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CHAPTER 20

Disorders of Foals

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EQUINE NEONATOLOGY

Tremendous advances have been made in the medical care of newborn foals over the past 50 years, thanks to the pioneering efforts of many individuals and research groups and the increasing sophistication of veterinary medicine as a whole. Although the field of human neonatology has provided critically important guidance regarding the physiology and pathophysiology of the neonatal foal, and will continue to do so, fundamental insights have been achieved into the unique characteristics of this special population. The foundations of equine neonatology were built on the earliest descriptions of specific conditions in foals by clinician researchers, such as septicemia, joint ill, and hemolytic icterus,[1-4] as well as the "dummy foal" syndrome and the respiratory distress syndrome (RDS) associated with primary surfactant deficiency.[5,6] Significant strides were also being made in the understanding of the physiology of the equine fetus and neonate, in large part because of the efforts of a group of researchers working in the UK.[5-23] As the knowledge base grew dramatically,[24-29] there was increasing interest in providing improved care for the equine neonate, in large part because of the substantial investments of time, energy, and equity involved in the lengthy process of conception, gestation, parturition, and juvenile development. Owners were very interested in optimizing foal survival, and this interest, along with the increasing capability for providing effective critical care for foals, led to the development of neonatal intensive care units (ICUs) worldwide in the 1980s. Since that time there has been a steady increase in our understanding and ability to successfully treat and manage the critically ill foal. The result has been a dramatic improvement not only in the likelihood of survival but also the ability of surviving foals to mature into sound, healthy individuals that are able to perform their intended function.[30] Our knowledge base in equine neonatology continues to grow, and the goal of this chapter is to provide an overview of the current knowledge in this field as well as to provide some insights derived from human medicine.

FETAL ASSESSMENT, MONITORING, AND MANAGEMENT

The efforts of owners, managers, and veterinarians to maximize equine reproductive success extend far beyond successful conception. Close attention must be paid to a variety of influences before, during, and after pregnancy. These influences include numerous maternal, placental, and fetal risk factors. By assessing these variables and monitoring for changes during the course of pregnancy, it may be possible to implement medical therapies to minimize some risks, or at least to ensure that management strategies are in place to reduce the risk of problems during or after delivery.

Regarding maternal risk factors one must begin with a detailed assessment of the mare's reproductive history including endometrial health before breeding; problems during conception; vaccination history; possibility of twinning; previous gestational length; number of previous foals; the number of successful deliveries; history of and types of dystocia; and the occurrence of any problems with previous foals after birth, such as neonatal isoerythrolysis.[31] In addition, a number of maternal factors during pregnancy should be assessed, including maternal under- or overnutrition, maternal illnesses (especially colic or other severe stressors), and endocrine or metabolic maternal abnormalities. Physical abnormalities, such as abdominal wall muscular tears or prepubic tendon rupture, represent serious risks to both the dam and the fetus. Uterine torsion represents a life-threatening situation for the mare and the fetus, and if correction is successful the fetus must be regarded at high risk for the duration of the pregnancy.

Although it can be very difficult to appreciate placental risk factors, this is a critical issue given the complete dependence of the fetus on the dam for energy and oxygen supplies. Conditions such as endometriosis or twinning can reduce the available surface area for placental attachment, resulting in impaired transfer of nutrients and waste products between the fetus and the dam and potentially causing intrauterine growth retardation (IUGR). Placental dysfunction can result from abnormalities such as placental detachment, placentitis, placental edema, hydrops, and vascular inflammation or injury.[31] Exposure of the mare to any possible infectious causes of abortion or maternal ingestion of endophyte-infested fescue also can represent serious risk factors to the fetus.[32,33] Although there are often no outward signs of placental abnormalities, the development of excessive abdominal distention, vulvar discharge, or premature udder development may suggest their presence. A number of fetal factors can complicate pregnancy as well, including fetal malformations (congenital or developmental), fetal malpositioning, twinning, exposure to infectious agents, and neonatal isoerythrolysis.

If any potential risk factors are identified then the pregnancy should be characterized as high risk, requiring assessment of

the mare, the placenta, and the fetus. Evaluation of the mare should include a thorough physical examination, paying particular attention to the external genitalia and the udder. The abdomen should be evaluated for signs of excessive enlargement, ventral edema, or a pendulous appearance. Evidence of systemic illness (fever, tachycardia, tachypnea, abnormal mucous membranes, etc.) will serve as an indication for additional diagnostic evaluation to ascertain the focus and severity of the inflammation. A complete blood count and serum chemistry profile may be helpful in that regard. Evaluation of the reproductive tract should include a rectal examination, if feasible, as well as a vaginal examination and transrectal and transabdominal ultrasound examinations. These will allow for detection of abnormalities such as cervical discharge, uterine torsion, hydrops, and prepubic tendon rupture.

Ultrasound examination will provide the opportunity to thoroughly evaluate the placenta to assess placental attachment, placental thickness, and the echogenicity of the fetal fluids.[34-36] The transabdominal approach allows for prolonged periods of examination and allows for a thorough assessment of the uterus, placenta, and fetus.[37] After 4 months' gestation both transabdominal and transrectal ultrasonographic examinations should be performed to ensure thorough assessment. After 6 months of gestation transrectal ultrasonography can also be used to regularly monitor variables such as fetal heart rate, eye diameter, and fetal activity.[38] Although transrectal ultrasound examination does not allow visualization of all fetal structures, it is very useful during late gestation, because the caudal uterine body is the most common site for ascending placentitis to develop.[35] Measurement of the combined thickness of the uterus and placenta (CTUP) is a useful indicator of placental abnormalities, but this assessment should only be performed in areas of the placenta not in contact with the fetus. Although the CTUP can be measured transabdominally, this approach is more challenging because of the variations in the location measured as well as the potential for fetal contact compressing the placenta.[39] It is preferred to measure the CTUP transrectally at a site near the cervicoplacental junction, at which a branch of the uterine can be visualized between the uterus and the bladder, using the average of several measurements.[36] Normal measurements of the CTUP have been reported to be 0.6 cm at 7 months' gestation, less than 0.8 cm at 9 months, less than 1.0 cm at 10 months, and up to 1.0 to 1.2 cm at the end of gestation.[36,40] It is important to remember that even though an increased CTUP may suggest placental abnormalities it does not represent a definitive finding. There are reports of increased CTUP measurements that were not associated with placental pathology, and conversely ascending placentitis is not always associated with an increase in CTUP.[35,36,41] Although there may also be breed and parity influences on CTUP measurements, the 1.2-cm upper limit represents a reasonable cutoff for most Light Horse and Warmblood breeds.[42] Placental detachment may be associated with accumulation of exudate between the placental and uterine surfaces, which is typically hyperechoic in ultrasonographic appearance.

In addition to CTUP there are a number of other ultrasonographic parameters that can be used for assessment and monitoring of the high-risk fetus. Fetal viability can be assessed using fetal heart rate and rhythm, as well as fetal activity patterns and fetal responses to stimulation. Fetal heart rates change throughout gestation, trending from a high of 135 ± 6 beats per minute at 91 to 120 days' gestation to 67 ± 12 beats per minute at 330 to 360 days' gestation.[43] Transient alterations in fetal heart rate may be observed but do not likely indicate fetal distress unless they persist. Persistent tachycardia or bradycardia may be an indication of impending fetal death.[44,45] Fetal heart rate should increase during periods of fetal activity and return to normal ranges thereafter. Fetal electrocardiography can be used for monitoring fetal heart rate and rhythm as well and was widely used several decades ago but has fallen out of favor because of the ready availability, ease of use, and diagnostic yield associated with ultrasonographic fetal assessment. A recent report described the use of telemetric electrocardiography equipment for monitoring fetal heart rate and fetal heart rate variability, and this tool may hold some promise for fetal assessment in the future.[46] A biophysical profile based on ultrasonographic fetal assessment has been developed for use in late gestation, and this includes fetal heart rate, fetal activity, fetal aortic diameter, CTUP, uteroplacental contact, and maximal allantoic fluid depth.[43,45,47]

Once the determination has been made that the pregnancy is high risk, and particularly if there are uteroplacental or fetal abnormalities indicative of the risk or presence of fetal compromise, the next challenge is if, when, and how to intervene appropriately. Because of the very late maturation of the equine fetus in the last 1 to 2 weeks of gestation, combined with the difficulty of determining fetal readiness for birth, it is rarely advisable to induce delivery. It is far better in most situations to attempt to support the fetus in utero as best as possible while awaiting natural delivery.[48] If there are complications that threaten the survival of the dam, then cesarean section or induction of parturition may be indicated, although the survival of the foal should be considered highly unlikely. The other situation in which intervention may be indicated is if the fetus is thought to be near term and the mare suffers from a condition such as severe colic that is endangering fetal survival, although the prognosis for foal survival again remains poor.

Medical management of the high-risk pregnancy has two goals: the first is treatment of the primary condition, if possible, and the second is treatment intended to support the fetus in utero and maintain the pregnancy. The primary condition most commonly encountered in the mare is placentitis, and specific treatment consists of antimicrobial therapy and antiinflammatory therapy. Antimicrobial therapy, although typically empiric in nature, should ideally rely on drugs that are capable of reaching therapeutic concentrations within the uterus. Trimethoprim-sulfamethoxazole, penicillin, and gentamicin have all been shown to reach appropriate levels within the allantoic fluid, but trimethoprim-sulfamethoxazole is most commonly used because of the ease of oral administration and low cost.[49,50] Ceftiofur crystalline-free acid (CCFA), although appealing from the perspective of ease of administration and expense, did not achieve therapeutic concentrations within the placenta or fetal fluids and was not effective in an experimental model of bacterial placentitis.[51]

Antiinflammatory therapy in most cases consists of flunixin meglumine and pentoxifylline, although other agents such as aspirin and corticosteroids have been investigated. Although the efficacy of antiinflammatory therapy in placentitis is uncertain, they are commonly used. Flunixin meglumine is the most common agent used, because it is a potent nonsteroidal antiinflammatory drug (NSAID), but it is not clear that it reaches therapeutic concentrations within the placenta or uterus.[52] Other antiinflammatory drugs have been of interest,

although one study did not find any benefit to the addition of an antiinflammatory (dexamethasone and aspirin) to trimethoprim-sulfamethoxazole therapy in experimentally induced bacterial placentitis.[53] In addition to the potential antiinflammatory effects of corticosteroids, their use has been of interest because of the widespread use of this treatment to accelerate fetal maturation in human patients.[54] The administration of corticosteroids to mares in late gestation was shown to accelerate fetal maturation in one experimental study, but there are no reports regarding the use of this therapeutic approach in clinical practice.[55]

Treatments that may be beneficial in supporting gestation include exogenous progestagens, tocolytics, and agents promoting oxygen delivery to the fetus. Progestagen supplementation may have a multitude of effects, including antiprostaglandin effects, but primarily it is thought to function as a tocolytic. This is typically accomplished using altrenogest, a synthetic progestin, although injectable progesterone is sometimes used.[43] Although the use of these agents has been somewhat controversial, altrenogest therapy has shown some indications of efficacy in reducing fetal losses from bacterial placentitis.[56-58] Clenbuterol, a β_2-sympathomimetic drug, has been shown to induce uterine relaxation during late gestation but is short-acting, with only 2 hours' duration of effect.[52] For this reason clenbuterol is most useful in the acute situation, such as in the management of dystocia while preparing for cesarean section or assisted delivery.[59]

Treatments that may improve fetal oxygen delivery in utero and during an assisted delivery include pentoxifylline and intranasal oxygen administration to the mare. In addition to its antiinflammatory effects, pentoxifylline has rheologic effects that may enhance oxygen delivery to the placenta by improving microcirculation.[60] Intranasal oxygen administration (10–15 L/min) to the pregnant mare will increase the partial pressure of oxygen and oxygen saturation in the arterial blood supplying the placenta and may improve oxygen delivery to the fetus.[30] Vitamin E has been used in the management of high-risk pregnancy as an antioxidant and is administered orally to the pregnant mare.[30]

At this time the combination of trimethoprim-sulfamethoxazole, flunixin meglumine, and pentoxifylline remain the most commonly used treatment protocol for the medical management of bacterial placentitis in the mare. Generally, when managing mares with high-risk pregnancies it is critical that a well-formed plan is developed for dealing not only with parturition but also the high-risk foal after delivery, if it survives. Ideally these mares will be housed in a facility that is able to provide 24-hour monitoring and that has a team available to deal with any eventualities appropriately and in a timely manner. All necessary equipment needs to be organized and readily available. Thorough discussions with owners and agents need to occur before any crises so that all involved know the priorities regarding what procedures are authorized and whether the mare's life or the foal's life is the focus of the teams' efforts.

EXAMINATION OF THE NEWBORN FOAL

When assessing an equine neonate, it is important to remember that the first minutes and hours after birth are a profound adaptive period and that the normal parameters used in assessment are continually changing during this time. All of the foal's body systems are transitioning from the protected intrauterine environment in which many of their functions were primarily performed by the mare via the placenta, to the external environment in which these systems assume full responsibility for maintaining homeostasis. The time required for this transition varies by body system, and the adaptations required of the cardiopulmonary system are the most time critical. At birth the lungs must expand and clear themselves of fluid for gas exchange to occur, and this process must be coordinated with a shift in blood flow into the pulmonary circulation. If all elements of this transition do not occur within a few minutes, the foal will not be able to survive in the external environment. The adaptations required of the nervous, musculoskeletal, endocrine, alimentary, and thermoregulatory systems are similarly critical but occur over a longer period of time following birth.

There are a number of endocrine changes occurring in the periparturient period, and these changes are critical in readying a number of body systems, such as the lungs, gastrointestinal tract, kidneys, and liver, for the functions they will be responsible for following birth.[61] The most critical of these appears to be the activation of the hypothalamic-pituitary-adrenal (HPA) axis. This process begins in the period starting approximately 5 days before birth, when the fetal cortisol concentration rapidly begins to rise.[17] This increase prepares the body for many of the processes that may have little or no role in utero but are critical for survival after birth, such as respiration, renal sodium conservation, and glucose metabolism.[62] Serum cortisol concentrations continue to rise in the first few hours after birth before decreasing to normal basal values by approximately 1 day of age in healthy foals.[63] Very premature foals (<320 days' gestation) have low cortisol concentrations at birth, and these do not increase appropriately in the first 2 hours of life.[64] In addition to changes in the HPA axis there are also increases in circulating catecholamines, insulin, and glucagon, as well as thyroid hormones (T_3, T_4) associated with the immediate postpartum period.[62]

The neurologic system of the equine fetus is fully developed and functional because the precocious nature of foals at birth requires the immediate ability to ambulate and function independently.[65] The fetus is maintained in a sleeping state in utero through a combination of inhibitory factors, which include physical factors such as warmth, cushioned tactile stimulation, and buoyancy, as well as chemical factors, which include high circulating and/or cerebral concentrations of adenosine, prostaglandin D_2, and the pregnane neurosteroids allopregnanolone and pregnanolone.[65,66] These inhibitory neurosteroids are synthesized from progesterone primarily within the placenta during late gestation, and following delivery their concentrations within the normal neonate decline rapidly, usually over the first 48 hours of life.[67,68] This loss of cerebral inhibition, in combination with potent stimulation arising from transiting the birth canal, the onset of breathing, and the onset of multiple external stimuli (light, cold, hard surfaces, unlimited space, gravity, etc.), lead to a rapid increase in activity and awareness in the neonate.[66]

As the foal passes through the birth canal the chest undergoes significant compression, which aids in shifting fluid out of the airways. Once the lungs begin to inflate the action of surfactant contributes to further clearance of airway fluid and the maintenance of alveolar stability and lung inflation. Before birth the fetal circulation functionally bypasses the pulmonary

circulation by shunting through the ductus arteriosus and the foramen ovale. Once the foal begins to breathe the resistance in the pulmonary vasculature dramatically decreases, allowing blood from the pulmonary artery to enter the pulmonary vasculature rather than passing through the ductus arteriosus into the aorta. As the pressure in the left side of the heart increases, the foramen ovale closes, preventing the shunting of blood from the right atrium to the left atrium. Complete closure of the ductus arteriosus may take several days, and it is not unusual to hear a "machinery"-type murmur associated with patency of the ductus arteriosus in foals during the first 1 to 3 days of life. It is rare for the foramen ovale to remain patent in foals.

