioamnionitis can have peripheral vasodilation and increased capillary permeability secondary to the release of cytokines, such as tumor necrosis factor and interleukin-1, as a response to inflammation.[64] Both peripheral vasodilation and increased capillary permeability can cause hypotension. Infants born with perinatal depression may also have hypotension due to myocardial dysfunction. Preterm infants have an immature HPA axis system, and although they can produce enough cortisol for growth and development, they are not able to produce adequate amounts in response to stress or illness.[65] Sepsis/septic shock and NEC, similar to chorioamnionitis, can also cause hypotension in both term and preterm infants. Although hypovolemia is not a common cause of hypotension in neonates, one should suspect this if the infant is pale with tachycardia and exhibits high blood loss.[63] Medications causing hypotension in neonates include opioids, benzodiazepines, dexmedetomidine, and exposure to maternal anesthesia.

Clinical Assessment

7 Appropriate treatment of neonatal hypotension is important since hypotension has been associated with impaired cerebral perfusion and ischemic damage. Because there is no clear consensus on the definition of neonatal hypotension, overall assessment of the infant's cardiovascular status should be used in addition to BP measurements. The gold standard for measuring BP is an intraarterial measurement using an umbilical arterial catheter or a peripheral arterial line. However, many clinicians have used noninvasive BP measurements as it is more readily available. Another controversy of BP measurement in neonates is whether the systolic or MAP measurement should be used. It remains unknown as to which BP measurement accurately correlates to long-term neurologic outcomes in these infants. Most clinicians will often set BP goals in an attempt to maintain adequate cerebral blood flow (CBF) and prevent ischemia (Table e22-5). Identifying maternal and neonatal factors associated with hypotension such as GA, the presence of chorioamnionitis or perinatal depression, or signs of blood loss is pertinent. Physical assessment indicative of hypotension may include tachycardia and prolonged capillary refill time. Capillary refill times of greater than 3 seconds may occur due to low CO. Tachycardia, with HR ≥ 160 bpm, is a compensatory mechanism for decreased CO. Other signs of inadequate perfusion include weak pulse, mottled skin, lethargy, metabolic

acidosis, and decreased urine output. Metabolic acidosis and decreased urine output can occur as a result of inadequate organ blood flow and perfusion. Decreased urine output in preterm infants may be helpful in assessing organ perfusion. However, because of the inability to concentrate urine effectively, infants may produce adequate urine output which could be mistaken for adequate kidney function and organ perfusion. Short- and long-term complications of neonatal hypotension include IVH, periventricular leukomalacia (PVL), neurodevelopmental disability, organ failure, and death.[62,66]

TABLE e22-5

Blood Pressure Thresholds at Third Percentile According to Gestational Age

Gestational Age (weeks)	Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)
24	32	15	26
25	34	16	26
26	36	17	27
27	38	17	27
28	40	18	28
29	41	19	28
30	43	20	29
31	45	20	30
32	46	21	30
33	46	22	30
34	48	23	31
35	49	24	32
36	50	25	32

Data from Reference 67.

Treatment

Management of neonatal hypotension should be focused on assessment as well as treatment of the suspected etiology rather than just numerical BP values. Preterm infants are usually treated for hypotension in the first 24 hours of life.[60] The goal is to preserve organ perfusion, especially CBF. Volume expansion is the first-line therapy of hypotension, regardless of the etiology. The administration of crystalloids (eg, 0.9% normal saline) can improve preload and decrease SVR.[60] Crystalloids are usually given at a dose of 10 to 20 mL/kg intravenously. No more than one fluid bolus should be administered unless there is evidence of fluid loss or hypovolemia, since excess fluid administration has been associated with increased morbidity (eg, PDA, NEC, chronic lung disease, abnormal neurodevelopmental outcomes) and mortality. Packed red blood cell transfusions can be administered to those with hemorrhage or anemia.

Pharmacologic Therapy

The decision to select one therapeutic agent over another for neonatal hypotension should be based on the patient-specific clinical assessment of the etiology of hypotension. Medications used to treat neonatal hypotension primarily act on three receptors: α- and β-adrenergic receptors and dopaminergic receptors. Medications that affect these receptors include dopamine, dobutamine, epinephrine, and norepinephrine. Because these medications are considered vesicants, they should be administered via a central venous catheter to minimize the possibility of extravasation; administration into an umbilical arterial catheter is not recommended. Other medications used to treat neonatal hypotension include hydrocortisone and vasopressin (Table e22-6).

TABLE e22-6

Pharmacologic Agents for Neonatal Hypotension

Medication	Site of Action	Physiological Effects	Dosing Range (mcg/kg/min)	Standard Concentrations
Dopamine	Dopaminergic	Renal and mesenteric vasodilation	1-4	• 1,600 mcg/mL • 3,200 mcg/mL • 6,000 mcg/mL
	β adrenergic	Inotrope	5-10	
	α adrenergic	Vasopressor, increased SVR and PVR	11 - 20	
Dobutamine	β_1 and β_2 adrenergic	Inotrope, decreased SVR, increased CO	5-20	• 1,000 mcg/mL • 2,000 mcg/mL • 4,000 mcg/mL • 5,000 mcg/mL
Epinephrine	$\beta_1 > \beta_2$ adrenergic	Inotrope, decreased SVR	0.05-0.1	• 16 mcg/mL • 32 mcg/mL • 64 mcg/mL
	α_1 adrenergic	Vasopressor, increased SVR	0.1-2.5	
Norepinephrine	α_1 and α_2 adrenergic	Vasopressor, increased SVR	0.05-2	• 4 mcg/mL • 16 mcg/mL
Hydrocortisone	Increased sensitivity to catecholamines	Stimulates endogenous cortisol	1-3 mg/kg/day in 3 divided doses IV × 2-5 days	• 1 mg/mL • 5 mg/mL
Vasopressin	$V_1 > V_2$ receptors	Increased SVR,no inotropic effect	0.0002-0.02 unit/kg/min	• 0.04 unit/mL • 0.1 unit/mL • 1 unit/mL

Data from References 49,68.

SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; CO, cardiac output; IV, intravenous.

Dopamine

Dopamine is the most commonly used medication for the treatment of neonatal hypotension and is considered first-line vasoactive agent, especially in preterm infants. However, more than 30% of preterm infants with systemic hypotension fail to respond to dopamine. Preterm infants (< 28 weeks' gestation) who receive normal saline alone require more adjunctive inotropic support compared to those who receive normal saline and dopamine. However, there are no differences in rates of mortality, IVH, PVL, and NEC.[60] Furthermore, when comparing dopamine to dobutamine, colloids, and hydrocortisone, dopamine is considerably more effective in increasing BP in preterm infants whereas dobutamine is more effective in increasing left ventricular output and CO.[69] Dopamine also increases CBF, with its effects more pronounced in hypotensive than in normotensive preterm infants. There is no difference in the incidence of tachycardia, IVH, PVL, or mortality between dopamine and dobutamine.[69] Furthermore, there are no differences in adverse neurologic outcomes between dopamine, dobutamine, epinephrine, colloids, or hydrocortisone.[69] In contrast, dopamine or dobutamine use during the first 72 hours of life in preterm infants ≤ 29 weeks' gestation increases risk of the composite of death and/or severe brain injury, severe IVH, and PVL.[70] The initial dopamine dose for treating neonatal hypotension is 5 to 7.5 mcg/kg/min (range, 2-20 mcg/kg/min), titrated gradually by 2.5 to 5 mcg/kg/min increments until optimal BP is obtained.

Dobutamine

Dobutamine's effects on BP are not as prominent as those seen with dopamine; therefore, it is generally used as third- or fourth-line agent for hypotension.[69] However, many institutions use dobutamine as a second-line agent after maximum dose of dopamine has been reached. Furthermore, because of its pure β effects, dobutamine is the inotrope of choice for infants with myocardial dysfunction since it increases SV by increasing contractility. Tolerance due to down-regulation of β receptors can be seen after 48 to 72 hours of infusion. Effective dobutamine doses range from 5 to 20 mcg/kg/min. If tachycardia occurs, reducing the dose will usually alleviate the adverse medication reactions.

Epinephrine

Epinephrine is a strong positive inotrope and increases myocardial blood flow at lower doses (0.03-0.1 mcg/kg/min). Similar to dopamine, higher doses (> 0.1 mcg/kg/min) of epinephrine have α receptor effects and can cause peripheral vasoconstriction. In children with septic shock, epinephrine or norepinephrine is the vasopressor agent of choice for the treatment of hypotension.[71] However, in neonates, epinephrine is typically used as a second- or third-line agent in the treatment of hypotension due to its risk of tachycardia and arrhythmias. As doses escalate (>0.5 mcg/kg/min), vasoconstriction can become more intense and can result in severe tachycardia, decreased blood perfusion to the kidneys and gastrointestinal (GI) tract, and increased oxygen consumption. When comparing dopamine (2.5-10 mcg/kg/min) to epinephrine (0.125-0.5 mcg/kg/min) in preterm infants with hypotension, there is no difference in BP measurements. However, there are greater increases in HR, lactate concentrations, and glucose concentrations requiring insulin therapy in patients treated with epinephrine.[60,69] Additionally, CBF increases dramatically in the lower GA (< 28 weeks) with epinephrine compared to increases with dopamine among higher GA (28-32 weeks). Epinephrine infusions are typically initiated at 0.05 to 0.1 mcg/kg/min; usual effective doses range from 0.5 to 4 mcg/kg/min. Generally, 0.1 mcg/kg/min of epinephrine is equivalent to about 10 mcg/kg/min of dopamine.[68]

Norepinephrine

Norepinephrine, similar to epinephrine, stimulates both α- and β- receptors, thereby increasing both SVR and CO. However, it has less β_2 activity and can cause more potent peripheral vasoconstriction as well as positive inotropic effects. Similar to epinephrine, norepinephrine may be used as first-line vasopressor agent for the treatment of hypotension in children with septic shock.[71] However, its use for treating hypotension in neonates is limited. Norepinephrine increases BP and urine output and decreases plasma lactate concentrations when used in term and preterm infants with septic shock refractory to IV fluid boluses, high doses of dopamine and dobutamine, and hydrocortisone.[68] Infants with persistent pulmonary hypertension of the newborn (PPHN) often have increased PVR, low systemic pressure, low CO, and myocardial dysfunction. Norepinephrine also causes reductions in the pulmonary to systemic pressure ratio and an increase in systemic BP, left ventricular output, and urine output without changes in HR when used in infants with PPHN.[68] Tachycardia is the most frequent adverse medication reaction, occurring in 31% of infants. The mortality rate is high, up to 46%, and higher in infants with a younger GA. Norepinephrine may be considered as rescue therapy for infants with septic shock refractory to other inotropes. Furthermore, norepinephrine may have a role in infants with PPHN and circulatory failure because it increases

both systemic and pulmonary artery pressure, thereby improving lung function. In addition, norepinephrine may be added when epinephrine doses exceed 0.1 to 0.2 mcg/kg/min, as it allows for de-escalation of epinephrine and hence, less hyperglycemia and tachycardia.