The foal's initial respirations primarily occur in response to the rapid rise of carbon dioxide in the bloodstream following the loss of placental gas exchange. The loss of placentally derived prostaglandins that suppress breathing in utero likely contributes as well, along with the initiation of cold and tactile stimuli associated with the external environment.[69] Spontaneous breathing may begin as soon as the chest clears the birth canal and should begin within 1 minute of birth. The first few breaths may be quite exaggerated in nature because of high carbon dioxide levels and the degree of effort required for initial lung expansion. Following these initial breaths most foals will continue to exhibit elevated respiratory rates of 50 to 75 breaths per minute for the first 20 to 30 minutes of life. The respiratory rate will then decrease to around 30 to 40 breaths per minute, and this remains fairly stable for the remainder of the first 2 days of life. By 2 to 3 days of age most foals will exhibit respiratory rates of approximately 20 breaths per minute. Foals show a much more exaggerated respiratory pattern than adult horses, with both inspiration and expiration requiring active respiratory effort because of the foal's highly compliant thoracic wall.

Immediately following birth the foal will typically exhibit bradycardia, with heart rates of 60 to 80 beats per minute.[8] The heart rate rapidly increases, peaking at 150 to 175 beats per minute around 40 to 60 minutes after birth, with the highest heart rates often observed in association with the foal's first attempts to stand.[70] The heart rate then gradually decreases, with a resting rate of 120 to 150 beats per minute from 1 to 2 hours after birth followed by a rate of 100 to 120 beats per minute by 3 hours after birth. By 1 day of age the normal resting heart rate will be in the range of 80 to 100 beats per minute. Because of the relatively late maturation of the HPA axis in the fetal foal, the cardiovascular system at birth does not appear to be as fully developed in the horse compared with other species.[71] As a result the neonatal foal does not have well-developed baroreceptor responses and is at risk for hypotension, especially if premature.[71]

The mare will begin interacting with the foal shortly after parturition, using both vocal and tactile stimuli. The normal foal should be responsive to stimulation shortly after birth, and by 20 to 30 minutes of age the foal should respond to visual stimuli by appropriate ocular and head movements.[72] Within 40 minutes the foal should be responding to auditory stimuli with independent orientation of the ears in the direction of the stimulus.[72] Because of the risks associated with prolonged recumbency for foals born in a natural environment, there is a strong imperative for foals to be able to stand quickly and become ambulatory. The normal foal will move into sternal recumbency within a few minutes after birth. It will begin making efforts to stand within 30 minutes after birth, and should be able to stand unassisted within 60 to 120 minutes.[73] There can be breed differences in the time to stand, with pony foals standing in less than 60 minutes and larger breed foals, such as Thoroughbreds, typically requiring 30 to 60 minutes longer.[9] When first standing the foal will exhibit some degree of incoordination and dysmetria and will assume a braced position, with all limbs spread laterally, the forelimbs positioned forward, and the hindlimbs extended posteriorly.[72] Once standing the normal foal will rapidly gain coordination and will begin circling the mare and attempting bursts of speed within 1 to 2 hours.[74]

Some foals will display flexor tendon laxity at birth, primarily noted in the form of dropped fetlocks.[75] Most foals with flexor tendon laxity will only demonstrate mild to moderate abnormalities, typically consisting of rocking back onto the heels and caudal hoof wall, which leads to pastern hyperextension and upward flipping of the toe.[76] Affected foals usually recover rapidly, with increasing strength and activity over the first few days of life.[77] Rarely, foals may demonstrate more dramatic musculoskeletal abnormalities, such as a "windswept" conformation, with either the front or hindlimbs affected by matching angular limb deformities. One limb will have a valgus deformity, whereas the opposite limb will exhibit a matching varus deformity. Unless there are underlying bony abnormalities most of these foals will also self-correct with time and activity.

The normal foal will begin displaying suckling behavior shortly after birth, even while still recumbent, and should be able to nurse unassisted within 1 hour of standing. Foals requiring more than 3 hours to suckle are considered abnormal. Successful nursing presents several challenges to the newborn foal, beginning with the absolute requirement for successful standing and ambulation to access the udder. Very weak foals, or those suffering from musculoskeletal or neurologic problems, will have great difficulty in nursing for this reason. Once able to stand successfully, the foal must locate the udder, which likely requires a combination of visual and olfactory abilities on the part of the foal. The ingestion of milk is a fairly complex neurologic process, beginning with successful capture of the teat by the lips, followed by coordination of the tongue, pharynx, larynx, epiglottis, and esophagus to ensure that milk enters the gastrointestinal tract rather than the respiratory tract. In addition to the potential adverse impact of muscular weakness or neurologic dysfunction on this process there may be physical abnormalities, such as cleft palate or subepiglottic cysts that may interfere with the normal passage of milk.

The gastrointestinal tract must undergo a number of changes to accommodate and use ingested colostrum and milk. During the first 12 to 24 hours after birth the small intestine remains permeable to macromolecules, most importantly immunoglobulins, allowing for the absorption of ingested antibodies contained in colostrum. Absorption occurs by a number of mechanisms, including pinocytosis, lymphatic transport, and exocytosis. The period of maximal absorption is the first 12 hours after birth, with approximately 50% of ingested immunoglobulins able to be absorbed during that time period.[78] From 12 to 18 hours after birth the efficiency of absorption decreases substantially, with only 28% of ingested immunoglobulins able to be absorbed, and this rate of absorption is not adversely affected by the prior ingestion of macromolecules.[78] Although some absorption may be possible after 18 hours, the efficiency of absorption continues to decrease and absorption is essentially absent by 36 hours of age.

Following the loss of maternally derived glucose supplied via the placenta, the foal must take control of glucose homeostasis. This is particularly challenging because nutrient intake transitions from a continuous mode, in which the dam ensures a continuous, regulated supply of glucose at all times, to intermittent energy intake based on milk ingestion. The pancreas must assume responsibility for the maintenance of normoglycemia through the differential production of glucagon and insulin. These dramatic alterations in energy metabolism may not always occur smoothly, and unfortunately the foal possesses limited energy reserves in the form of glycogen and fat. The result is that hypoglycemia occurs over the first 1 to 2 hours of life even in the normal neonatal foal, and the sick foal is at risk of profound hypoglycemia if deprived of energy intake for even a few hours. The metabolic response of the foal is to increase production of glucagon, epinephrine, and cortisol and suppress insulin production, increasing circulating blood glucose concentrations. Glycogenolysis provides a ready source of glucose, but hepatic glycogen stores are minimal in the foal, so gluconeogenesis rapidly becomes the primary route of endogenous glucose production. Premature or dysmature foals often have impaired glucose regulation and are susceptible to pathologic hypoglycemia in the absence of appropriate dietary or parenteral supplementation.

At birth the foal transitions from the normally sterile intrauterine environment into an environment teeming with nonpathogenic and pathogenic organisms. Colonization of the various tissues exposed to the outside environment occurs rapidly, beginning during the birthing process. This phenomenon is particularly important in the gastrointestinal tract, in which microbial activity is critical for full functionality of the local immune system and digestion. Colonization occurs through environmental exposure and is likely facilitated by the coprophagic behavior routinely exhibited by foals. Colostral immunoglobulins and oligosaccharides may play a role in regulating the composition of the gastrointestinal flora by affecting the ability of certain bacteria to attach to the mucosal surface and by opsonizing certain bacteria, facilitating the mucosal immune response to these organisms.[79] By 2 to 4 weeks of age the microbial population has become similar in composition and complexity to that of the foal's dam, which indicates a transition to an adult pattern in readiness for the dietary transition from a milk-based diet to a roughage-based diet.[80,81]

Thermoregulation can be a challenge for the neonatal foal as it transitions from the uterine environment into what is typically a much colder external environment. This challenge is increased by the presence of an initially wet hair coat, which enhances thermal losses to the environment as well as a large surface area to body mass ratio and minimal stores of fat. The healthy foal has a high resting metabolic rate compared with the adult, and in the immediate neonatal period the metabolic rate will be increased at two to three times the basal rate, in association with high concentrations of T_3, T_4, and cortisol.[82] This high metabolic rate allows for substantial endogenous heat production to achieve and maintain normothermia. This metabolic heat production requires substantial inputs of energy in the form of fats and carbohydrates derived from colostrum and milk, reinforcing the critical need for early successful nursing in foals. Another important mechanism that foals rely on for heat production in the immediate neonatal period is shivering thermogenesis. This appears to be particularly important, because foals do not appear to use nonshivering thermogenesis because of minimal or nonexistent stores of brown fat.[83] Foals also use behavioral approaches to thermoregulation, ranging from maintenance of sternal recumbency to minimize heat losses to vigorous activity when attempting to stand and once ambulatory, which generates substantial additional heat.

PREMATURITY, DYSMATURITY, AND INTRAUTERINE GROWTH RETARDATION

Abnormalities of gestation are associated with substantial risk for affected foals, both as a primary syndrome and as a risk factor for a number of other syndromes. Unfortunately, these abnormalities of gestation, which have also been termed *unreadiness for birth*, can be difficult to characterize because of the highly variable duration of equine gestation.[84] In humans the generally accepted definition of prematurity is birth more than 21 days before full term. This concept has been applied to horses as well, with delivery before 320 days' gestation considered premature.[85] Unfortunately gestational duration in the horse is much less consistent than in humans, with reported gestational lengths resulting in live foals ranging from 286 to 380 days (mean 344 days) in Thoroughbred mares and from 313 to 370 days (mean 339 days) in Warmblood mares.[86-88] Pony breeds typically have similar gestational lengths, ranging from 337 to 343 days.[89] Although there are anecdotal reports of draft mares routinely having gestational lengths over 365 days in duration, one recent report suggests that median duration of gestation in heavy horses is only 5 days longer than in light breeds.[90] In addition to the influence of breed there are a number of other variables that impact the duration of gestation including fetal gender; fetal weight; maternal age and parity; and environmental factors such as month of conception or foaling, maternal nutrition, and climate.[88]

Because of the difficulty in defining a specific time point that would be indicative of fetal maturity, equine prematurity should be considered as much a physical and functional characterization as a temporal one. The foal's size and physical appearance are important characteristics related to prematurity. Small body size and low birth weight, along with a prominent rounded forehead, silky hair coat, entropion, and floppy ears, are all common findings in premature foals. Some affected foals may have a prominent reddish discoloration of the tongue, and the mucous membranes may appear somewhat pale. Flexor and periarticular laxity are also common, although some premature foals may exhibit carpal or fetlock contracture. Incomplete ossification of the cuboidal bones in the carpus and tarsus is also a common finding in premature foals, and these areas are at risk of crushing injury when affected foals stand and ambulate. This risk can be minimized by limiting the amount of time that these foals are allowed to stand and by minimizing their activity level.

From a functional perspective premature foals typically exhibit generalized weakness and have great difficulty in standing without assistance. Affected foals often have impaired thermoregulation and abnormal glucose metabolism, as well as impaired cardiovascular, pulmonary, gastrointestinal, and renal function. Impaired thermoregulation is likely caused by inadequate endocrine responses to the change from the uterine environment to the external environment. Abnormal glucose regulation is also indicative

of endocrine dysfunction, potentially caused by impaired insulin production or peripheral insulin insensitivity. Cardiovascular dysfunction most often presents as persistent hypotension that is poorly responsive to pressor therapy. Increased vascular permeability may be present as well, potentially resulting in fluid shifts from the vasculature to the interstitium. For these reasons fluid, inotrope, and pressor support should target the maintenance of perfusion, rather than a target blood pressure range. Failure to use this approach will put the patient at risk of fluid overload and other complications. Respiratory dysfunction may be caused by surfactant deficiency but is also frequently associated with decreased respiratory drive, weak muscles of respiration, a highly compliant chest wall, and poorly compliant lungs. Gastrointestinal dysfunction is typically caused by inadequate motility, which can result in distention, colic, and diarrhea. Renal dysfunction may manifest primarily as decreased urine output rather than azotemia, and care must be taken to avoid fluid overload in these patients.

Clinicopathologic assessment may aid in characterizing these foals. Leukopenia caused by neutropenia combined with lymphocytosis leads to a neutrophil:lymphocyte ratio (N:L ratio) of less than 1.0, as opposed to a normal ratio of greater than 2.0. This reversal of the N:L ratio is a commonly used defining characteristic of equine prematurity and is directly associated with impaired adrenocortical function.[91] This impairment of adrenal function happens because maturation of the HPA axis normally occurs in the last several days of gestation and continues in the first weeks, and perhaps even months, after birth.[64,92-95] As a result, premature foals exhibit low serum cortisol concentrations at birth, in combination with elevated serum adrenocorticotropic hormone (ACTH) concentrations.[92] The inability of premature foals to produce appropriate concentrations of cortisol is caused by an impaired adrenal response to endogenous ACTH, and they exhibit impaired response to exogenous ACTH as well. Assessment of the response to exogenous ACTH may be helpful in characterizing foals as premature, although there is a subset of clinically ill full-term foals that may also exhibit impaired responses to ACTH stimulation testing.[96-98] Although not specific for prematurity, other clinicopathologic changes may include arterial hypoxemia and hypercapnia; hypoglycemia; acidosis; and low-grade macrocytic, normochromic anemia.

Dysmaturity typically refers to foals that are delivered at what appears to be full term but exhibit the characteristics of premature foals discussed earlier. Dysmaturity is most common secondary to placental insufficiency resulting in IUGR.[99] Placental insufficiency can be caused by placental disease, placental separation, or twinning. Other causes of IUGR may include maternal undernutrition or systemic disease. Postmaturity should be distinguished from dysmaturity, and refers to foals born postterm. These foals have been in utero for an excessive length of time, most commonly secondary to maternal ingestion of fescue infected with the endophyte fungus *Acremonium coenophialum*.[32] Physical characteristics associated with postmaturity include a normal to high birth weight associated with a large frame size but with poor body condition. Affected foals may also display flexor contracture, a long hair coat, and fully erupted incisors. They may share a number of other functional characteristics with premature foals, including impaired thermoregulation and abnormal glucose metabolism, as well as impaired gastrointestinal and renal function.

The severity of the abnormalities associated with prematurity are to some extent associated with the duration of the predisposing disease process that led to premature delivery. Foals that have suffered prolonged in utero stress caused by placental disease may be surprisingly "ready for birth" because of stimulation of endogenous cortisol production and early maturation of the endocrine system.[100] In rare cases such foals may survive with aggressive medical intervention even if born as early as 286 days of gestational age, based on the author's personal experience. Foals that have not experienced in utero stress and that suffer from some acute onset condition resulting in premature delivery are much more likely to be "unready" for birth and will exhibit the most dramatic clinical abnormalities. These foals are unlikely to survive if born more than 2 weeks before their expected due date.

Most premature and dysmature foals will require medical intervention and supportive care to survive. These conditions affect all body systems, so thorough evaluation is indicated. Because of substantial crossover in the clinical presentation of these foals with that of the term, septic foal it can be difficult to discriminate among syndromes. Given that premature and dysmature foals are also at heightened risk of sepsis the clinician should reasonably assume that bacterial infection is present at presentation in most cases. Appropriate broad-spectrum antimicrobial therapy is indicated. Specific recommendations for the treatment and support of the critically ill foal will be discussed in detail in the relevant sections of this chapter.

The prognosis for survival of foals suffering from prematurity, postmaturity, and dysmaturity is good with appropriate care. Survival rates can be as high as 80% to 85%, and many of these foals will "catch up" with their peers and attain a normal adult size and normal function. It is important, however, for the owners of foals born profoundly premature (less than 300 days' gestation) to understand that if they survive to adulthood these foals will not likely reach a normal adult size and morphology, and they are unlikely to be able to function as athletes.

Prevention

The best approach for preventing abnormalities of gestation is close monitoring of the pregnancy to identify any conditions that may affect fetal viability or that may lead to premature delivery. Early treatment of placental infections with antimicrobials, antiinflammatories, and progesterone (altrenogest) may allow for prolongation of gestation and minimization of the abnormalities associated with premature delivery. Induction of parturition should be avoided if at all possible, but if it must be performed then care should be taken to avoid induction of delivery in mares unless the gestational length is known with great certainty. Removing mares from pastures containing endophyte-infected fescue, in combination with administration of dopamine receptor antagonists (domperidone), can decrease the risk of dysmaturity.

NEONATAL RESUSCITATION

Although the need to resuscitate a foal is uncommon, the critical and time-sensitive nature of this intervention requires that all those involved are appropriately trained in recognizing when and how to implement resuscitation efforts. It also requires that the appropriate equipment and drugs are organized and readily available before the event so that there are no delays in implementation. Cardiopulmonary arrest (CPA)

in foals most commonly begins with respiratory arrest, which subsequently leads to cardiac arrest caused by asphyxia, because primary cardiac disease is very rare in foals. This is a very different situation from that seen in most human patients, in which cardiac arrest is usually the primary initiating factor.[101] Because of this the protocol for resuscitation of foals differs substantially from the approach used in human patients. Establishment of a patent airway and the provision of ventilatory support is the initial priority in foals, rather than cardiac compressions (Box 20.1).

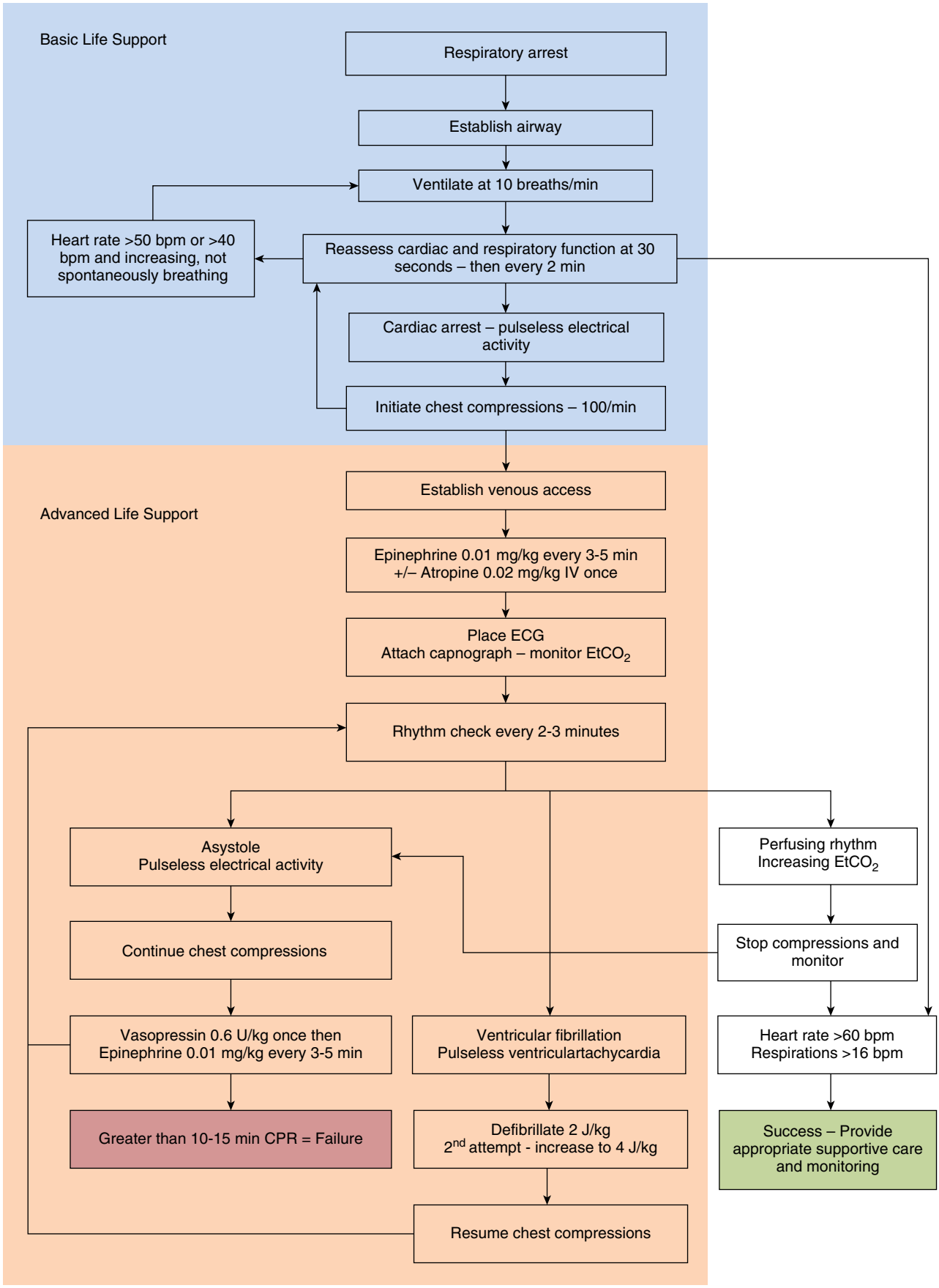
The first challenge is in recognizing which foals require resuscitation, because early intervention before cardiac arrest is associated with a much higher likelihood of successful resuscitation, potentially as high as 50%.[102] The situation in which foals are most likely to require resuscitation is parturition, because asphyxia can occur in utero or during dystocia, and the foal may have been in arrest for a prolonged period of time and will be unable to establish normal respirations without resuscitation.[30] The clinical signs that may indicate the need for resuscitation in the immediate postparturient period include absence of breathing, irregular gasping, respiratory rate less than 10 breaths per minute, heart rate less than 40 beats per minute, irregular or absent muscle flaccidity, or lack of response to tactile stimulation.[103] Other situations in which resuscitation may be required include primary lung disease, septic shock, hypovolemia, metabolic acidosis, hyperkalemia, hypoglycemia, vasovagal reflex, and hypothermia.[102,104] It is important to recognize that the prognosis for successful resuscitation and patient survival is much lower with these disease processes because of the severity of systemic illness and likelihood of multiple organ failure. Although it may be possible to resuscitate the patient, unless the underlying disease can be effectively addressed, the likelihood of survival is very low. Cardiac causes of CPA in foals may include secondary myocardial damage associated with severe hypoxia or sepsis, myocarditis, congenital cardiac defects, endocarditis with coronary artery embolism, and cardiac tamponade.[102,104]

Direct monitoring of the foal during delivery by veterinary staff is unlikely except in cases of dystocia and hospitalized high-risk pregnancies. When foaling is attended the assessment of the foal's respiratory and cardiovascular function should begin during delivery. If the foal is noted to be meconium stained the upper respiratory tract should be suctioned immediately, preferably while still in the birth canal and before the first breath. After delivery suctioning of the trachea may be required if the foal is heavily meconium stained or if meconium is detected in the upper respiratory tract. Mechanical suction is discouraged because it is often too aggressive and may actually worsen hypoxemia and potentiate bradycardia caused by vagal reflexes, and if used it should be limited to no more than 5 to 10 seconds of suction time. Following delivery the foal may gasp a few times but should establish a regular breathing pattern within 30 seconds. Persistent gasping, open-mouth breathing, or severe respiratory distress may be an indication of severe or total upper airway obstruction, such as bilateral choanal atresia, dorsal displacement of the soft palate, or stenotic nares. Tactile stimulation, such as vigorous drying with towels, may aid in stimulating the initiation of respiration. A rapid examination should be performed during this time to identify any congenital defects that would render resuscitation inappropriate or inhumane. If the foal fails to begin breathing spontaneously and regularly then an airway needs to be established immediately and basic life support (BLS) should be implemented. The best approach to establishing an airway is to pass a cuffed nasotracheal tube, which is facilitated by placing the foal's head in an extended position. Because of the urgency of the situation a maximum of two attempts to place a nasotracheal tube should be allowed, up to a maximum of 15 seconds. If nasotracheal intubation is unsuccessful then one should immediately proceed with orotracheal intubation or placement of a tracheotomy tube. If nasotracheal tubes are not available then mouth-to-nose ventilation can be used, because the foal is an obligate nasal breather. Care should be taken to occlude the opposite nostril manually to prevent air leakage from that site when ventilation is attempted, and the effectiveness of ventilation can be easily gauged by monitoring the chest rise during ventilation.[104]

After intubation ventilation should be provided with a self-inflating valved manual resuscitation device (Ambu Inc., Ballerup, Denmark) at 10 breaths per minute with a tidal volume of 10 mL/kg.[104] It is very difficult to limit breaths to this low rate, however, because of the stress and excitement of the resuscitation effort, which often leads to ventilation rates upward of 60 breaths per minute. Unfortunately excessive ventilation negatively affects cardiac return and coronary perfusion and has been associated with worsened outcomes.[105] Another challenge is associated with monitoring tidal volume, because there is a tremendous range of manual resuscitation bags available, all of which have different internal volumes and deliver variable amounts of air depending on how fully they are compressed. For this reason it is best to monitor ventilation by observing chest excursion during ventilation, keeping in mind that aggressive ventilation is contraindicated. Although somewhat controversial there may be some benefit to ventilating the newborn foal with 100% oxygen for a brief period of time (1 minute) immediately after delivery to encourage the reversal of persistent fetal circulation.[30,106] However, there is no indication for continued administration of supraphysiologic oxygen concentrations, because these may actually be harmful, and the delivery of room air is most appropriate in foals without underlying respiratory dysfunction.[104] Following 30 seconds of assisted ventilation discontinue ventilation, and observe the foal for spontaneous breathing while also assessing cardiovascular function by monitoring for a heartbeat. If a heart rate of 50 or greater (or between 40 and 50 but increasing)[104] is present but respirations are not, then resume ventilations, stopping every 2 minutes to monitor for spontaneous efforts or sooner if such efforts are obvious. As many as 90% of foals that require resuscitation at birth will respond to ventilatory support alone and require no additional therapy.[30]

If a heartbeat is absent or the rate is too low then immediately initiate thoracic compressions, because any delay may be very deleterious. No more than 10 seconds should be spent trying to assess cardiac function, and the risk associated with unnecessary thoracic compressions is less than that associated with the failure to provide compressions to an animal that needs them. Place the foal in lateral recumbency on a firm surface and quickly palpate for rib fractures before initiating compressions. If there are unilateral rib fractures position the foal with the affected side facing down, and if there are bilateral rib fractures place the side with more cranial rib fractures facing down.[104] The person providing compressions should position themselves to the dorsal aspect of the foal, with their knees against the spine, which will prevent the foal from shifting during compressions. Both hands should be used, with one closed in a fist and placed with the palm down over the

BOX 20.1 Cardiopulmonary Resuscitation Flowchart



Bpm, beats per minute; *$EtCO_2$*, end-tidal CO_2.

foal's heart, and the other hand placed on top of the closed fist. The arms should be kept straight, with the upper body weight being used to drive compressions. A rapid rate of 100 compressions per minute is advised.[102] The depth of compression is difficult to gauge, but "pushing hard" is recommended.[104] Chest compressions should be briefly stopped every 2 to 3 minutes to monitor for the presence of a heartbeat but should be resumed within 10 seconds. If there is only a single individual available to initiate resuscitation for a patient requiring chest compressions, then adjustments must be made. If the patient is not intubated, then it is recommended to provide 30 chest compressions to 2 ventilations, whereas for the intubated patient it is recommended to provide continuous chest compressions and no ventilatory efforts.[104] Although it is not feasible in single-rescuer resuscitation, if multiple individuals are participating in the resuscitation effort then an intravenous (IV) catheter should be placed while resuscitation efforts are ongoing to have IV access for administration of drugs or fluids.

If the foal is not responding to BLS then more aggressive measures (advanced life support) are indicated. These may include administration of pharmacologic agents and implementation of improved monitoring. Many drugs have been used empirically in foal resuscitation, but none has been specifically studied in the foal. The utility of many of these agents is debatable, either because they are directed toward primary cardiac dysfunction, which is rare in foals, or because their use in human cardiopulmonary resuscitation (CPR) has been discontinued. The drug that is most likely to be used is epinephrine, although this is the subject of ongoing debate in the human literature.[107] Epinephrine is administered at 0.01 mg/kg IV every 3 to 5 minutes. If IV access is not available then epinephrine can be administered intratracheally at 0.1 mg/kg, preferably diluted in a small volume (3–5 mL) of sterile water or saline.[104] Vasopressin has been used either in place of, or in combination with, epinephrine in CPR.[108] If used it should be given as a single dose of 0.6 U/kg IV following the first dose of epinephrine.[102] Doxapram has been commonly used in foal resuscitation as a respiratory stimulant, but it is contraindicated because it does not reverse secondary apnea and has been shown to decrease cerebral blood flow and increase cerebral oxygen consumption.[104,109] Atropine and glycopyrrolate have also been used in foal resuscitation, but as high vagal tone is an unlikely cause of bradycardia the benefit of these treatments is unclear. The administration of a single dose of atropine seems unlikely to be harmful, however, and if used atropine should be administered at 0.02 mg/kg IV. Corticosteroids, calcium gluconate, lidocaine, magnesium sulfate, and sodium bicarbonate, while potentially indicated in the treatment of primary cardiac arrest, are not recommended in routine resuscitation of neonatal foals at this time.[104]

Defibrillation

Defibrillation is indicated in cases of ventricular fibrillation and pulseless ventricular tachycardia. Access to appropriate equipment is often limited, however. The widespread availability of human automated electrical defibrillators may alter this situation, but at this time there are no published studies regarding their use in foals. When performing defibrillation the cardiac compressions and ventilation should continue until the moment of defibrillation and resumed immediately afterward. The initial charge should be 2 J/kg, which should be increased to 4 J/kg for subsequent attempts.[102] Defibrillation presents danger to the operator and anyone in contact with the foal, and operators should receive appropriate training before using a defibrillator.

Monitoring Resuscitation

Patient status during resuscitation is extremely dynamic, requiring constant reassessment, and it can be difficult to monitor for return of spontaneous circulation and spontaneous respiration without interfering with the process of resuscitation itself. Following initiation of resuscitation efforts cardiac and respiratory function should be reassessed at 2- to 3-minute intervals unless the foal shows obvious signs of response (Box 20.1). Monitoring via electrocardiography can be challenging, because electrical activity does not necessarily represent effective cardiac contractility, which is a phenomenon termed *pulseless electrical activity*. Respiratory efforts are much more readily observed and their effectiveness subjectively evaluated. One technique that can greatly facilitate monitoring during resuscitation is the monitoring of end-tidal CO_2 ($EtCO_2$), if capnography is available. The sensor is placed on the endotracheal tube and real-time monitoring is readily performed. Normal resting $EtCO_2$ in a healthy spontaneously breathing patient is approximately 40 mm Hg (35–45 mm Hg), whereas the CO_2 in room air is 0.3 mm Hg. During resuscitation a reasonable target for $EtCO_2$ is 10 mm Hg, because this indicates that an adequate degree of perfusion and ventilation is being achieved. If resuscitation is successful then a rapid increase in $EtCO_2$ toward the normal range will be observed, indicating that both perfusion and ventilation are improving. A decrease in $EtCO_2$ during resuscitation indicates inadequate ventilation and perfusion, requiring reevaluation of how resuscitation is being performed. If no response is detected after 10 to 15 minutes of resuscitation it is extremely unlikely that the patient will respond with further efforts.

Postresuscitation Support

Following successful resuscitation the patient should be considered at high risk because of the presence of any primary, initiating diseases and the likelihood of secondary hypoxic injury.[110] Appropriate medical care and monitoring are critical during this period of time. Foals should receive intranasal insufflation of humidified oxygen at 5 to 10 L/min until they have been demonstrated to be stable with adequate cardiopulmonary function. Fluid therapy will likely be of benefit in ensuring normovolemia and supporting cardiovascular function. Care should be taken to avoid overhydration, because these patients may be at risk of pulmonary edema. Pressor and inotrope therapy may be indicated if cardiovascular function is inadequate. Glucose support is important, especially in neonates, but care should be taken to avoid hyperglycemia. If resuscitation occurred in the field then serious consideration should be given to immediately referring the foal to a facility equipped to provide intensive care.

NEONATAL SEPSIS

The management of critically equine neonates is extremely challenging, but there have been tremendous advancements in the care of these foals over the past several decades. The gradual decline in mortality rates for hospitalized foals over the past 30 years, although likely because of a number of factors in addition to advances in treatment, serves as strong evidence of the progress that has been achieved. Reported survival rates

for hospitalized foals in North America have slowly trended upward from approximately 60% in the 1980s to around 70% in the 1990s and then 70% to 80% in the 2000s.[111-116] As encouraging as these numbers are it is important to note that the survival rates for foals suffering from sepsis are lower than those for all sick foals presenting to a hospital. In the 1980s it was reported that only 26% of septicemic foals survived, whereas a more recent study in 2006 reported that 57% of septic foals survived.[117,118] This is compared with reported survival rates of hospitalized sick, nonseptic foals of 75% to 95%.[118-122] The relatively poor prognosis for septic foals is caused by many factors, not least of which is the fact that sepsis represents a systemic inflammatory response to infection or injury and can rapidly progress to septic shock and death despite aggressive treatment. Traditionally, the term *septicemia* is used to refer to this process in the equine neonate and describes a systemic disease process involving the presence of pathogenic microorganisms and/or their toxins in the blood.[123,124] Historically the typical presentation of sepsis in foals was that of disseminated gram-negative bacterial infections; however, it has become clear that an identical syndrome may occur in patients with gram-positive or mixed bacterial infections, viral infections, trauma, hypovolemia, hemorrhage, and immunologic and drug reactions.[125-127]

Pathophysiology

The abnormalities associated with the clinical syndrome of sepsis result from a nonspecific innate inflammatory response, which has been termed the *systemic inflammatory response syndrome* (SIRS).[125] SIRS represents a common terminal phase of the inflammatory response characterized by malignant global activation of multiple proinflammatory pathways and is characterized by parameters that can be readily defined in clinical patients. These manifestations of disease are the same as those previously used to define sepsis, but the appreciation that many different stimuli can induce this response has resulted in sepsis being redefined as SIRS because of infection (Table 20.1).[128,129] The changes associated with SIRS can lead to shock, which is characterized by severe hypotension not responsive to IV fluid therapy (Box 20.2). Shock can result in hypoperfusion and organ dysfunction such that homeostasis cannot be maintained without intervention. This process is termed *multiple organ dysfunction syndrome* (MODS).[125] MODS represents a progressive syndrome with initial dysfunction seen in the cardiovascular system, followed by involvement of the respiratory, hepatic, gastrointestinal, renal, cardiac, and neurologic systems. These processes result in the development of refractory hypotension, lactic acidosis, and oliguria and may progress to death. SIRS criteria were proposed 15 years ago for the neonatal foal population and are based on human criteria using information regarding normal values in foals.[124,130] SIRS criteria have been used in a number of studies of clinically ill foals since that time and have been correlated with increases in both lactate concentration and mortality.[130,131] A recent report has proposed a revised set of SIRS criteria that are age dependent and based on insight from revised human pediatric SIRS criteria and that incorporate the changes in normal values that occur with increasing age in foals (Table 20.2).[132]

Inflammation represents the response of tissues to either injury or the presence of microorganisms. It serves a vital role because it enhances the movement of phagocytic cells and defensive molecules, such as immunoglobulin and complement, from the bloodstream to the site of infection or injury.