Hydrocortisone

Preterm infants commonly have relative adrenal insufficiency, which can result in hypotension refractory to vasopressor medications. Hydrocortisone has become widely used and is effective in the treatment of refractory hypotension in neonates. However, due to the lack of safety data as well as the potential risk of cerebral palsy, hydrocortisone is generally not recommended for routine use for hypotension.[72] Other controversial issues regarding the use of hydrocortisone include optimal dosing regimens and duration of therapy. Doses ranging from 20 to 100 mg/m^2/day (in 3-4 divided doses) have been suggested, which is 2 to 6 times the physiologic dose. Others have used a dose of 1 mg/kg/dose every 8 hours, which is the dose to simulate endogenous physiologic secretion of cortisol.[73] Low-dose steroids (1-3 mg/kg/day) are as effective in increasing BP as high doses (> 3 mg/kg/day), while high and prolonged duration of glucocorticoid exposure can result in adverse medication reactions, including neurodevelopmental impairment and oliguria.[73,74] Infants with volume-resistant hypotension, undergoing therapeutic hypothermia who receive low-dose hydrocortisone (0.5 mg/kg/dose every 6 hr) plus dopamine more often achieve targeted MAP compared to those who receive dopamine alone.[75] Additionally, the duration of cardiovascular support and cumulative and peak inotrope dosage are much lower in patients receiving hydrocortisone. Serum cortisol levels are low in patients receiving hydrocortisone plus dopamine or dopamine alone.[75] Some clinicians measure cortisol concentrations prior to hydrocortisone administration to determine adrenal insufficiency. Although cortisol concentrations do not correlate with GA, BW, or response to hydrocortisone therapy, infants who are not cortisol deficient have less improvement in BP measurements, more hyperglycemia, and increased death, independent of the hydrocortisone dose.[74] Therefore, hydrocortisone therapy should be avoided in infants who are not cortisol deficient due to these increased risks, independent of hydrocortisone dose, GA, or BW.

Upon initiation of hydrocortisone in infants with vasopressor-resistant hypotension, clinicians need to find a balance between optimal dosing and duration and potential adverse medication reactions. One recommendation is to give a single dose of hydrocortisone and determine if there is a response. If there is no response within 2 to 4 hours, further dosing is not recommended. However, if BP improves, subsequent doses of 0.5 mg/kg/dose every 12 hours for <34 weeks GA and every 8 hours for >34 weeks GA are recommended.[73] Based on cardiovascular status of the infant, the dose and timing of subsequent administrations can be modified. Other common dosing regimens include hydrocortisone 1 mg/kg/dose every 8 hours. Hydrocortisone can be slowly discontinued once an infant is either weaned off vasopressors completely or when vasopressors doses have been decreased. Infants should be monitored for signs of adrenal insufficiency, such as hypotension, hyponatremia, or decreased urine output. Hydrocortisone therapy should be restarted at the lowest dose if symptoms reoccur.

Vasopressin

In patients with septic shock, the body is not able to produce large amounts of endogenous vasopressin, which can lead to hypotension commonly seen in those with uncompensated septic shock. Vasopressin is effective in increasing BP and urine output and decreases the need for catecholamines without ischemic adverse effects.[76] Vasopressin is equally as effective as dopamine in increasing BP in ELBW infants with hypotension during the first 24 hours of life.[69,76] Infants treated with vasopressin require fewer surfactant doses, have lower $PaCO_2$ values, and exhibit less tachycardia compared to infants treated with dopamine. Furthermore, there are no differences in serum sodium or lactate concentrations or the number of infants with hyponatremia, before and during vasopressin administration. Additionally, low dose vasopressin (0.0003 units/kg/min) is associated with improvements in BP and reduction in oxygenation index, lactic acidosis, and inotropic support in infants with PPHN and catecholamine refractory shock.[77] Vasopressin administration is not associated with infants developing NEC.[76,77] While vasopressin may be considered as rescue therapy when high-dose catecholamines and steroids fail to increase BP in infants with refractory hypotension, its role as first-line treatment of neonatal hypotension is unclear at this time. Potential adverse medication reactions of vasopressin are hyponatremia and poor end organ perfusion; however, it is difficult to assess if the poor end organ perfusion is due to vasopressin or a clinical manifestation of septic shock or refractory hypotension. The initial vasopressin dose is 0.0002 to 0.0003 units/kg/min; doses as high as 0.02 units/kg/min have been used.[77] A common error with vasopressin is the dosing units as vasopressin can be prescribed as “units/kg/*min*” vs “units/kg/*hr*” vs “*milliunits*/kg/min” depending on the indication for use. Caution should be used when prescribing and preparing vasopressin for neonates.

Administration Challenges

One of the challenges with dosing and administering inotropes in preterm infants is the low infusion rates needed for continuous IV medications. Oftentimes, the flow rates of these medications can be as low as 0.1 to 0.2 mL/hr. These low infusion rates, as well as the dead space volumes of the IV catheter and connection, can lead to longer times to reach onset and steady state. This can result in variable and unpredictable doses delivered to the infant especially after a change in dosing. Factors that may influence flow rate variability when medications are infused at low rates include volume of the IV administration set, presence of valves or inline filters, and hydrostatic pressure changes.[78] Therefore, it is important to recognize these factors when prescribing medications with narrow therapeutic indices especially when infusion rates are low and to monitor for clinical efficacy and potential adverse medication reactions. In 2008, the American Society of Health-System Pharmacists (ASHP) recommended the development and implementation of national standardized concentration of IV medications, known as the *Standardize 4 Safety*, to reduce medication errors (administration and preparation) and improve transition of care.[79] Patients at greatest risk for these errors are often the most vulnerable populations, including neonates. When implementing standard concentrations of IV medications, it is important to select concentrations that allow for appropriate infusion rates.