TABLE **20.1 Definitions of Terms Used to Describe Clinical Syndromes Associated with Systemic Inflammation**

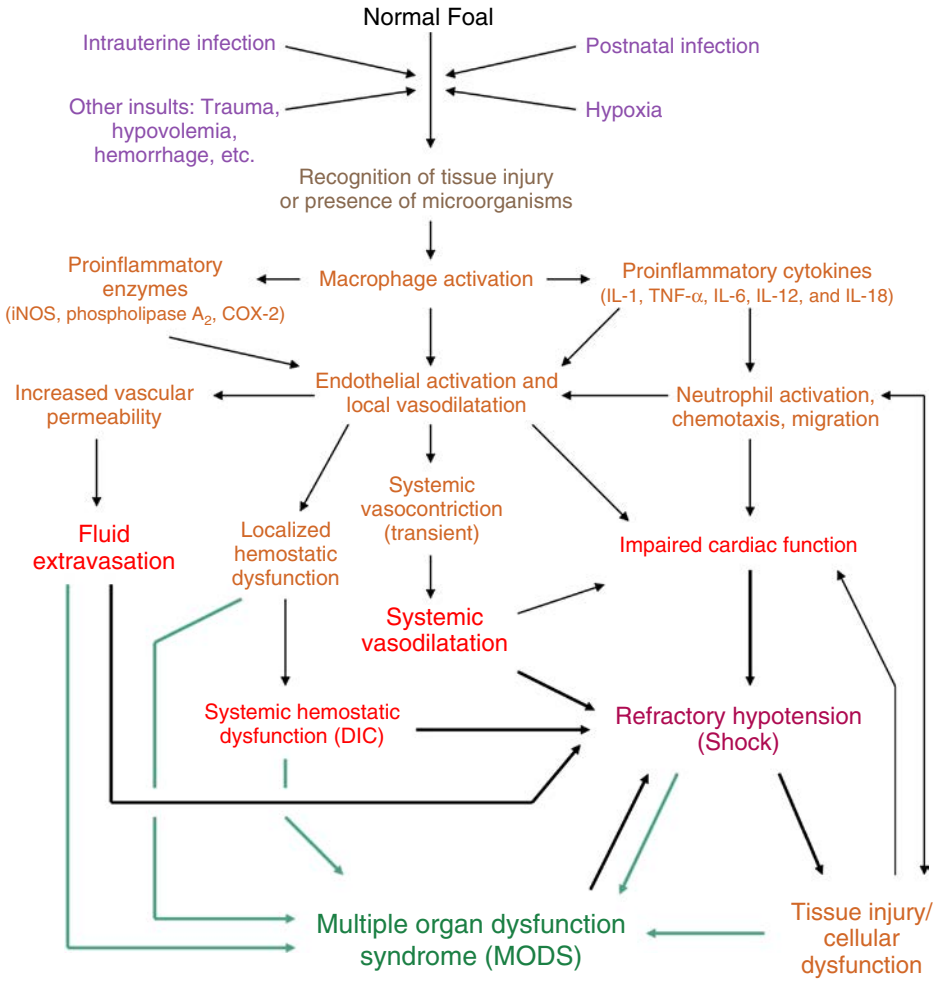
Infection	Inflammatory Response to the Presence of Microorganisms or the Invasion of Normally Sterile Host Tissue by Microorganisms
Bacteremia/septicemia	Presence of viable bacteria in the bloodstream
SIRS	Systemic response to an array of severe clinical insults
Shock	SIRS-induced hypotension refractory to fluid resuscitation in association with hypoperfusion
Sepsis	SIRS caused by infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension
Septic shock	Sepsis-induced shock
MODS	Altered organ function in an acutely ill patient requiring intervention to maintain homeostasis

MODS, multiple organ dysfunction syndrome; *SIRS,* systemic inflammatory response syndrome.
Adapted from Nathens AB, Marshall, JC. Sepsis, SIRS, and MODS: What's in a name? *World J Surg*. 1996;20(4):386-391; Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest*. 1997;112(1):235-343.

The first step in this process is the recognition of tissue injury or microbial invasion. Trauma or microbial invasion results in tissue injury, and injured cells then release or produce damage-associated molecular patterns, and these mediators can initiate a nonspecific inflammatory response.[133] Alternatively, specific bacterial cell components, termed *pathogen-associated molecular patterns* (PAMPs), may be recognized by immune cells that produce inflammatory mediators, leading to the initiation of an inflammatory response and subsequent amplification of that response.[133,134] Some of the PAMPs that can be recognized by the immune system include lipopolysaccharide (LPS; endotoxin), exotoxins from gram-negative bacteria, peptidoglycan, lipoteichoic acids, enterotoxins, or superantigenic exotoxins from gram-positive bacteria.[124,135] The development of an inflammatory response is dependent on the production, primarily by the activated mononuclear phagocyte, of numerous inflammatory mediators, including proinflammatory cytokines (tumor necrosis factor-α [TNF-α,] interleukin [IL]-1, IL-6), proinflammatory enzymes (inducible nitric oxide synthase, phospholipase A_2, cyclooxygenase-2 [COX-2]) and adhesion molecules (selectins and intercellular adhesion molecules).[136] The transcription of many of the genes encoding for these mediators, or the enzymes that produce them, is dependent on the transcription activator nuclear factor-κB, and this molecule may be a potential target for intervention in SIRS.[137-139]

It is important to understand that although bacterial infection may be responsible for the initiation of an inflammatory response, the inflammatory process itself results solely from the production of endogenous mediators. The initial changes seen in an inflammatory response are primarily the result of local vasodilatation and increased vascular permeability

BOX 20.2 Pathophysiology of Shock in the Neonatal Foal



COX-2, cyclooxygenase-2; *DIC,* disseminated intravascular coagulation; *IL,* interleukin; *iNOS,* inducible nitric oxide synthase; *TNF,* tumor necrosis factor.

Adapted from McKenzie HC, Furr MO. Equine neonatal sepsis: the pathophysiology of severe inflammation and infection. *Comp Contin Educ Pract Vet.* 2001; 23:661-672.

TABLE **20.2 Proposed Systemic Inflammatory Response Syndrome Criteria for Foals That Require the Presence of at Least Three of the Following Criteria, One of Which Must Be Abnormal Temperature or Leukocyte Count**

Parameter	Newborn (Birth to 3 Days)	Neonate (4–14 Days)	Juvenile (15 Days to 6 Months)	Weanling (7 Months to 1 Year)
Fever or hypothermia	>102.6°F (39.2°C) or <99°F (37.2°C)	>102.6°F (39.2°C) or <99°F (37.2°C)	>102.6°F (39.2°C) or <99°F (37.2°C)	>102.6°F (39.2°C) or <99°F (37.2°C)
Tachycardia (beats/min)	>115	>120	>96>44	>60>20>12.5 or <4.0
Tachypnea (breaths/min)	>56	>56	>44	>20
Leukocytosis (×10^3), leukopenia, or >5% band neutrophils	>14.4 or <6.9	>12.5 or <4.0	>12.5 or <4.0	>12.5 or <4.0
Venous blood lactate (mmol/L)	>5.0	>2.5	>2.5	>2.5
Venous blood glucose (mg/dL)	<50	<50	<50	<50

From Wong DM, Wilkins PA. Defining the systemic inflammatory response syndrome in equine neonates. *Vet Clin North Am Equine Pract*. 2015;31(3): 463-381.

caused by the effects of vasoactive mediators released by the injured or infected cell. On their arrival at the site of tissue injury, neutrophils and macrophages phagocytose foreign material and injured or dead tissue cells and attempt to destroy the phagocytosed material. In addition, macrophages release a number of factors that augment the immune response, including the proinflammatory cytokines IL-1, TNF-α, IL-6, IL-12, and IL-18. These proinflammatory cytokines increase the production of secondary inflammatory mediators, including phospholipid derivatives (prostaglandins, thromboxane A_2, and leukotrienes), and reactive oxygen species (ROS), further increasing the activity of the inflammatory response. The systemic manifestations of inflammation/infection (fever, lethargy, malaise, loss of appetite, and cachexia) are primarily caused by TNF-α and IL-1. The cytokines IL-6, IL-1, and TNF-α initiate the acute phase response in which the liver increases production of acute-phase proteins (fibrinogen, serum amyloid A, plasminogen, complement, haptoglobin, ceruloplasmin, ferritin, C-reactive protein, etc.).[140] These substances are important in many phases of the response to inflammatory stimuli, including complement activation, coagulation, fibrinolysis, transport of substances within the bloodstream, inhibition of neutrophil proteases, and modulation of the inflammatory response.[141] The acute phase response is critical in inflammation, healing, and adaptation to noxious stimuli. Also included in the acute phase response is a counterregulatory antiinflammatory component that normally functions to minimize and resolve the inflammatory response to localized stimuli. This counterregulatory response consists of antiinflammatory mediators that inhibit macrophage activation (IL-4, IL-10, IL-13, adrenal corticosteroids, transforming growth factor-β and prostaglandin-E_2), antagonists to the receptors for proinflammatory cytokines (IL-1 receptor antagonists), and soluble receptors of proinflammatory cytokines (soluble IL-1 receptor type II and soluble TNF receptors).[142] The balance between these proinflammatory and antiinflammatory components is very important in determining the characteristics of the inflammatory response, because excessive activity of the antiinflammatory component may result in immunosuppression during or after a severe inflammatory response, which has been termed the *compensatory antiinflammatory response syndrome*.[125]

In moderation the changes associated with an inflammatory response are protective, resulting in the enhanced killing of microbes by antigen-specific and nonspecific mechanisms, generalized immune stimulation, and increased activity of the systems required for healing damaged tissue. SIRS, the excessive, malignant form of the inflammatory and acute-phase responses, is characterized by the systemic activity of numerous proinflammatory mediators. These mediators all represent components of the normal inflammatory response to a localized stimulus, but the systemic activity of these proinflammatory mediators may result in an excessive, and often detrimental, response. One of the first effects seen in SIRS is widespread endothelial activation, resulting in the increased production of vasoactive mediators and alteration of vascular homeostasis. Inflammatory cytokines are responsible for activation of the endothelium, and the activated cells produce inflammatory cytokines, as well as increased amounts of nitric oxide (NO), prostaglandins, and endothelin-1.[143] Activated endothelial cells retract from one another, increasing the size of the intercellular pores and allowing for increased vascular permeability, and increase their production of tissue factor and von Willebrand factor, resulting in localized thrombosis and platelet adherence.[144]

One of the earliest systemic effects is pulmonary vasoconstriction leading to pulmonary hypertension.[145] This phase is followed by systemic hypotension caused by decreased arterial tone resulting in decreased left ventricular afterload, combined with venous vasodilatation in the large-capacity vessels that decreases venous return and right ventricular preload. These effects can progress to the syndrome of hyperdynamic shock, with increases in heart rate and cardiac output developing as compensatory mechanisms to maintain tissue perfusion.[146] This compensatory response is impaired by the reduction in left ventricular preload resulting from decreased peripheral vascular resistance, combined with decreased cardiac contractility.[147] Changes occurring in the microvasculature further contribute to the impairment of tissue perfusion. Arteriolar vasoconstriction develops because of the impairment of the normal autoregulatory systems caused by inflammatory cytokines and endothelin-1, combined with the increased production of vasoconstrictive substances. Adherence of neutrophils to the endothelium and endothelial cell swelling further reduces blood flow. Accumulation of fibrin and aggregation of platelets and red blood cells secondary to activation of the clotting system results in occlusion of the vasculature, resulting in tissue hypoperfusion. Arteriovenous shunting occurs in some tissues, whereas increased vascular permeability results in leakage of intravascular fluid into the interstitial space, further contributing to hypotension and hypovolemia and contributing to the development of tissue edema. Progressive alteration of the microcirculation leading to failure may represent the "common final pathway" of SIRS-related injury contributing to or resulting in MODS.[148]

Activation of coagulation occurs primarily through the extrinsic pathway, and endothelial injury secondary to neutrophil degranulation results in increased platelet adhesion.[149] In the normal state the accumulation of the resulting excessive amounts of fibrin would be prevented by the action of plasmin, the primary mediator of fibrinolysis. In the presence of SIRS the fibrinolytic system is suppressed because of the increased plasma concentration of plasminogen-activator inhibitor type 1, the primary inhibitor of fibrinolysis.[150] The widespread activation of the clotting system combined with impairment of fibrinolysis and depression of the inhibitors of coagulation can result in a consumptive coagulopathy potentially leading to disseminated intravascular coagulation (DIC).[150,151] Several reports have demonstrated that clinicopathologic and histopathologic evidence of coagulopathy is common in septic foals, and these findings are associated with a worsened prognosis for survival.[152-156]

The progression of these processes affecting the cardiovascular system ultimately results in shock. Shock occurs when cardiovascular function is severely impaired to the point that hypotension cannot be corrected with IV fluid administration, requiring the use of inotropic and/or vasopressor agents.[157] Shock represents severe cardiovascular dysfunction associated with SIRS and is a primary component of MODS. The development of MODS is likely the result of cardiovascular dysfunction leading to tissue hypoperfusion combined with changes in cellular metabolism that result in impairment of oxygen delivery and uptake.[158] Tissue hypoxia is manifested by increased oxygen extraction ratios and metabolic acidosis caused by increased lactate production. Pulmonary dysfunction is manifested by refractory hypoxemia, potentially caused

by increased pulmonary vascular permeability, microthrombi formation, pulmonary epithelial injury, pulmonary edema, and impairment of surfactant production.[159] Renal dysfunction is manifested by the development of azotemia and oliguria, and this acute renal failure is likely caused by alterations in the distribution of intrarenal blood flow arising from microvascular alterations with or without systemic hypotension.[158] Gastrointestinal dysfunction is primarily manifested by the presence of ileus but may also result in loss of the normal barrier function of the gastrointestinal mucosa. Impairment of the mucosal barrier may further contribute to the pathogenesis of MODS caused by bacterial translocation or endotoxin absorption.[160] Hepatic dysfunction is manifested by the development of hyperbilirubinemia and in some cases increased serum activities of hepatic enzymes (sorbitol dehydrogenase [SDH] and aspartate aminotransferase [AST]).[158] Hepatic dysfunction may result from hypoperfusion but may be heightened by the production of inflammatory mediators by the hepatic Kupffer cells secondary to the actions of systemic mediators or stimuli derived from the gastrointestinal tract.[161] Dysfunction of the central nervous system (CNS) is frequently present and may manifest as depression, which can progress to septic encephalopathy with extensive neuronal injury.[162] The development of consumptive coagulopathy (DIC) could also be considered a component of MODS, rather than merely a pathophysiologic process contributing to the development of organ failure.

Risk Factors for Neonatal Sepsis

A number of factors have been identified that increase the likelihood of septicemia in equine neonates. These risk factors may include history of placentitis, prenatal vulvar discharge, dystocia, maternal illness, premature or delayed parturition, premature placental separation, induced parturition, partial or complete failure of transfer of passive immunity (FTPI), poor sanitary conditions, improper umbilical care, prolonged transport of the pregnant mare, and the presence of localized disease in the neonate (anterior uveitis, diarrhea, pneumonia, infectious arthritis, and open wounds).[163,164] Inadequate transfer of passive immunity (serum IgG concentration of <800 mg/dL) represents a critical risk factor for septicemia and death in foals, with the risk of infection and death increasing proportionally with decreasing IgG concentrations (see later section Immunologic Disorders).[165] Pathogenic organisms can infect the equine neonate by numerous routes, although in the intrauterine environment the fetus may be exposed to organisms that have invaded the placenta or that cross the placentochorial barrier and gain direct access to the foal's bloodstream. Bacteria associated with placental disease may enter the amniotic fluid and gain access to the respiratory and gastrointestinal tracts of the fetus. After birth, infection can occur following contamination of the umbilical stump, ingestion, inhalation, or secondary to wounds.[123,164]

Clinical Presentation and Identification of the Septic Neonate

The presenting signs associated with sepsis in the neonatal foal are often vague and nonspecific. Foals may exhibit depression, lethargy, and partial or complete absence of nursing behavior. Tachycardia and tachypnea are also common initial signs but are not consistently present. Signs of systemic inflammation may include abnormal mucous membranes, with a prolonged capillary refill time, and a dark red or injected appearance. Petechiation of the mucous membranes or the skin of the inner pinnae may be present. Fever is not consistently present, because neonatal foals may exhibit impaired thermoregulation, and hypothermia is not uncommon in this population. There may be additional signs of localized infection, such as diarrhea, joint effusion (with or without lameness), respiratory disease or distress, lameness, uveitis, seizures, subcutaneous abscesses, omphalitis, or patent urachus.[164] Additional diagnostic evaluation using ultrasonography may be useful in identifying the presence of pulmonary inflammation or infection, joint or physeal infection, and internal involvement of the umbilical remnants.

Clinicopathologic evaluation of the clinically ill foal can be helpful in supporting the clinical suspicion of sepsis. Septic neonatal foals have been demonstrated to exhibit lower white blood cell (WBC), neutrophil and lymphocyte counts, and higher band neutrophil and monocyte counts compared with healthy age-matched control foals.[152] Azotemia is commonly encountered in this population but may reflect placental insufficiency (spurious hypercreatininemia) rather than neonatal sepsis or renal insufficiency.[114,166] Azotemia typically resolves rapidly with standard treatment unless underlying renal disease or uroperitoneum is present.[166] Blood glucose abnormalities are common in septic foals, with hypoglycemia being the most common.[131] This is likely caused by decreased milk intake combined with limited endogenous energy stores but may also be associated with SIRS. Arterial blood gas evaluation is extremely useful and often reveals the presence of acidosis, which may be metabolic, respiratory, or mixed in nature. Hypoxemia and/or hypercapnia may also be identified, typically in more severely affected patients. The measurement of blood lactate concentration is increasingly performed because of the availability of handheld lactate meters, and hyperlactatemia is a common finding.[167-169] Blood lactate concentrations are consistently higher in normal neonatal foals than normal adult horses for the first 24 to 72 hours of life, with normal foals exhibiting values of up to 5.0 mmol/L in the first 24 hours,[20,64] with a recent report finding values as high as 10.2 mmol/L immediately after birth.[167] In that study lactate concentrations steadily decreased over the first 3 days of life, but the median concentration at 72 hours remained slightly increased relative to normal adult concentrations, at 1.7 mmol/L. Serial measurement of blood lactate may be useful in assessing the foal's response to therapy, because the failure to normalize lactate over time has been associated with a poor prognosis for survival.[170]

The most definitive test for antemortem identification of the septicemic equine neonate remains blood culture, which should be performed at presentation in any equine neonate with a clinical suspicion of sepsis, ideally before the administration of antimicrobial therapy. This test has been reported to have fairly poor sensitivity, with false negative results obtained in up to 37% of cases of fatal septicemia.[171] It is likely that the false negative rate would be much higher in less severely ill foals that recover with antimicrobial therapy. For this reason, it has been recommended that multiple samples be collected to maximize the sensitivity of blood culture, but the majority of isolates have been reported to be present in the first culture sample, and the need for immediate antimicrobial therapy usually results in only one sample being obtained. Although it is recommended that blood culture sampling should occur before the initiation of antimicrobial therapy, there is evidence

in human patients that a delay in the initiation of antimicrobial therapy of more than 3 hours from the onset of clinical signs is associated with increased morbidity and mortality, and current recommendations suggest a delay of no more than 1 hour.[172-175] In the referral setting most foals will have been exhibiting signs of sepsis for longer than that period of time, so early blood culture collection and initiation of antimicrobial therapy is critical. For this reason when a case is being referred from the field it is advisable to initiate antimicrobial therapy on the farm before referral if transport to the referral center is likely to require more than 30 minutes. Although this may decrease the likelihood of obtaining a positive blood culture, the benefit of early treatment likely outweighs the loss of diagnostic information. It is also important to obtain bacterial cultures from suspected areas of infection during the course of treatment because the blood culture may be falsely negative or nosocomial infection may have developed during the course of treatment. The appropriate samples are dependent on the system affected but could include transtracheal aspirate, blood, urine, synovial fluid, peritoneal fluid, cerebrospinal fluid (CSF), and umbilical remnants following surgical resection.

Although historically gram-positive organisms were most commonly associated with neonatal infections, over the past 30 years the most common bacteria isolated from infected foals have been gram-negative organisms (Table 20.3).[120,171,176-182] Gram-positive organisms isolated from infected foals are often present in mixed infections with gram-negative organisms, and streptococcal species are most common. Other organisms associated with severe systemic inflammation in the equine neonate include equine herpesvirus type 1 (EHV-1) and equine viral arteritis.[183,184] It is also possible that severe hypoxia leading to hypoxic ischemic encephalopathy (HIE; neonatal encephalopathy [NE], neonatal asphyxia, and dummy foal syndrome) represents a causative factor for induction of SIRS in the equine neonate.[185]

Rapid identification of the septic neonate is critically important in ensuring that appropriate treatment is administered and in determining the prognosis for survival. The identification of the septic neonate remains problematic, however, because neonates presenting with clinical abnormalities consistent with sepsis (SIRS) may be negative on blood culture with no evidence of a focal site of infection. Attempts to identify equine neonates with septicemia have included the development of a sepsis scoring system combining historical information, objective data, and subjective measures to derive a numerical representation of the patient's condition.[24,117] Using a cutoff of ≥12 the sensitivity and specificity of the modified version of this scoring system were reported to be 93% and 86%, respectively. Unfortunately the specificity and sensitivity may not always be this high; a subsequent study found that the modified sepsis score yielded sensitivity of 67%, a specificity of 76%, a positive predictive value (PPV) of 84%, and an NPV of 55%.[186] The authors of that report suggested that it might be that this scoring system must be adapted to each ICU in which it is applied to achieve reasonably high levels of sensitivity and specificity. In another study the modified sepsis scoring system failed to predict sepsis in 49% of bacteremic foals.[178] A more recent study investing the application of the modified sepsis scoring system in a large population of 1065 foals proposed a revised cutoff value of >7, resulting in a sensitivity of 84.4% and a specificity of 41.8%, compared with the original cutoff of ≥12, which had a sensitivity of 56.4% and specificity of 73.4%.[187]

TABLE **20.3 Organisms Isolated from Foals with Sepsis/ Septicemia with Frequency of Isolation**

	Organism	Pre-2000 Isolates	Post-2000 Isolates
Gram negative	*Escherichia coli*	30.6–56	22.4
	Klebsiella pneumoniae	3.7–12.9	0.8–5.7
	Actinobacillus spp.	8–30	6.5–12.4
	Enterobacter spp.	3.5–14	3.2–8.1
	Pseudomonas aeruginosa	2–4.7	2.9
	Citrobacter spp.	4.7	—
	Pasteurella spp.	3.7	—
	Salmonella spp.	2.8–5	3.4
	Serratia marcescens	2.8–3.7	—
	Acinetobacter spp.		5.6
Gram positive	β-Hemolytic streptococci	1.2–8.8	10.6
	Other streptococci	5.9–7.1	4.1
	Staphylococcus spp.	2.8–4.8	6.3–9.7
	Clostridium spp.	2.4–3.7	1.6
	Enterococcus spp.	4.6–14	12.0–12.1

Data from Brewer B, Koterba A. Bacterial isolates and susceptibility patterns in foals in a neonatal intensive care unit. *Comp Contin Educ Pract Vet*. 1990;12(12):1773-1781; Koterba AM, Brewer BD, Tarplee FA. Clinical and clinicopathological characteristics of the septicaemic neonatal foal: review of 38 cases. *Equine Vet J*. 1984;16(4):376-382; Stewart AJ, et al. *Actinobacillus* sp. bacteremia in foals: clinical signs and prognosis. *J Vet Intern Med*. 2002;16(4):464-471; Theelen MJ, et al. Temporal trends in prevalence of bacteria isolated from foals with sepsis: 1979–2010. *Equine Vet J*. 2014;46(2):169-173; Wilson WD, Madigan JE. Comparison of bacteriologic culture of blood and necropsy specimens for determining the cause of foal septicemia: 47 cases (1978–1987). *J Am Vet Med Assoc*. 1989;195(12):1759-1763; Russell CM, et al. Blood culture isolates and antimicrobial sensitivities from 427 critically ill neonatal foals. *Aust Vet J*. 2008;86(7):266-271.

Ultimately, no sepsis score can substitute for clinical judgment, and these scores should be used as a diagnostic aid in the identification of high-risk individuals, with full consideration given to their limitations.[163,188] There has been interest in the use of serum amyloid A (SAA) as an early and accurate biomarker of bacterial infection in neonatal foals, and an early report suggested a cutoff of >100 mg/L as being highly suggestive of infection.[189] A recent unpublished study by Jokisalo et al.[104] found that using the cutoff point of >100 mg/L yielded a sensitivity of 68.6% and specificity of 68.5%, and the NPV was 87%.[190] Unfortunately 11 of 36 foals considered to be septic in that study had SAA concentrations below 25 mg/L, and 9 of 36 septic foals had SAA concentrations less than 10 mg/L, which indicates that low SAA concentrations do not rule out the possibility of bacterial sepsis.[190] Other potential biomarkers of sepsis in foals, such as IL-1β, plasma C-reactive protein, and haptoglobin, have been investigated but do not appear to be strong or accurate predictors of sepsis.[191,192] Although abnormalities of blood glucose concentration and lactate concentration are common in septic foals, these biomarkers appear to be most useful in prognostication rather than identification of the septic neonate.[126,131,193]

Because of the difficulty of definitively identifying neonates with bacterial infection it is appropriate to make the assumption that all high-risk neonatal foals presenting with clinical illness are septic.[194] Aggressive, early antimicrobial therapy is indicated, and although there are some risks associated with antimicrobial therapy these are greatly outweighed by the risks associated with withholding antimicrobial therapy from a patient with sepsis secondary to bacterial infection. An initial antimicrobial regimen should provide broad-spectrum coverage including organisms commonly identified in the practice population or region. While a detailed discussion of antimicrobial therapy can be found in the antimicrobial section of this chapter, a reasonable initial approach is the use of penicillin or ampicillin in combination with an aminoglycoside, typically amikacin. If there are concerns regarding renal insufficiency then the aminoglycoside can be replaced by a third-generation cephalosporin. Monotherapy with a third- or fourth-generation cephalosporin may be a reasonable alternative to combination therapy, particularly in the severely dehydrated patient, but may not provide full coverage for gram-positive pathogens.

Management

Management of the septic neonate can be challenging because of the requirement for constant monitoring and the need for substantial nursing care. Fluid therapy is indicated in the resuscitation and stabilization of clinically ill foals and can initially take the form of intermittent 20-mL/kg boluses given over 10 to 30 minutes. This typically needs to be accompanied by appropriate maintenance fluid therapy (see later section Fluid Therapy in the Foal). The presence of fluid-refractory hypotension may require the use of inotropic and vasopressor therapies (see later section Inotrope and Vasopressor Therapy). Respiratory support is beneficial, and in most cases it consists of intranasal insufflation of humidified oxygen at 5 to 10 L/min using a nasal cannula. Respiratory stimulants (caffeine and doxapram) may be beneficial in foals with decreased respiratory drive. If these interventions are not adequate then mechanical ventilation may be necessary. Additional therapies may include the administration of hyperimmune plasma, either for supplementation of immunoglobulins, colloidal support, or the treatment of SIRS. Antiinflammatory therapies are sometimes used, primarily consisting of nonsteroidals, but these sometimes including corticosteroid therapy if critical illness–associated corticosteroid insufficiency (CIRCI) is suspected (see later sections Antiinflammatory and Analgesic Therapy and Endocrine Disorders). Care should be taken regarding the use of antiinflammatory therapies in critically ill foals, however, because of the risk of gastrointestinal ulceration or renal injury. Gastroprotectant therapy using proton pump inhibitors is generally not used in the first few days of life because of concerns regarding increased susceptibility to nosocomial infections, but sucralfate may be a reasonable option to those drugs (see later section Gastrointestinal Disorders). The use of low-molecular-weight heparin and/or the administration of fresh or fresh frozen plasma have been suggested to address coagulopathies in the critically ill foal.[190,195]

Nursing care is one of the most important aspects of treating septic foals. Foals should be kept warm and dry, which can be difficult in the recumbent patient because of frequent urination and defecation. The placement of a urinary catheter should be considered in these patients, even though it may present a risk regarding urinary tract infections, because it greatly facilitates their nursing care, decreases the risk of decubital ulceration, and provides a means of monitoring urine output. Recumbent foals should be kept in a sternal position as much as possible to minimize the development of atelectasis in the dependent lung, and they should be turned at no longer than 2-hour intervals. Feeding septic foals can be a challenge if gastrointestinal function is abnormal, and parenteral nutrition may be needed (see the later section Nutritional Support for the Foal). Blood glucose levels should be monitored frequently, especially in foals receiving parenteral nutritional support. The development of persistent hyperglycemia may require the institution of insulin therapy. If at all possible, foals should be weighed daily; this can be another means of monitoring for fluid retention.

Prognosis

The costs associated with the intensive care of affected foals are substantial, and for that reason it is important to strive to provide an accurate prognosis for survival as well as for long-term athletic function. Given the broad range of prognostic indicators that one can use to assess the odds for survival of a critically ill foal, it can be challenging to provide an accurate and timely prognosis for the owner of such a patient. Experienced clinicians are able to provide accurate predictions for survival, but given that there will always be variations in clinician experience level and performance there has been substantial interest in developing a scoring system that could be used prospectively to enhance prognostic accuracy. In 1992 Hoffman et al. performed a study of predictive variables for survival in hospitalized neonatal foals.[111] In that study they retrospectively identified two predictive variables, anion gap and the venous partial pressure of oxygen (Pvo_2), and when these were applied prospectively in a population of 48 foals their model showed a PPV for survival of 62% and an NPV of 100%. In 1997 Furr et al. performed a similar study, developing a predictive equation for outcome in a population of 99 hospitalized neonatal foals.[112] They identified several variables associated with nonsurvival, but their model ultimately retained a different set of predictive variables, which were heart rate, rectal temperature, and neutrophil count. This model yielded a PPV of 78% and an NPV of 78% in the retrospective population. When applied prospectively to two populations of hospitalized foals the model performed differently in the two populations, with a PPV of 93% and an NPV of 72% in one population as opposed to a PPV of 83% and an NPV of 44% in the other. This was likely caused by fundamental differences in the types of cases referred and the timing of presentation to the two different hospitals.

Rohrbach et al. performed a large, multicenter study to create a predictive model for the probability of hospital discharge in hospitalized foals less than 7 days of age.[196] The variables retained in their model were foal age, ability to stand, presence of a suckle reflex, WBC count, serum creatinine concentration, and anion gap. This model yielded a PPV of 95% and an NPV of 65% in the retrospective population. When applied prospectively the model demonstrated a PPV of 90% and an NPV of 46%. Rohrbach et al. also reported the accuracy of clinician prediction of outcome, which was 83% in the retrospective population, as opposed to 81% accuracy for the mathematical model; however, the predictions were not well correlated. Interestingly, by combining the clinician's initial prediction with the model output they were able to improve the accuracy of

TABLE **20.4 Survival Scoring System Proposed by Dembek et al.**[115]

Variable	Value	Points	Value	Points	Score
Cold extremities	No	2	Yes	0	
Prematurity (<320 days)	No	1	Yes	0	
>2 infection/inflammatory sites	No	1	Yes	0	
IgG (mg/dL)	<400	0	≥400	1	
Glucose (mg/dL)	<80	0	≥80	1	
White blood cells × $10^3/\mu L$	≤4	0	>4	1	

From Dembek KA, et al. Development of a likelihood of survival scoring system for hospitalized equine neonates using generalized boosted regression modeling. *PLoS One*. 2014;9(10):e109212.