MANAGEMENT OF PAIN AND SEDATION

Historically, it was believed that neonates especially those born prematurely were unable to perceive pain. Although it is now widely known that this belief was incorrect, NICU patients routinely undergo multiple painful procedures without analgesic therapy being provided.[80–82] Failure to provide sufficient analgesia may occur for various reasons including inadequate pain assessment and fear of adverse medication reactions. The consequences of untreated pain can be significant including altered and exaggerated responses to painful and nonpainful stimuli, physiological instability, abnormal brain development, and altered neurodevelopment.[82]

In the NICU, two types of pain typically are encountered: (1) acute pain which is associated with surgeries or procedures (eg, heel-stick for blood collection, endotracheal intubation) and (2) prolonged pain which is caused by disease (eg, NEC) or some interventions (eg, mechanical ventilation, chest tubes).[83,84] Environmental factors (eg, temperature, soiled diaper, positioning) may also contribute to discomfort. These should be addressed and noxious stimuli should be removed before a pharmacological intervention is employed to manage pain or agitation.[83]

Assessment of Pain and Agitation

9 Self-reporting is the standard method used to assess comfort in most patient populations, but is not plausible in the preverbal neonatal population.[80,81] Therefore, clinicians caring for neonates must rely on physiological (eg, HR change) and behavioral (eg, facial grimace, crying) parameters to evaluate the degree of pain and sedation.[82,83] These observations can be subjective and biased by perceptions and beliefs of healthcare providers. Additionally, the presence of a pain response and its magnitude may be affected by GA, PNA, illness severity, and neurological impairment which further complicates assessment.[82,84] The use of pain assessment scales is recommended to better standardize this practice.[82,83] Many tools have been developed in an attempt to better assess pain in neonates; however, most have not been validated using psychometric testing.[82,83] Furthermore, most of these tools have only been validated for procedural (ie acute) pain not prolonged pain.[84] Some tools utilize both physiological and behavioral parameters while others only consider behavioral variables.[80,82] The tools have also been validated in varying gestational and PNA ranges.[82] These factors make it unlikely that one pain assessment tool will be appropriate for use in all NICU patients.[80] Some of the most commonly used tools, which are generally known by acronyms, are described in Table e22-7. Regardless of the tool used, assessment should be repeated after each intervention to determine its effectiveness in relieving pain.

TABLE e22-7

Commonly Used Neonatal Pain Assessment Tools

Tool Name	Type(s) of Pain Assessed	Population	Parameters Included
PIPP (Premature Infant Pain Profile)	Acute	28-40 week GA	• GA • Behavioral state

			• HR increase • O_2 saturation decrease • Brow bulge • Eye squeeze • Nasolabial furrow
NIPS (Neonatal Infant Pain Score)	Acute	26-41 week GA (PNA: up to 6 weeks)	• Facial expression • Crying • Breathing pattern • Limb movements • State of arousal
NFCS (Neonatal Facial Coding System)	• Acute • Prolonged	24-32 week GA (PNA: up to 56 days)	• Brow lowering • Eye squeeze • Nasolabial furrow • Lip opening/pursing • Mouth stretch • Taut tongue • Chin quiver
N-PASS (Neonatal Pain, Agitation, and Sedation Scale)	• Acute • Prolonged • Level of sedation	23-40 week GA (PNA: up to 100 days)	• Behavioral state • Facial expression • Crying • Tone of extremities • HR, BP, respiratory rate, O_2 saturation
CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness)	Prolonged	27-40 week GA (PNA: up to ~8 months)	• Crying • Requires O_2 to keep saturation >95% (0.95) • Increased HR, blood pressure • Facial expression • Sleep / alertness
COMFORT scale	Prolonged	24-42 week GA	• Calmness / alertness • Movement • Facial tension • Respiratory rate • Crying • Tone

Data from References 80,82.

BP, blood pressure; GA, gestational age; HR, heart rate; PNA, postnatal age.

Assessment of nonpain-related distress can be even more difficult in neonates. Many of the physiological and behavioral findings overlap with those

observed in neonates suffering from pain, drug withdrawal, or delirium.[83] Agitation or undersedation may contribute to accidental displacement of endotracheal tubes and IV catheters, as well as anxiety and fear in neonates because they are developmentally unable to understand and cope with stressful situations.[83] Conversely, oversedation can result in a prolonged need for mechanical ventilation, longer duration of hospitalization, and increased healthcare costs.[83] The N-PASS (Table e22-7) is one of the few tools available to assess the level of sedation in neonates.[82]

Nonpharmacologic Treatment Options

The first steps toward minimizing pain and agitation in neonates should be to reduce the number of painful interventions (eg, limit blood collection) and to coordinate or "bundle" bedside care (eg, diaper changes, physical examinations, endotracheal tube suctioning) to allow the neonate longer periods of restfulness.[81] When painful procedures are necessary, nonpharmacologic modalities should be the first tier of interventions used. Nonpharmacologic therapies often used in the NICU include swaddling, non-nutritive sucking, skin-to-skin care (commonly called "kangaroo care"), massage, and breast or bottle feeding.[81,82] These interventions are most effective when used in combination with each other or as adjuvants to pharmacologic therapies.[81,85]

Pharmacologic Treatment Options

Medication selection is dependent on the indication (ie, type and severity of pain, need for sedation) and the adverse medication reactions profile. Neonatal dosing recommendations for many analgesics and sedatives are frequently not supported by well-designed pharmacokinetic and outcomes studies in neonates of various gestational and postnatal ages (Table e22-8).

TABLE e22-8

Neonatal Dosing Recommendations for Commonly Used Analgesics and Sedatives

Medication	Uses	Dosing Regimen	Comments
Sucrose 24% solution	Analgesia; mild procedural pain	• <1 kg: 0.1 mL/dose • 1-2 kg: 0.1-0.2 mL/dose • >2 kg: 0.1-0.5 mL/dose	• Administer 1-2 minutes prior to procedure • May be applied to pacifier or directly to tongue • Do not exceed 3 doses per procedure
Acetaminophen	• Analgesia; mild-to-moderate postoperative or prolonged pain • Analgesia; moderate-to-severe postoperative pain when used in combination with an opioid	• **Oral:** • GA 28-32 weeks: 10-12 mg/kg/dose Q 6-8 hours; max dose 40 mg/kg/day • GA 33-37 weeks: 10-15 mg/kg/dose Q 6 hours; max dose 60 mg/kg/day • Term, ≥10 days: 10-15 mg/kg/dose Q 4-6 hours; max dose 75 mg/kg/day • **IV:** • PMA 28-32 weeks: 10 mg/kg/dose Q 12 hours; max dose 22.5 mg/kg/day • PMA 33-36 weeks: 10 mg/kg/dose Q 8 hours; max dose 40 mg/kg/day	Not effective for acute procedural pain