TABLE **20.5 Probability of Survival Using Survival Scoring System of Dembek et al.**[115]

Total Score	Probability of Survival (%)
0	3
1	8
2	18
3	38
4	62
5	82
6	92
7	97

From Dembek KA, et al. Development of a likelihood of survival scoring system for hospitalized equine neonates using generalized boosted regression modeling. *PLoS One*. 2014;9(10):e109212.

the survival estimate by 12%.[196] Another multicenter study was performed by Dembek et al., in which they developed a survival scoring system for critically ill foals.[115] Their final model retained six variables, which were cold extremities, prematurity, ≥2 infection/inflammation sites, IgG concentration, glucose concentration, and WBC count. These variables were assigned scores depending on their respective values, and totaling of the individual scores yields the final survival score (Table 20.4). A score of 0 was associated with a 3% probability of survival, whereas the maximum score of 7 was associated with a 97% probability of survival (Table 20.5). They validated their foal survival score (FSS) prospectively using score cutoffs of ≥4 for foals predicted to survive and <4 for foals predicted to die, which resulted in values for a PPV of 91% and an NPV of 86%. Foals with an FSS of 4 to 5 were 24.2 more likely to survive than foals with a score <4, and foals with a score of 6 to 7 were 91 times more likely to survive.[115] Most recently, Giguère et al. reported a retrospective study examining factors associated with survival in a population of 1065 hospitalized foals over 26 years at one academic referral hospital.[116] The variables retained in their model included positive blood culture, neutropenia, hypothermia, bicarbonate, P_{CO_2}, presence of infectious orthopedic disorders, and sepsis score. The reported sensitivity of their model was 97%, and the specificity was 75%. Of particular interest was the increase in the odds of survival for foals born in the 1990s, which were 2.2 times greater compared with those born in the1980s, whereas foals born in the 2000s had a 3.4 times greater odds of survival compared with those born in the 1980s.[116]

NEUROLOGIC DISORDERS

Weakness and abnormal behavior are common presenting signs in clinically ill foals and may be associated with neurologic dysfunction; however, they may also be caused by a myriad of other conditions. For this reason thorough evaluation and assessment of abnormal foals is extremely important. This evaluation should include the collection of a thorough history (to include maternal health and reproductive history) and performance of a complete physical examination, which should include a detailed neurologic assessment. The first objective of neurologic assessment is to ascertain whether true neurologic dysfunction is present and, subsequently, to establish neuroanatomic localization of any lesions. This information is then used to direct further diagnostic and therapeutic efforts.

The first stage of the neurologic examination should be assessment of the foal's behavior and level of alertness, but when doing so it is important to remember the normal development and progression of foal behavior. In the first few hours after parturition foals exhibit fairly dramatic increases in consciousness, strength, and coordination, as well as awareness of and interaction with their environment. Thus it is important to understand at what point they should be along that continuum based on the time since birth. Most foals will be able to stand within 1 to 2 hours of birth, and it is typical for the initial efforts at standing to be poorly coordinated and at times unsuccessful. The initial stance will be base wide, with prominent swaying back and forth. However, once the foal stands successfully rapid improvement in ambulation should be noted and the foal will begin seeking the mare's udder. A suckle reflex should be present within minutes after birth, and foals will actively engage in suckling behavior even while recumbent and without access to the udder. Most foals suckle successfully within 1 to 3 hours after birth, but this can range from 0.5 to 7 hours. Nursing episodes should last from 1 to 5 minutes and are typically followed by periods of drowsiness, recumbency, and sleep.[197] Foals become increasingly coordinated and confident over the first few days of life and will avoid handlers if possible. Once restrained they typically struggle vigorously but will become limp when compressed along their long axis.[198] This relaxation response in response to squeezing is particularly pronounced in the first several hours after birth.[199]

The next stage of the examination is an assessment of the foal's conformation, posture, and gait. The head should be above the horizontal plane when foals are standing, and no head tilt or rotation should be noted.[197] Foals carry their heads with pronounced flexion of the atlantooccipital joint and tend to move their heads with jerky motions that may resemble cerebellar dysfunction in the adult.[198] The foal's gait should be evaluated by observing the foal in unrestrained, spontaneous movement, and this can be facilitated by leading the dam and observing the foal as it follows.[200] The neonatal foal may appear somewhat dysmetric compared with an adult, but this typically improves with exercise.[201] Foals typically have a somewhat exaggerated "bouncy" and hypermetric gait compared with an adult.[197]

Examination of the cranial nerves is similar to the adult, and begins by observation of facial expression, muscle tone, and symmetry. Touching the nasal septum and the inside of the ear canal, which should elicit avoidance behavior, will aid in the assessment of facial sensation. The flick reflexes should be evaluated by gently touching the tip of a hemostat to the pinna of the ear, the medial and lateral canthi of the eyes, and the commissure of the lips.[197] The eyes should be examined for orientation, pupillary size, and pupillary light reflexes. The globe typically shows a ventromedial deviation that will resolve by 1 month of age.[198] The pupil is somewhat round at birth, but direct and consensual pupillary light reflexes, although somewhat slow initially after birth, should be present in normal foals in the first day of life.[202] Dazzle reflexes should be present as well. A menace response is not present at birth but will develop within 1 to 2 weeks of life.[202] Even though a menace response is not present, most foals will show visual avoidance by moving their head away from a threatening gesture toward the eye.[197] The eyes should be assessed for the presence of nystagmus, and although lateral movements of the head will elicit normal physiologic nystagmus, spontaneous nystagmus with the head stationary is abnormal.[197] The suckle reflex and jaw tone should be assessed by inserting a gloved finger into the mouth. The foal should also be observed to nurse, paying close attention to swallowing movements in the pharyngeal region and observing for nasal regurgitation after nursing.

Testing the cervicofacial reflex along the neck and the cutaneous trunci reflex along the thorax will allow assessment of the long spinal reflexes. If these are abnormal, then segmental cutaneous sensation should be assessed. Further assessment of spinal reflexes is best accomplished after placing the foal into lateral recumbency, which also allows for better assessment of muscle tone in the limbs. There should be substantial extensor tone, but the limbs should be able to be flexed with persistent gentle pressure. The triceps, extensor carpi radialis, biceps, patellar, sciatic, and gastrocnemius reflexes should all be able to be reliably elicited and are more pronounced than in adults. The foal should respond to pressure on the sole of the hoof and flexion of the upper limb with an extensor response, known as the extensor thrust reflex.[197] A flexor or withdrawal reflex should be present in response to pinching of the skin of the distal limb, and most foals will exhibit a crossed extensor response by extending the opposite limb at the same time.[197] This crossed extensor reflex should be absent after the first 3 weeks of life.[200]

Although most foals with neurologic dysfunction will display generalized signs, such as abnormal behavior, seizures, depression, poor affinity for the mare, and loss of suckle, the findings of the neurologic examination can be used to assess the nature and severity of the dysfunction and to provide neuroanatomic localization of any lesions that may be present (Table 20.6).

Selected Disorders

Neonatal Encephalopathy and Hypoxic Ischemic Encephalopathy

NE in humans is a clinically defined syndrome of neonatal brain dysfunction, manifested by difficulty with the initiation and maintenance of respiration, depression of tone and reflexes, subnormal levels of consciousness, and frequently seizures.[203] NE represents a very broad categorization that encompasses any neonate with neurologic signs, regardless of etiology. This term has recently come into use in the equine literature as well.[65,185,197,204] HIE is a specific type of NE typically associated with adverse peripartum events that result in episodes of cerebral hypoxia and ischemia. A wide variety of terms have been used synonymously with HIE in reference to affected foals, including neonatal maladjustment syndrome, perinatal asphyxia syndrome, dummy foal, wanderer, and barker foal.[185,205] The clinical presentation associated with HIE in foals can range quite dramatically from mild behavioral abnormalities to severe neurologic abnormalities including central blindness, seizures, coma, and death.[206] Unfortunately these clinical signs are not specific for HIE, and diagnosis is typically made based on elimination of other potential etiologies. Indeed, the confusion associated with the nomenclature reflects the clinical challenges associated with determining the etiology of neurologic dysfunction in the neonatal foal, because it has long been recognized that many foals presenting with the clinical signs typically associated with HIE have no documented evidence of asphyxiation or a hypoxic-ischemic event.[65,207] The fact that many affected foals recover rapidly and demonstrate no neurologic sequelae, in contrast to the situation in human infants, further reinforces this dilemma.[65] There is evidence that elevations in neurosteroid concentrations may be associated with NE in some cases, particularly those with no discernible history of a hypoxic insult.[65,67,68,205,208,209] A novel "squeeze" technique has been reported primarily as an aid in foal restraint and, although only anecdotal, in time this technique may have some benefit in moderating excessive inhibitory neurosteroid concentrations and improving foal consciousness.[199]

With the introduction of the term *NE* in human medicine there has been an effort toward restricting the term *HIE* to the subset of cases of NE in which there is evidence of a hypoxic-ischemic cause, and that approach will be used here.[203] Multiple conditions have been associated with peripartum asphyxia and HIE in foals, including dystocia, induction of parturition, cesarean section, placentitis, premature placental separation, meconium aspiration, twinning, in utero infection, severe maternal illness or surgery, and postterm pregnancy.[185,210,211] Affected foals may appear normal at birth but will typically demonstrate neurologic dysfunction within the first 72 hours of life.[65] The clinical signs of HIE can be highly variable but may include behavioral changes (loss of affinity for the mare, inappropriate nursing behavior, loss of awareness of the environment, head-pressing, and abnormal vocalization), altered mentation (depression, stupor, somnolence, difficult to arouse, and coma), cranial nerve dysfunction (loss of suckle reflex, weak tongue tone, tongue protrusion, and dysphagia), and CNS dysfunction (hypotonia, tremors, hypertonia, proprioceptive deficits, central blindness, irregular respiratory patterns, opisthotonus, and seizures).[65,185,210-213] Two major categories of HIE-affected foals have been described, with Category 1 foals born normally but then developing signs within the first 48 hours of life, and Category 2 foals being abnormal from birth, usually in association with documented risk factors for HIE.[197] It is common to see multisystem involvement, because hypoxic injury will adversely affect most body systems. The gastrointestinal tract and renal system appear most susceptible, but the cardiovascular system, pulmonary system, and liver and endocrine systems may all be involved.

The pathophysiology of hypoxic injury is complex and may vary to some extent in different body systems, but the focus will be on the nervous system here. The initial insult of tissue

TABLE **20.6** **Neuroanatomic Localization Based on Results of the Neurologic Examination**

Evaluation	Pathways	Major Signs of Disorder
Behavior	Forebrain (primarily cerebrum)	Reduced affinity for dam, restlessness, head pressing, compulsive walking
Alertness	All of brain	Lethargy, stupor, semicoma, coma
Avoidance, nasal	Cranial nerve Va, pons, cerebral cortex	Facial hypoalgesia
Avoidance, visual	Cranial nerve II, thalamus, cerebral cortex	Blindness
Head position	Cranial nerve VIII, hindbrain	Head tilt, turn, body lean, walking in circles, ataxia, nystagmus
Eye position and movement	Cranial nerves III, IV, VI, and VIII, midbrain, hindbrain	Strabismus, nystagmus
Flick reflexes	Cranial nerves V and VII, pons, hindbrain	Facial paralysis, facial hypoalgesia, absent flick reflexes
Dazzle reflex	Cranial nerve II, subcortex, midbrain, cranial nerve VII	Absent dazzle reflex
Pupillary light reflex	Cranial nerve II, midbrain, cranial nerve III	Absent pupillary light reflex
Suckle	Cranial nerves V, VII, and XII, pons, hindbrain, cerebrum	Weak or absent suckle
Swallow	Cranial nerves IX and X, hindbrain	Flow of milk from the nose
Cervicofacial reflex	Cervical spinal nerves and spinal cord, cranial nerve, VII, (hindbrain)	Diminished cervicofacial reflex
Cutaneous trunci reflex	Thoracic spinal nerves and spinal cord, brachial plexus, lateral thoracic nerve	Diminished reflex caudal to spinal cord lesion
Cutaneous sensation	Peripheral nerves, spinal cord, cerebral cortex	Cutaneous hypoalgesia/anesthesia
Gait	Cranial nerve VIII, cerebellum, hindbrain, spinal cord, peripheral nerves	Ataxia
Limb strength	Spinal cord, peripheral nerves	Limb weakness at or caudal to the level of the lesion
Flexor reflex (pelvic), patella, sciatic reflexes	Spinal cord, peripheral nerves (L3-S2)	Pelvic limb weakness, diminished or absent reflexes
Flexor reflex (thoracic), biceps, triceps reflexes	Spinal cord, peripheral nerves (C6-T2)	Weakness of thoracic with or without pelvic limbs, diminished or absent reflexes
Anal/tail clamp reflex	Spinal cord, cauda equine, peripheral nerves (S2-Coccyx)	Reduced or absent anal/tail clamp reflex

From MacKay RJ. Neurologic disorders of neonatal foals. *Vet Clin North Am Equine Pract*. 2005;21:387-406, vii.

hypoxia initiates a cascade of deleterious events. First, there is a shift toward anaerobic metabolism that leads to depletion of high-energy phosphate (adenosine triphosphate [ATP]) reserves, accumulation of lactate, and a failure of cellular homeostasis.[204] Decreased activity of transcellular pumps that depend on ATP leads to intracellular accumulation of sodium, calcium, and water.[214] Membrane depolarization leads to release of the potent excitatory amino acid glutamate, which accumulates in the extracellular space. Glutamate then acts on the *N*-methyl-D-aspartate (NMDA) receptor, opening NMDA channels, potentiating calcium influx into the neurons, and contributing to neuronal injury.[215] This cascade of events results in the development and perpetuation of excitotoxicity, which ultimately leads to neuronal cell death and brain injury.[204,214] Hypoxia and subsequent reperfusion also initiate the increased production of ROS and NO, ultimately resulting in the process known as *reperfusion injury* and leading to further tissue damage via cell death and activation of apoptotic cascades.[204,214] Tissue injury initiates an inflammatory response, leading to increased local blood flow and vascular permeability, which may result in the development of edema. Inflammatory cell infiltration leads to further tissue injury and upregulation of ROS production.[185,216] Increased concentrations of neurosteroids have been documented in affected foals, but their role in the pathophysiology of HIE is unclear because they may actually have a neuroprotective effect.[65,66,68] In situations where the degree or duration of hypoxia is not overwhelming, a biphasic pattern of injury may be observed in which the initial acute phase of injury is stabilized, followed by an ongoing latent phase of injury that results in more severe clinical deterioration several hours later.[214]

The diagnosis of HIE is challenging because of the substantial overlap between the clinical signs associated with HIE and other causes of NE, as previously discussed. Unfortunately

there is no definitive test for HIE, so diagnosis is typically made based on historical information, clinical presentation, and the elimination of other potential causes. Additional diagnostics that are used in human infants include electroencephalography (EEG) as well as imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI).[204] An EEG is difficult to accomplish in the unsedated foal, and interpretation can be confounded by patient movement or sedation, rendering this modality of limited use in foals. Brainstem auditory evoked response testing is widely used in human neonatal ICUs to aid in the assessment of CNS function and the diagnosis of HIE, and this technique has been described and validated in foals.[217,218] A recent report described the MRI findings associated with a presumptive case of NE in a foal, and the increasing availability of MRI in equine referral centers may render this modality of utility in the future.[219] There has been tremendous interest in identifying biomarkers of HIE in human infants, and two potential biomarkers of HIE have been investigated in foals.[206,220] A recent study measured the plasma concentration of the phosphorylated axonal forms of neurofilament H (pNF-H) and ubiquitin C-terminal hydrolase 1 (UCHL1) and found that the diagnostic performance of UCHL1 was significantly higher than that of pNF-H, with the sensitivity and specificity of UCHL1 for diagnosis of neonatal HIE reported as 70% and 94%, respectively.[206] This test is not available for clinical use at this time, however.