		• PMA ≥37 weeks: 10 mg/kg/dose Q 6 hours; max dose 40 mg/kg/day	
Morphine	Analgesia; moderate-to-severe prolonged or postoperative pain	• **IV, intermittent:** • 0.05-0.1 mg/kg/dose Q 4-6 hours • **IV, continuous:** • 0.01-0.03 mg/kg/hr	• Preterm neonates may be more susceptible to hypotension, respiratory depression, apnea • Titrate to effect • Practitioners should be aware of potential adverse effects on neurodevelopment
Fentanyl	Analgesia; moderate-to-severe acute procedural pain, prolonged, or postoperative pain	• **IV, intermittent:** • 0.5-3 mcg/kg/dose Q 2-4 hours • **IV, continuous:** • 0.5-3 mcg/kg/hr	• Administer bolus over 3-5 minutes, more rapid rates may cause chest wall rigidity • Titrate to effect
Midazolam	Sedation; procedural or prolonged	• **IV, intermittent:** • 0.05-0.1 mg/kg/dose • **IV, continuous:** • GA 24-26 weeks: 0.02-0.03 mg/kg/hr • GA 27-29 weeks: 0.03-0.04 mg/kg/hr • GA ≥30 weeks: 0.03-0.06 mg/kg/hr	• Myoclonus may occur especially in preterm neonates • Titrate to effect • Practitioners should be aware of potential adverse effects on neurodevelopment
Dexmedetomidine	Sedation, analgesia; prolonged	• **IV, continuous:** • 0.1-0.3 mcg/kg/hr	Limited neonatal data

Data from Reference 49.

GA, gestational age; IV, intravenous; PMA, postmenstrual age.

Sucrose

Oral sucrose administered 2 minutes prior to a mildly to moderately painful procedure reduces Premature Infant Pain Profile (PIPP) scores.[86] The exact mechanism of action is unknown, but it has been postulated that sucrose stimulates endogenous opiate and endorphin pathways to mediate the pain response. The optimal dose is unknown, but the typical dose used in practice is 0.1 to 1 mL of 24% sucrose administered on the tongue or buccal surface. Its effects are potentiated when combined with non-nutritive sucking (eg, pacifier) and/or swaddling. Since the duration of effect is about 4 minutes, doses may need to be repeated during longer procedures.[82] While sucrose administration is safe for treating a single painful procedure, there are concerns that repeated doses may be associated with hyperglycemia, NEC, and worse neurodevelopment.[82,86]

Acetaminophen and Cyclooxygenase-1 Inhibitors

Acetaminophen is used for mild-to-moderate pain in the NICU although its slow onset of effect compared to other options does not make it an ideal agent for preventing and treating acute procedural pain (eg, heelstick, venipuncture, intubation).[85] When used in combination with opioids for treating neonates with moderate-to-severe postoperative pain, acetaminophen reduces opioid requirements by more than 50%.[82,87]

Acetaminophen is primarily metabolized by glucuronidation and oxidation in older children and adults; however, the activity of these pathways is low in neonates especially those born prematurely. Instead, sulfation is the primary pathway through which acetaminophen is metabolized in neonates. This may provide a protective effect to the neonate against acetaminophen-induced acute liver injury because *N*-acetyl-*p*-benzoquinone imine (NAPQI), the toxic metabolite, is formed by oxidation.[88] Additionally, NAPQI is detoxified by glutathione, the synthesis of which is increased in neonates.[89] There may be an association between prenatal and early postnatal exposure to acetaminophen and the development of atopy, autism spectrum disorder, and attention deficit hyperactivity disorder. While causation and a pathologic mechanism have not been proven, this potential link warrants consideration and further evaluation.[87]

Cyclooxygenase-1 inhibitors (eg, ibuprofen) may not be as effective in premature neonates because of decreased receptor expression in the spinal cord.[82] This finding along with associated adverse medication reactions (eg, nephrotoxicity, platelet dysfunction, GI bleeding) make cyclooxygenase-1 inhibitors a non-ideal choice for analgesia in neonates.

Opioids

10 Opioids are generally used for moderately to severely painful procedures in the NICU. Morphine and fentanyl are the most commonly used agents from this class.[82,85] Although the American Academy of Pediatrics recommends that analgesia should be provided during painful procedures (eg, circumcision, chest tube placement, endotracheal intubation), the safety and efficacy of scheduled/continuous analgesia during prolonged painful events (eg, mechanical ventilation) remain in question.[81,82] Despite a lack of evidence to support the practice, opioids are often administered to mechanically ventilated neonates to prevent pain and provide sedation.

Morphine undergoes glucuronidation to two active metabolites. Neonates younger than 10 postnatal days have about half the glucuronidation activity as those who are older. Maturation of glucuronidation continues over the first few months. This suggests that younger neonates, especially those under 10 days, will require lower doses of morphine than their older counterparts.[87,88] Similarly, fentanyl clearance is correlated with GA. Neonates with younger GA have slower fentanyl clearance suggesting that lower doses should be used in this population. Increases in clearance occur around 2 weeks of PNA.[90]

Hypotension associated with morphine use, especially after a bolus dose, may occur for preterm neonates, while this adverse medication reaction is less common with fentanyl. This difference is attributed to histamine release that occurs in response to morphine administration.[81,85] Both agents impair GI motility, but fentanyl causes less dysmotility.[81] Respiratory depression may occur with both agents, potentially prolonging mechanical ventilation.[81] Rapid administration (ie, dose infused over less than 3 to 5 minutes) of fentanyl is associated with chest wall rigidity.[82,85] In such patients, naloxone or a neuromuscular blocking agent may be required to relax the respiratory muscles and facilitate ventilation.[85] Tachyphylaxis may occur with both agents, but develops more rapidly during treatment with fentanyl.[81] Prolonged exposure to opioids can lead to physiological dependence and predispose a neonate to withdrawal if these agents are abruptly discontinued or too rapidly tapered off.[82,83]

The effect of opioids on short- and long-term neurological outcomes is unclear. Opioid exposure during early brain development may result in neural cell apoptosis and reduced neuronal concentration, manifesting as reduced brain growth, impaired motor movement, and learning disability.[81] Preterm neonates who receive continuous infusion morphine or midazolam while mechanically ventilated may have a higher incidence of IVH, PVL, or death compared to neonates who receive fentanyl or no sedative or analgesic agent.[91–94] Long-term complications such as impaired motor development, lowered intelligence quotient, and altered short-term memory may occur in preterm neonates exposed to morphine.[81,82]

Benzodiazepines

Benzodiazepines are commonly used for sedation in the NICU. Unlike opioids, they do not provide a beneficial analgesic effect.[82] Despite limited data regarding efficacy and dosing, midazolam is the most commonly used benzodiazepine in neonates.[82,95] It is preferred because of its shorter time for

elimination compared to lorazepam or diazepam and availability as a preservative-free product.[85,95]

When used in combination with opioids, benzodiazepines can potentiate the respiratory depression and hypotension associated with opioid use.[82] Neonates receiving benzodiazepines may exhibit myoclonic jerks which may be misconstrued as seizures.[81] Also, neonates who receive midazolam for sedation during mechanical ventilation may have longer lengths of hospital stay than those who do not receive midazolam.[95] Early benzodiazepine exposure may result in reduced formation and increased apoptosis of neural cells which could result in poor long-term neurodevelopment.[81]

Dexmedetomidine

Dexmedetomidine, an α2-adrenergic receptor agonist, is an effective sedative and analgesic agent for adult patients and may be efficacious in neonates.[96–100] The optimal dosing range has not been delineated, but younger neonates require lower weight-based doses.[101] Dexmedetomidine offers the advantage of not affecting respiratory drive; therefore, neonates treated with it require shorter durations of mechanical ventilation than those sedated with morphine or benzodiazepines.[98] Gastric motility is minimally altered by dexmedetomidine thus neonates tolerate enteral feeding sooner than when treated with opioids.[98] Additionally, dexmedetomidine may have neuroprotective effects.[85,98] However, the propensity for dexmedetomidine to cause hypotension is a concern for its use in neonates.[85,100] As with opioid and benzodiazepine use, withdrawal symptoms may occur upon weaning and discontinuation of dexmedetomidine.[100]

CONCLUSION

The neonatal population is complex owing to differences in anatomy and physiology when compared to older children and adults. These differences impact disease presentation; medication selection, dosing, and monitoring; as well as the patient's response to medication therapy. Clinicians need to be aware of the complexity of this population to assist with optimizing medication therapy, ensuring patient safety, and identifying research opportunities.

ABBREVIATIONS

AKI	acute kidney injury
BP	blood pressure
BPD	bronchopulmonary dysplasia
BW	birth weight
CPR	cardiopulmonary resuscitation
CBF	cerebral blood flow
CHD	congenital heart defect
CNS	central nervous system
CO	cardiac output
CONS	coagulase negative Staphylococcus
CRP	C-reactive protein
CSF	cerebrospinal fluid

EID	extended interval dosing
ELBW	extremely low birth weight
EOS	early-onset sepsis
GI	gastrointestional
GA	gestational age
GBS	group B Streptococcus
HPA	hypothalamic-pituitary-adrenal
HR	heart rate
HSV	herpes simplex virus
I/T	immature to total ratio
IO	intraosseous
IV	intravenous
IVH	intraventricular hemorrhage
LOS	late-onset sepsis
LP	lumbar puncture
MAP	mean arterial pressure
MIC	minimum inhibitory concentration
MRSA	Methicillin resistant *Staphylococcus aureus*
NAPQI	*N*-acetyl-*p*-benzoquinone
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
PCT	procalcitonin
PN	parenteral nutrition
PDA	patent ductus arteriosus
PMA	postmenstrual age
PNA	postnatal age

PPHN	persistent pulmonary hypertension of the newborn
PVL	periventricular leukomalacia
PIPP	Premature Infant Pain Profile
PVR	pulmonary vascular resistance
SV	stroke volume
SVR	systemic vascular resistance
TDM	therapeutic drug monitoring
VLBW	very low-birth weight
WBC	white blood cell count

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SELF-ASSESSMENT QUESTIONS

1. The pharmacist plays a key role on the interprofessional team in the NICU for all of the following reasons except:

   A. Ability to diagnose diseases specific to the neonatal population

   B. Experience with conducting clinical research

   C. Knowledge of age-related pharmacokinetic changes

   D. Understanding of technology (eg, “smart” IV pumps, dose-range checking)

2. Why is the IV route preferred over the endotracheal route for administration of epinephrine during a newborn cardiopulmonary arrest?

   A. The optimal dose of IV epinephrine for neonatal resuscitation has been well studied.

   B. IV access is readily available in neonates who are likely to experience a cardiopulmonary arrest.

   C. Efficacy of endotracheal epinephrine may be lower because of impaired absorption from reduced blood flow to the pulmonary circulation.

   D. Adverse medication reactions occur more commonly when epinephrine is administered by the endotracheal route.

3. A newborn has respiratory depression immediately after birth resulting in a respiratory acidosis. The newborn’s HR is 80 bpm. The mother has a history of chronic oxycodone use. Which intervention is most appropriate for this newborn at this time?