Prevention of HIE is difficult because of the occult nature of the injury in many cases, but all efforts should be made to identify mares at risk of maternal or placental disease during pregnancy and to implement appropriate treatment and monitoring. Close observation of at-risk mares during parturition may allow for early intervention and assistance, if needed. Foals should be closely observed during and after parturition for signs of distress or neurologic dysfunction and appropriate supportive care or resuscitation provided.[185] Foals that exhibit seizure activity within the first 24 hours of hospitalization have been shown to have poorer outcomes than foals that do not exhibit seizure activity.[205] The prognosis for survival for foals with uncomplicated disease that survive the first 5 days of life and demonstrate neurologic improvement during that time appears to be good.[185]

Sepsis-Associated Encephalopathy

Brain dysfunction occurring as a result of severe systemic inflammation secondary to infection, but not involving overt CNS infection or other types of encephalopathies, has been termed *sepsis-associated encephalopathy* (SAE).[221] This syndrome has also been referred to as septic encephalopathy and sepsis-associated brain dysfunction.[222] SAE is thought to represent a neglected cause of neurologic dysfunction in human patients because of the difficulty in diagnosing a condition that has no precise clinical or biological markers, and the situation is likely similar in NE of foals.[223] In humans the clinical spectrum of SAE may include signs ranging from mild behavioral abnormalities and altered sleep states to severe disturbances of consciousness and even coma.[224] The pathophysiology of SAE appears to involve direct neuronal cell injury, mitochondrial and endothelial dysfunction, disturbances of neurotransmission, and derangements of neuronal calcium homeostasis.[223,224] Given the substantial overlap between the presentations of HIE and SAE, and the frequent involvement of sepsis in the critically ill foal population, SAE should be considered as a potential cause of NE in foals.

Seizure Disorders

Seizures are a common manifestation of neurologic dysfunction in human neonates and in foals.[65,225] Seizures in foals can be idiopathic, the result of primary CNS disorders, or secondary to numerous conditions involving other body systems or diffuse disease. Seizures are defined as abnormal, stereotyped, and paroxysmal alterations in neurologic function and may include behavioral changes, motor dysfunction, autonomic dysfunction, and loss of consciousness.[226] Seizure activity indicates neurologic dysfunction of the forebrain associated with abnormal electrical activity. Neonates appear to be at increased risk of seizure activity because of the relative excitability of the developing brain combined with the high risk of brain injury in the neonatal period.[227] Diagnosis of seizure activity is primarily based on clinical signs but can be challenging because of the subtle signs in some cases, the potential confounding effects of other conditions altering patient behavior, neurologic function, or level of consciousness. Subtle signs may include abnormal eye movements, tremors, excessive stretching, excessive extensor tone, hyperesthesia, and apneustic breathing, whereas overt signs of seizures typically include rapid nystagmus, paddling, hyperextension, and excessive movements of the mouth.[198] Unexplained physical trauma may represent evidence of unobserved seizure activity. Confirmation of seizure activity is achieved by EEG examination, but this can be challenging in foals. Specific treatment may not be required in individuals with very subtle or rare signs of seizure activity but is clearly indicated in patients with repeated, generalized seizure activity. Foals that exhibit seizure activity within the first 24 hours of hospitalization have been shown to have poorer outcomes than foals that do not exhibit seizure activity.[205]

Bacterial Meningitis

Bacterial meningitis is an uncommon condition but appears to be more frequent in foals than adults.[228] It has been reported to occur in 2.6% to 10% of foals suffering from sepsis and is associated with high mortality rates.[25,176,228,229] The most common clinical findings in foals with bacterial meningitis are lethargy, weakness, recumbency, decreased suckling reflex, abnormal pupillary light reflexes, hyperesthesia, cervical pain, fever, blindness, seizures, and coma.[228,230,231] Clinicopathologic findings may include FTPI, neutropenia or neutrophilia, and hyperfibrinogenemia and most often reflects systemic inflammation related to sepsis.[197,228,230,231] Definitive diagnosis is by means of CSF analysis, with neutrophilic pleocytosis (total nucleated cell count >7 cells/μL) and increased total protein (TP) concentration (TP >120 mg/dL) being present in most cases.[232,233] Cellular degeneration is frequently observed in the CSF, along with intracellular bacteria.[197,233] Meningitis is most commonly associated with the same types of bacteria associated with neonatal sepsis, and *Escherichia coli, Actinobacillus* spp., *Klebsiella* spp., *Streptococcus* spp., and *Salmonella* spp. are the most commonly reported.[228,233,234] Treatment depends on intensive antimicrobial therapy using drugs capable of achieving therapeutic concentrations within the CNS and is ideally guided by culture results.[235] Drugs such as penicillin, ceftiofur, and the aminoglycosides are unlikely to be effective because of poor penetration, so consideration should be given to other treatments such as ceftriaxone, cefepime, cefotaxime, imipenem, chloramphenicol, and rifampin (as an adjunct).[235] Because

much of the damage occurring in the CNS in meningitis is secondary to the inflammatory response, there is a rationale for using antiinflammatory therapy in these cases. The use of corticosteroids as adjunct therapy in human patients has been associated with a reduction in neurologic sequelae but did not alter mortality.[236,237] The prognosis for survival in foals with appropriate treatment is fair to poor, depending on the severity of the presenting signs.[228]

Trauma

Trauma should always be considered when evaluating the foal with acute onset of neurologic signs. Brain trauma may be associated with blunt force trauma in the region of the frontal or parietal bones or may be secondary to trauma to the poll or temporal region secondary to the foal flipping over backward.[197] Vertebral injury can occur as well and may be associated with the foal running into an immobile object. Outward signs of trauma may not be obvious, and imaging studies may be required for confirmation. Examination may reveal superficial abrasions, pain on palpation of affected areas, soft tissue swelling, crepitus, or bleeding from the nares or ears. Treatment is supportive in nature along with stabilization of bony injuries if possible. Antiinflammatory and antioxidant therapy may be of some benefit, but corticosteroid administration is not recommended. Appropriate antimicrobial therapy is indicated when there is the possibility that the CNS may have been contaminated.

Botulism

Botulism is a syndrome of flaccid paralysis caused by the neurotoxins produced by *Clostridium botulinum,* colloquially known as "shaker foal syndrome." Most equine cases are associated with toxin types B and C, although type A cases have been reported.[238] The syndrome in foals is thought to be toxicoinfectious in nature, in which the foal ingests spores from the environment that germinate in the gastrointestinal tract and spread toxin, as opposed to the more common form of "forage poisoning" associated with ingestion of a preformed toxin as seen in adults.[239] Botulism toxin acts presynaptically at the neuromuscular junction by inhibiting the release of the neurotransmitter acetylcholine. Severely affected foals may be found dead, but more commonly there is a sudden development of weakness, trembling, and dysphagia in a previously healthy foal.[238] Progressive deterioration is typically observed, even with appropriate treatment, and respiratory paralysis is the cause of death in most cases. Diagnosis is typically presumptive based on the history and clinical presentation because confirmation requires demonstration of spores and/or toxin in the feces of affected animals, which can be difficult. A mouse bioassay has been validated for the diagnosis of botulism in horses and foals.[240] This assay is highly specific in foals, with specificity and PPV reported as 100%, but it exhibits low sensitivity (53%) and NPV (52%).[240] Treatment is based on the administration of antitoxin and the provision of supportive care. Foals that become recumbent will likely die unless they receive ventilatory support in the form of mechanical ventilation, which may be required for as long as 2 weeks.[238] With early and appropriate care the prognosis for survival in cases of types B and C botulism is reported to be good.[238] Type A botulism has been associated with more severe clinical signs and a higher case fatality rate, but a recent report described the successful treatment of a foal affected by type A botulism.[241]

Tetanus

Tetanus is a syndrome of spastic paralysis caused by the neurotoxin tetanospasmin produced by *C. tetani.* Although rare because of the widespread use of tetanus toxoid vaccines, recent cases have been reported in foals.[242,243] This syndrome usually affects foals over 7 days of age and is associated with the development of an anaerobic site of infection, reportedly most often within the umbilical remnants.[244] Tetanospasmin acts to prevent the release of the inhibitory neurotransmitter GABA by spinal interneurons, leading to disinhibition of spinal motor neurons, resulting in excessive motor activity and spastic paralysis.[245] The primary clinical signs are rigidity, excessive autonomic activity, and episodic muscle spasms, which lead to trismus, facial spasm, third-eyelid protrusion, and dysphagia. Progression leads to recumbency, and death is usually caused by respiratory failure. Treatment of tetanus depends on the administration of tetanus antitoxin, supportive care, control of muscle spasms, and source control.[242,246] Control of muscle spasms is often accomplished using benzodiazepines, either administered as needed or by continuous rate infusion (CRI). Magnesium sulfate represents an affordable and viable option to benzodiazepines in humans and may be a reasonable option in foals as well.[197] Source control may involve surgical excision or drainage of the site of infection in combination with antimicrobial therapy. Penicillin has been the standard treatment, but metronidazole may also be used. The prognosis for survival is good in cases that do not progress to recumbency, but it is guarded to poor once recumbency occurs, although recent success has been reported.[242,243]

Metabolic Encephalopathies

There are a number of metabolic derangements that have the potential to adversely affect neurologic function and potentially cause neurologic injury in foals. These include hypoglycemia, hyponatremia and hypernatremia, hypocalcemia, hyperbilirubinemia, and hyperammonemia. Hypoglycemia is common in critically ill foals, and severe hypoglycemia is associated with nonsurvival to hospital discharge.[131] Persistent, severe hypoglycemia is associated with neuronal degeneration in both the central and peripheral nervous systems, but interestingly this phenomenon is only seen in human patients receiving insulin therapy or suffering from hyperinsulinemias.[247,248] Although short-term hypoglycemia may not cause permanent injury, it certainly can cause neurologic dysfunction and adversely affects other body systems and should therefore be addressed with dextrose supplementation.[249,250]

Sodium disorders are fairly common in critically ill foals, but they are not typically associated with neurologic dysfunction unless the derangements are very severe or there are dramatic, acute changes in the serum sodium concentration. These rapid changes in sodium concentration cause dramatic fluid shifts in the tissues of the CNS, with hyponatremia potentially being associated with the development of cerebral edema, whereas hypernatremia may cause an osmotic demyelination syndrome.[250] Hyponatremia is more common than hypernatremia, and neurologic signs are most typically associated with sodium concentrations less than 120 mEq/L.[249,251] The neurologic manifestations of hyponatremia may include an abnormal stance or gait, depression, blindness, or seizures.[252,253] Treatment of these disorders involves correction of the underlying whole body sodium/water imbalances, because hyponatremia represents a free-water excess and hypernatremia a free-water deficit.[254] Hyponatremia should be addressed

by administering fluids that are relatively hypertonic compared with the plasma osmolality, and although the literature suggests that initial correction should be rapid followed by slower correction, a more conservative approach may be appropriate in foals.[249] Hypernatremia should be addressed using fluids that are relatively hypotonic but should be gradual (<0.5 mEq/L/h).[249]

Hypocalcemia is often asymptomatic but can be associated with tetany and seizures.[254] Rapid decreases in the ionized calcium concentration appear more likely to be associated with clinical signs in critically ill foals.[250] A syndrome of hypocalcemic seizures has been described in young foals, typically from 2 to 5 weeks of age.[255,256] This condition is thought to be caused by primary hypoparathyroidism.[249,256]

Bilirubin is capable of crossing the blood-brain barrier, especially when plasma concentrations of bilirubin are very high and in neonates where the blood-brain barrier is more permeable. Bilirubin is neurotoxic and can cause neurologic dysfunction and irreversible brain damage, which is a clinical syndrome termed *kernicterus*.[257,258] The most important cause of clinical icterus in equine neonates is neonatal isoerythrolysis (NI). Treatment of NI is discussed elsewhere in this chapter, but primarily it consists of supportive care and blood transfusions. These treatments do not address the hyperbilirubinemia, which can only be reduced using therapeutic plasma exchange.[258]

Hyperammonemia has been associated with neurologic dysfunction in foals and adult horses, and the clinical signs associated with hyperammonemia include depression, blindness, aimless wandering, head pressing, ataxia, circling, recumbency, and death.[259-262] Hyperammonemia may develop secondary to hepatic insufficiency, portosystemic shunts, or increased gastrointestinal production (intestinal hyperammonemia).[259-262] A disorder suspected to represent hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, a genetic defect in the urea cycle resulting in persistent hyperammonemia, has been reported in Morgan foals.[263] Intestinal hyperammonemia is typically seen in association with clinical signs of gastrointestinal disease.[261]

Congenital Disorders

Hydrocephalus

Hydrocephalus is a condition resulting from impaired drainage of CSF caused by congenital defects or inflammation that results in the compression of the brain caused by increased intracranial pressure.[264,265] This condition is considered to be uniformly fatal and is rare in horses but may be more frequent in the Friesian breed.[265] Diagnosis is typically presumptive and confirmed on postmortem examination, but CT and MRI can be used for definitive antemortem diagnosis if necessary.[266]

Occipitoatlantoaxial Malformation

Foals born with occipitoatlantoaxial malformation typically exhibit paresis and ataxia of all four limbs, but in some cases foals may be born dead or comatose.[197] Foals may have a head tilt or abnormal head carriage, movement of the head may reveal a clicking sound, and neurologic deficits may range from inapparent to severe enough to result in quadriplegia.[197,267] The condition is familial in the Arabian breed but may occur in other breeds as well.[267] Diagnosis is typically confirmed radiographically, although contrast myelography, CT, or MRI may be useful in some cases.[268,269] Foals exhibiting clinical signs are typically euthanized because of the poor long-term prognosis.

Cerebellar Abiotrophy

Equine cerebellar abiotrophy is a neurodegenerative condition affecting the cerebellum, which results in ataxia, head tremors, and loss of equilibrium.[270,271] Cerebellar abiotrophy is relatively rare in horses, and, although it can occur in multiple breeds, it is most common in Arabian horses. It is inherited as an autosomal recessive trait, with clinical signs generally detectable between 4 weeks and 6 months of age.[270-272] Diagnosis is typically presumptive based on breed association and clinical presentation because definitive antemortem diagnosis is difficult.

Epilepsy

A syndrome of juvenile idiopathic epilepsy (JIE) has been described in Arabian foals of Egyptian lineage.[273,274] This syndrome is characterized by recurrent tonic-clonic seizures and resembles benign-familial neonatal convulsion syndrome in humans.[275] JIE exhibits an early onset of clinical signs in the first days to months of life but appears to be self-limiting and resolves by 1 to 2 years of age.[273,275]

Narcolepsy and Cataplexy

Narcolepsy in the horse is characterized by paroxysmal sleep attacks, and affected animals may remain standing, whereas cataplexy represents the complete loss of muscle tone combined with areflexia leading to recumbency.[276] Narcolepsy without cataplexy has been described in Thoroughbred, Warmblood, and Icelandic horses, and in some cases there may be a familial component.[276,277] Narcolepsy with cataplexy is very rare, but it has been described in horses.[276,278]

Treatment of Neonatal Encephalopathy

Because of the broad range of disease processes associated with the development of NE in foals, there is no single treatment strategy. This discussion will focus on treatments directed toward the prevention of CNS injury and normalization of nervous system function. Foals with NE are typically suffering from severe systemic inflammation as well, and specific treatment recommendations for supportive care; infection control; correction of metabolic disorders; and normalization of cardiovascular, pulmonary, gastrointestinal, and renal function in critically ill foals is covered in detail elsewhere in this chapter.

The first objective is stabilization of the patient systemically, because the restoration and maintenance of CNS perfusion is critical in ensuring adequate delivery of oxygen and glucose. IV fluid therapy is often required to correct hypovolemia and support cardiovascular function, but vasopressors and inotropes may be required to normalize blood pressure. It is important to avoid overhydration or hypertension, however, because these may potentiate CNS injury.[185,279] Normalization of blood glucose concentrations is important as well, but care must be taken to avoid hyperglycemia, because critically ill foals may be intolerant of dextrose infusions. Intranasal oxygen supplementation is recommended in weak or recumbent foals, or those with documented arterial hypoxemia, to support oxygen delivery, and blood transfusions may be needed in anemic patients for the same reason.