   A. Epinephrine

   B. Naloxone

   C. Sodium bicarbonate

   D. Supportive respiratory care

4. Which of the following adverse medication reactions is most likely to be experienced by a neonate treated with indomethacin for closure of a patent ductus arteriosus?

   A. Thrombosis

   B. Neutropenia

   C. Acute kidney injury

   D. Anaphylaxis

5. What is the rationale for administering prostaglandin E1 (ie, alprostadil) to a newborn with hypoplastic left heart syndrome?

A. Maintain patency of the ductus arteriosus to allow systemic to pulmonary shunting

B. Maintain patency of the ductus arteriosus to allow pulmonary to systemic shunting

C. Promote closure of the ductus arteriosus to prevent systemic to pulmonary shunting

D. Promote closure of the ductus arteriosus to prevent pulmonary to systemic shunting

6. A preterm neonate born at 27 weeks gestational age is requiring multiple needlesticks for frequent blood collections. Which pain assessment tool would be best to evaluate this neonate's pain?

A. COMFORT

B. CRIES

C. NIPS

D. PIPP

7. A neonate born at 29 weeks gestational age requires endotracheal intubation because of sepsis-associated respiratory failure at 30 days postnatal age. Which intervention would be most appropriate to prevent pain in this neonate?

A. Acetaminophen

B. Fentanyl

C. Sucrose

D. No analgesic agent should be recommended

8. What is a potential long-term detrimental effect of prolonged morphine exposure in neonates?

A. Decreased visual acuity

B. Lowered intelligence quotient

C. Respiratory depression

D. Sedation

Please refer to the following case for questions #9-10:

SM is an ex 25 weeks' gestation preemie who is now 21 days old, postmenstrual age of 28 weeks. Overnight, SM has multiple apneas and desaturations requiring mechanical ventilation. The NICU does not have a high rate of methicillin-resistant *Staphylococcus aureus* (MRSA).

9. The medical team would like to initiate IV antibiotic therapy for presumed sepsis. Which empiric antibiotic regimen is most appropriate for SM at this time?

A. Gentamicin and vancomycin

B. Nafcillin and gentamicin

C. Ampicillin and gentamicin

D. Cefepime and vancomycin

10. SM's blood culture is positive for *E. coli*. The cerebrospinal fluid (CSF) cell counts are normal and CSF culture is negative. What is the optimal duration of antibiotic therapy for SM?

A. 2 days

B. 7 days

C. 10 days

D. 21 days

11. What are the most common pathogens associated with early-onset sepsis in neonates?

A. *Listeria monocytogenes*, *Staphylococcus* coagulase negative, and Group B *Streptococcus*

B. *Enterobacteriaceae*, *Staphylococcus aureus*, and Enterococcus

C. *Escherichia coli*, Group B *Streptococcus*, and *Listeria monocytogenes*

D. *Staphylococcus* coagulase negative, *Klebsiella pneumoniae*, and *Enterobacter cloacae*

12. The NICU medical team would like to initiate prophylactic fluconazole for all high risk preterm infants. Which statement is correct with regards to the administration of prophylactic fluconazole?

A. All preterm infants born less than 1,500 g should receive prophylactic IV fluconazole 12 mg/kg/dose for 6 weeks.

B. NICUs with high rates of invasive candidiasis should prescribe prophylactic fluconazole for high-risk very low birth weight infants.

C. Prophylactic fluconazole has not been shown to significantly decrease the incidence of invasive candidiasis in very low birth weight infants.

D. Amphotericin should be used rather than fluconazole for the prevention of invasive candidiasis in very low birth weight infants.

Please refer to the following case for questions #13-14:

JR is a 27 weeks' gestation infant, birth weight of 840 g, born to a 26-year-old woman with placenta abruptio. Apgar scores were 1, 3, and 7 at 1, 5, and 10 min, respectively. JR was immediately intubated in the delivery room and transferred to the NICU. At about 20 min of life, JR had BP instability with MAP ranging from 20 to 25 mm Hg. One dose of normal saline 0.9% NaCl 20 mL/kg was infused over 30 min with minimal improvement of MAP.

13. The neonatologist would like to initiate a pharmacologic agent for JR's hypotension. Which medication is the most appropriate first-line treatment for JR's neonatal hypotension?

A. Dobutamine

B. Dopamine

C. Epinephrine

D. Hydrocortisone

14. There is evidence of myocardial dysfunction on JR's echocardiogram. Which treatment is most appropriate for JR at this time?

A. Dobutamine

B. Dopamine

C. Epinephrine

D. Norepinephrine

15. Which parameters are measurements of cardiac instability in neonates?

A. White blood cell count, urine output, and temperature

B. Capillary refill time, heart rate, and C-reactive protein level

C. Temperature, heart rate, and oxygen saturation

D. Capillary refill time, urine output, and heart rate

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Identification and diagnosis of diseases is the primary role of physicians on the medical team. Pharmacists are trained, and skilled, in applying pharmacokinetics to medication dosing, utilizing technology to promote medication safety, and conducting research to improve the efficacy and safety of medications.

2. **C.** Shunting of blood from right-to-left (ie, from the pulmonary artery to the aorta) through the patent ductus arteriosus reduces blood flow to the lungs and; therefore, absorption of endotracheally administered epinephrine into the systemic circulation is reduced. Thus, decreased efficacy of endotracheal epinephrine makes IV the preferred route of administration despite potential difficulties with obtaining IV access and the lack of studies evaluating the optimal dose.

3. **D.** In utero exposure to oxycodone is the likely cause of this neonate's respiratory depression; however, naloxone is not recommended to reverse the effect because its administration may precipitate withdrawal symptoms. Sodium bicarbonate may correct metabolic acidosis or mixed acidosis, but could worsen respiratory acidosis. The newborn's heart rate is adequate so epinephrine is not indicated. Supplemental oxygen and positive pressure ventilation will support the newborn's respiratory effort until the respiratory depressant effects of oxycodone wear off.

4. **C.** The most common adverse medication reactions of the cyclooxygenase inhibitors (ie, indomethacin, ibuprofen) used to close the patent ductus arteriosus are AKI, thrombocytopenia, bleeding, and spontaneous intestinal perforation.

5. **B.** The left ventricle of neonates with hypoplastic left heart syndrome is not developed enough to support systemic circulation. Therefore, the ductus arteriosus (connecting the pulmonary artery to the aorta) must remain patent to allow blood to shunt from the pulmonary circulation to the systemic circulation.

6. **C.** This newborn is experiencing acute procedural pain. The NIPS tool has been validated for this patient's gestation age and type of pain. PIPP is validated in neonates born between 28 and 40 weeks. COMFORT and CRIES are validated for prolonged pain (eg, from prolonged intubation and mechanical ventilation).

7. **B.** Premature neonates are capable of experiencing pain; therefore, this patient population should receive appropriate interventions to prevent and treat pain. Endotracheal intubation is considered a moderately painful procedure. Because this procedure needs to be performed quickly, an agent with a longer onset of action such as acetaminophen would not be appropriate. Sucrose is a more appropriate intervention for mildly painful procedures (eg, heel sticks for blood collections) and requires 1 to 2 min for onset of effect. Fentanyl has a quick onset of effect and is recommended for moderate-to-severe acute procedural pain.

8. **B.** Respiratory depression and sedation are known short-term adverse medication reactions of opioids; however, tolerance typically develops with prolonged use. Evidence of neural cell apoptosis, reduced neuronal concentration, and reduced brain growth resulting from prolonged morphine exposure are thought to be associated with learning disabilities and lower intelligence quotient. Altered visual acuity may be a complication of prematurity, but has not been associated with opioid exposure.

9. **B.** This patient has concerns for late-onset sepsis (LOS) since SM is 21 days old and common pathogens associated with LOS are usually hospital acquired. Vancomycin, in combination with gentamicin, has traditionally been the first-line empiric therapy for LOS in neonates, mainly due to the prevalence of coagulase-negative *Staphylococcus* (which are generally resistant to antistaphylococcal penicillins) and concern over methicillin-resistant *Staphylococcus aureus* (MRSA). However, due to the concerns over the use of vancomycin in this population, including potential adverse medication reactions (eg, nephrotoxicity, ototoxicity) and the development of resistant organisms, particularly enterococcal and staphylococcal isolates, vancomycin use should be limited to cases of MRSA or if blood culture isolates reveal coagulase-negative *Staphylococcus*, at which time, nafcillin can be replaced with vancomycin. Ampicillin and gentamicin are the antibiotics of choice for the treatment of early-onset sepsis. Cefepime

should be reserved for patients with resistant gram-negative organisms.

10. **C.** SM has *E. coli* bacteremia and hence, the duration of antibiotic therapy for bacteremia is 10 to 14 days. SM does not have bacterial meningitis since the CSF cell counts are normal and CSF culture is negative. If SM has bacterial meningitis, the duration of antibiotic therapy is 14 to 21 days depending on the organism.

11. **C.** Early-onset sepsis in neonates is acquired either transplacentally or via ascending bacteria from the vaginal environment due to ruptured amniotic membranes. Hence, the common organisms are Group B Streptococcus (also known as *Streptococcus agalactiae*) and *E. coli*. Other pathogens include *Listeria monocytogenes*, other streptococci (most commonly viridans group streptococci), and Enterococcus species. *Staphylococcus* coagulase negative, *Staphylococcus aureus*, and other Enterobacteriaceae are hospital-acquired pathogens commonly associated with late-onset sepsis.

12. **B.** Very-low-birth weight (VLBW) infants are at highest risk for *Candida* species colonization. Prophylactic fluconazole significantly decreases the incidence of invasive candidiasis, *Candida* species colonization, and mortality in VLBW and extremely-low-birth-weight (ELBW) infants. However, there is concern for the potential development of resistant pathogens as well as adverse medication reactions from prolonged use of fluconazole. Therefore, the IDSA guidelines only recommend prophylactic fluconazole for all ELBW born in NICUs with high rates (> 10%) of invasive candidiasis at a dose of 3 to 6 mg/kg/dose twice weekly for 6 weeks orally or parenterally. If fluconazole is not available or if there are concerns for resistance, oral nystatin at dose of 100,000 units three times a day for 6 weeks can be used as an alternative in VLBW infants. Amphotericin B deoxycholate should not be used for prophylaxis; instead, it is the medication of choice for the treatment of invasive candidemia in neonates.

13. **B.** Dopamine is the first-line vasoactive agent of choice for neonatal hypotension, especially in preterm infants mainly due to its effects on the α-adrenergic receptors. When compared to dobutamine and hydrocortisone, dopamine is significantly more effective in increasing BP. Similar to dopamine, epinephrine at higher doses (>0.1 mcg/kg/min) has α-adrenergic receptor effects and can cause peripheral vasoconstriction, severe tachycardia, and arrythmias. Due to its safety profile, epinephrine is usually reserved as a second- or third-line agent for the treatment of neonatal hypotension. Since preterm infants may have relative adrenal insufficiency, oftentimes, they are refractory to vasopressor medications. Hydrocortisone is effective for the treatment of refractory hypotension in neonates. However, due to the potential risk of cerebral palsy, it is generally not recommended as routine use in neonates.

14. **A.** Dobutamine exerts its effects mainly on β-receptors and therefore is the inotrope of choice for infants with myocardial dysfunction since it increases SV by increasing contractility. Dopamine, epinephrine, and norepinephrine stimulate both α- and β-receptors.

15. **D.** Physical assessment indicative of cardiac instability or hypotension may include tachycardia, prolonged capillary refill time, decreased urine output, and metabolic acidosis. WBC, C-reactive protein, and temperature can all be used to assess sepsis which can result in hypotension. However, they are not clinical signs of cardiac instability.