The second objective is to control seizure activity, if present. Specific treatment may not be required in individuals with very subtle or rare signs of seizure activity, but it is clearly

TABLE **20.7 Drugs Used for the Control of Seizures in Foals**

Drug	Dosage	Route	Frequency	Comments
Diazepam	0.1–0.4 mg/kg	IV	As needed	Short-term seizure control
Midazolam	0.04–0.1 mg/kg 0.02–0.06 mg/kg/h	IV IV	As needed CRI	Short-term seizure control For persistent seizures
Phenobarbital	2–10 mg/kg 3–10 mg/kg	IV PO	12 h 12 h	For persistent seizures Monitor serum concentrations
Pentobarbital	2–10 mg/kg	IV	Single dose	For status epilepticus—use caution
Phenytoin	1–5 mg/kg 1–5 mg/kg	IV, PO PO	4 h, up to 6 doses 12 h	—
Potassium bromide	10 mg/kg 60 mg/kg	PO PO	8 24 h	Monitor serum concentrations

CRI, Continuous rate infusion; *IV,* intravenously; *PO,* orally.
From Wilkins PA. Disorders of foals In: Reed SM, Bayly WM, Sellon DC, eds. *Equine internal medicine*. St. Louis, MO: Saunders Elsevier; 2010; Morresey PR. Neurological conditions and seizure management. *AAEP Focus on the First Year of Life*. 2014;29-35; Wong D, Wilkins PA, Bain FT, et al. Neonatal encephalopathy in foals. *Comp Contin Educ Pract Vet*. 2011;33:E5; Magdesian KG. Foals are not just mini horses. In: Cole C, Bentz B, Maxwell L, eds. *Equine pharmacology*. Oxford, UK: Wiley-Blackwell; 2015:99-117.

indicated in patients with repeated, generalized seizure activity. Benzodiazepines (diazepam and midazolam) represent the first-choice therapy for control of acute seizures in foals because of their rapid onset of action and minimal depressive effects (Table 20.7).[30,198] Bolus IV doses are used for the control of single seizure episodes, but CRI of midazolam can be used to control persistent seizures. Other options for the control of persistent seizures include phenobarbital, pentobarbital, and potassium bromide. Phenobarbital can cause substantial CNS depression when first administered but is generally well tolerated, even with prolonged use. Serum phenobarbital levels should be monitored when used long term to ensure that concentrations remain within the therapeutic range, which has been reported to be 5 to 30 μg/mL in foals.[280] Pentobarbital should only be used in cases with status epilepticus that cannot be controlled with other medications and is associated with substantial risk caused by profound respiratory and cardiovascular depression. Phenytoin has unpredictable kinetics and is not widely used but has been suggested for anticonvulsant use in foals. Potassium bromide may be useful for long-term maintenance in foals with epilepsy because it has fewer side effects than phenobarbital and is well tolerated. Reported effective plasma concentrations of bromide in other species are 70 to 240 mg/dL, but this has not been validated in foals.[281]

The next goal is to control ongoing CNS injury and prevent further damage. Hypothermia is considered the standard of care in the treatment of human neonates suffering from HIE. This involves cooling the patient to 92.3 to 95.0°F using whole body hypothermia, although selective head-cooling approaches can be used as well.[214] A recent systematic review confirmed that therapeutic hypothermia is beneficial in human infants suffering from HIE, because hypothermia reduced mortality without increasing long-term neurologic disability in survivors.[282] There are some complications associated with hypothermia, most notably overcooling, skin problems, altered drug metabolism, and an increased risk of seizure during rewarming.[283] The logistics of providing therapeutic hypothermia in foals, including the appropriate techniques of cooling, patient selection, and duration of cooling remain, is to be defined before clinical application of this approach in equine medicine.

A number of pharmacologic approaches to neuroprotection have been used empirically in foals with HIE, but their use has not been validated (Table 20.8). One of the most widely used drugs for decades has been dimethyl sulfoxide (DMSO), which has been used because of its purported free radical scavenging and antiinflammatory effects, which are perhaps reinforced by ease of administration and low cost.[284] DMSO has osmotic and diuretic effects, which may be helpful in reducing intracranial pressure, and reportedly blocks sodium channel activation, suppresses calcium influx and prevents glutamate excitotoxic cell death.[284] As promising as this appears, there is actually little to no scientific evidence of efficacy regarding DMSO treatment of HIE, and clinical consensus on its use is lacking.[30,211] Mannitol has been administered to reduce cerebral edema, but evidence of efficacy is also lacking for this treatment modality, and it is not commonly used.[185] Magnesium sulfate treatment has been of interest because of its NMDA-receptor antagonist effects, and magnesium may also stabilize cell membranes, inhibit free radical production, and reduce secondary CNS inflammation and associated injury.[285] The use of magnesium sulfate in foals with HIE has been reported, and treatment appears to be well tolerated, although excessive doses can cause muscular weakness and hyotension.[279] No data are available regarding efficacy in foals and, although there are some studies with encouraging results, this therapeutic approach currently remains preclinical in human infants with HIE.[285,286] Pentoxifylline, a phosphodiesterase inhibitor, has antiinflammatory and immune-modulating effects and may improve local tissue perfusion.[287] It has been suggested that pentoxifylline may inhibit TNF-α production in foals with NE.[185] Antioxidant administration may be of some benefit in addressing CNS inflammation, and vitamins C and E and thiamine (vitamin B_1) have all been administered to foals with HIE.[65] Allopurinol is an antioxidant that has shown promise in human infants, but it remains preclinical at this time.[288] Allopurinol administration has been suggested for foals with HIE, but there are no reports of its use.[185] A myriad of additional treatments have been investigated in human neonatal HIE, and some of those that appear promising include inhaled xenon as an antiexcitotoxic agent, melatonin as an antioxidant, erythropoietin as a growth factor, and stem cell therapy.[204,289,290]

RESPIRATORY DISORDERS

Lower respiratory tract disease is common in foals and accounts for substantial morbidity and mortality. Foals are at risk for the development of respiratory disease caused by

TABLE **20.8 Drugs Used for the Treatment of Central Nervous System Disorders**

Drug	Dosage	Route	Frequency	Comments
DMSO	0.1–1 g/kg as a 10% solution	IV	12–24	Hemolysis, dehydration, OSHA restrictions
Mannitol	0.25–2.0 g/kg as a 20% solution over 15–20 min	IV	12–24	Dehydration
Magnesium sulfate	0.05 mg/kg/h (loading) 0.025 mg/kg/h	IV	CRI	Can precipitate other fluids
Pentoxifylline	10 mg/ kg	PO	12	—
Gabapentin	3–5 mg/kg	PO	6–8	—
Allopurinol	44 mg/kg	PO	Once in first 4 h	—
Vitamin E	5000 IU	PO	24	—
Vitamin C	100 mg/kg	IV, PO	24	—
Thiamine	1–20 mg/kg	IV	Added to fluids	—

CRI, Continuous rate infusion; *DMSO,* dimethyl sulfoxide; *IV,* intravenously; *OSHA,* Occupational Safety and Health Administration; *PO,* orally.
From Wilkins PA. Perinatal asphyxia syndrome. In: Sprayberry KA, Robinson NE, eds. *Robinson's current therapy in equine medicine*. St. Louis, MO: Elsevier Saunders; 2015:732-736; Wong D, Wilkins PA, Bain FT, et al. Neonatal encephalopathy in foals. *Comp Contin Educ Pract Vet*. 2011;33:E5.

complex interactions between innate immunologic factors and a number of risk factors. Immunologic factors include possible FPTI, delayed endogenous immunoglobulin production, and potentially impaired immunologic responses. Risk factors in neonates include systemic sepsis, congenital abnormalities, meconium aspiration, milk aspiration, and birth trauma. Risk factors in older foals include the stresses of weaning, sales preparation, and transport, as well as confinement in crowded or dusty conditions that result in heavy exposure to potential respiratory pathogens.

Respiratory Distress

There are several syndromes associated with respiratory distress in the foal, and these syndromes can result from a variety of initiating causes. The defining characteristics change with age, caused by the normal maturation of pulmonary function in the newborn foal, and to some extent caused by the changing nature of the insults that result in respiratory distress. The finding of acute respiratory distress immediately after birth is likely associated with extrapulmonary disorders causing upper respiratory obstruction, such as bilateral choanal atresia, stenosis of the nares, severe laryngeal edema or collapse, dorsal displacement of the soft palate, subepiglottic cysts, or severe congenital pulmonary abnormalities.[30] Congenital cardiac anomalies, such as malpositioning of the great vessels, resulting in severe right-to-left shunts may also be involved.[30]

Acute Lung Injury and Acute Respiratory Distress Syndrome

When dealing with respiratory distress in foals beyond the immediate postpartum period the situation can become confusing because of the broad range of etiologies involved and the broad spectrum of the clinical syndromes. Although this has been appreciated in human and veterinary medicine for many years, it is only in the past decade that a consensus approach to this situation has been developed in veterinary medicine.[291] The terms *acute lung injury* (ALI) and acute RDS (ARDS) were originally developed in human medicine to refer to a syndrome of respiratory failure associated with noncardiogenic pulmonary edema, decreased pulmonary compliance, and ventilation/perfusion mismatching.[292,293] These syndromes are associated with an exaggerated and self-perpetuating inflammatory response, which results in severe tissue damage within the lungs. Protein-rich edema fluid accumulates within the alveoli and interstitium, resulting in impairment of gas exchange leading to hypoxemia.[294] ALI and ARDS are not primary disease syndromes and always occur secondary to other disease processes. Risk factors for ALI and ARDS in human patients include processes resulting in both direct pulmonary injury (pneumonia, aspiration of gastric contents, smoke inhalation, pulmonary contusion, and drowning) and indirect pulmonary injury (nonpulmonary sepsis, pancreatitis, multiple transfusions, and major trauma).[294]

Accurate assessment of respiratory function in the neonate requires arterial blood gas analysis, and the ready availability of portable blood gas analyzers has greatly improved access to this important diagnostic tool. Management of critically ill foals without this information is extremely difficult, because it is important in initial evaluation, formulation of an appropriate treatment plan, monitoring the response to treatment, and prognostication. Foals are most readily sampled in lateral recumbency using the lateral metatarsal artery and the brachial or transverse facial artery. Sampling should be performed quickly after placing the foal in lateral recumbency, and the patient should be returned to a sternal or standing position as soon as possible, because positioning in lateral recumbency has a substantial negative impact on arterial oxygenation (10–14 mm Hg). Diagnostically this impact can be addressed by using appropriate reference ranges derived from foals sampled in lateral recumbency (Table 20.9). The other major element that has to be factored in to interpretation of arterial blood gas data in neonatal foals is the changes in pulmonary function that occur over the course of the first several days of life, because newborn foals have a small degree of shunt fraction that renders them relatively hypoxemic and less responsive to oxygen supplementation than adults. This phenomenon is also addressed in Table 20.9.

The most common arterial blood gas abnormalities identified in neonatal foals are hypoxemia with normocapnia or hypocapnia and hypoxemia with hypercapnia. Hypoxemia can result from several mechanisms: hypoventilation, ventilation/perfusion mismatching, impaired diffusion, intrapulmonary or extrapulmonary (cardiac) shunts, and decreased

TABLE **20.9** **Normal Arterial Blood Gas Values for Foals**[a]

Gestational Age	Postnatal Age	Pa_{O_2}	Pa_{CO_2}	pH
Term	2 min	56.4 ± 2.3	54.1 ± 2.0	7.31 ± 0.02
	15 min	57.5 ± 3.6	50.4 ± 2.7	7.32 ± 0.03
	30 min	57.0 ± 1.8	51.5 ± 1.5	7.35 ± 0.01
	60 min	60.9 ± 2.7	47.3 ± 2.2	7.36 ± 0.01
	2 h	66.5 ± 2.3	47.7 ± 1.7	7.36 ± 0.01
	4 h	75.7 ± 4.9	45.0 ± 1.9	7.35 ± 0.02
	12 h	73.5 ± 3.0	44.3 ± 1.2	7.36 ± 0.02
	48 h	74.9 ± 3.3	46.1 ± 1.1	7.37 ± 0.01
	4 days	81.2 ± 3.1	45.8 ± 1.1	7.40 ± 0.01
	7 days	86.9 ± 2.2	46.7 ± 1.1	7.37 ± 0.01
Premature	0.5–11 hours	53.7 ± 1.5	55.3 ± 3.6	7.21 ± 0.05

Adapted from Wilkins PA: Disorders of foals. In: Reed SM, Bayly WM, Sellon DC, eds. *Equine Internal Medicine*. St. Louis, MO: Saunders Elsevier; 2010:1311-1363; Stewart JH, Rose RJ, Barko AM: Respiratory studies in foals from birth to seven days old. *Equine Vet J*. 1984;16:323-328; Rose RJ, Rossdale PD, Leadon DP: Blood gas and acid-base status in spontaneously delivered, term-induced and induced premature foals. *J Reprod Fertil Suppl*. 1982;32:521-528.

concentration of oxygen in the inspired air (high altitude or inappropriate ventilator setting). Weak, recumbent neonatal foals will frequently suffer from hypoventilation, whereas the presence of intrapulmonary inflammation or surfactant deficiency will cause substantial ventilation/perfusion mismatching with intrapulmonary shunting of blood. Severe inflammation or pulmonary edema can cause diffusion impairment, whereas extrapulmonary shunts are most commonly associated with persistent fetal circulation or cardiac anomalies. Foals suffering from pneumonia typically show profound hypoxemia initially, but the development of hypercapnia and respiratory acidosis indicates substantial worsening of pulmonary function and is associated with a poorer prognosis for survival.[111,295]

ALI in human patients is characterized by an acute onset, the presence of bilateral pulmonary infiltrates on thoracic radiographs, a decreased ratio of the partial pressure of oxygen in arterial blood (Pa_{O_2}) to the fraction of inspired oxygen (Fi_{O_2}) of ≤300 mm Hg, and a pulmonary arterial wedge pressure of less than 18 mm Hg or the absence of clinical evidence of left atrial hypertension.[292] ARDS represents a more severe degree of dysfunction and is characterized by the same criteria but with a lower Pa_{O_2}/Fi_{O_2} ratio of ≤200 mm Hg.[292] Similar terminology and definitions have been proposed for foals suffering from respiratory distress.[291] Multiple classifications have been defined, including neonatal equine RDS (NERDS), equine neonatal ALI (EqNALI) and equine neonatal ARDS (EqNARDS), and veterinary ALI (VetALI) and veterinary ARDS (VetARDS).[291] The diagnostic criteria for these syndromes are provided in tabular form (Boxes 20.3–20.5).

Although the term *NERDS* is new, the syndrome of severe, progressive respiratory distress in foals within the first 24 hours of life has been recognized for at least 50 years.[5] NERDS is very similar to infant RDS in human infants, which is caused by primary surfactant deficiency associated with premature delivery.[291] Surfactant has three primary roles within the lung: to prevent atelectasis at the end of expiration, to increase

BOX 20.3 **Definition of Neonatal Equine Respiratory Distress Syndrome**

Etiology: Primary surfactant deficiency caused by the failure of final fetal pulmonary surfactant metabolism maturation. Diagnosis requires meeting all criteria listed next:

1. Persistent hypoxemia in combination with progressive hypercapnia
   a. Hypoxemia defined as Pa_{O_2} <60 mm Hg with the foal breathing room air and in lateral recumbency
2. The presence of at least one of three appropriate risk factors:
   a. Very early gestational age: less than 290 days' gestational age or less than 88% of the average of the dam's previous gestation lengths
   b. Induction of parturition
   c. Caesarean section
3. Failure to develop normal immediate postpartum respiratory patterns: development/persistence of paradoxic breathing over the first several hours of life, persistent tachypnea
4. Ground glass appearance of lateral thoracic radiographs at ≤24 hours of age (standing or lateral recumbency)
5. Absence of evidence of fetal inflammation
   a. Normal white blood cell count, differential, and fibrinogen concentration for gestational age
6. Congenital cardiac disease ruled out as a cause of hypoxemia

Adapted from Wilkins PA, Otto CM, Baumgardner JE, et al. Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: the Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine. *J Vet Emerg Crit Care*. 2007;17:333-339.

pulmonary compliance, and to facilitate recruitment of collapsed airways.[296] Surfactant deficiency leads to progressive atelectasis and decreased pulmonary compliance, worsening of ventilation/perfusion mismatching caused by intrapulmonary and possibly extrapulmonary shunting of blood, hypoventilation, and increased work of breathing. If not addressed the end result is progressive hypoxia and hypercapnia and ultimately respiratory failure.[296]

Treatment of NERDS is challenging, because the primary interventions used in human infants are not readily available in equine medicine (exogenous surfactant) or are only available in tertiary care referral centers (mechanical ventilation). Given the benefits of surfactant therapy in human respiratory distress syndrome (RDS) patients,[297] this intervention is of great interest in affected foals, but the author's personal experience and the limited references to this therapy in the literature suggest that the effect of this therapy has a short duration and needs to be repeated frequently, making it difficult to justify the significant expense, if surfactant is even available.[298,299] Interestingly, one of the primary changes in the management of human neonates with RDS has been driven by the recognition that mechanical ventilation via endotracheal intubation, although life-saving in many cases, is also associated with the potential for serious acute complications and long-term pulmonary dysfunction.[300] The acute complications may include trauma to the upper respiratory tract associated with intubation, increased risk of lower respiratory tract infections, pulmonary barotrauma

BOX 20.4 Definition of Veterinary Acute Lung Injury and Acute Respiratory Distress Syndrome

Must meet at least one each of the first four criteria; criterion five is a recommended but optional measure.

1. Acute onset (<72 hours) of tachypnea and labored breathing at rest
2. Known risk factors
3. Evidence of pulmonary capillary leak without increased pulmonary capillary pressure[a] (any one or more of the following):
   a. Bilateral/diffuse infiltrates on thoracic radiographs (more than one quadrant per lobe)
   b. Bilateral dependent density gradient on CT
   c. Proteinaceous fluid within the conducting airways
   d. Increased extravascular lung water
4. Evidence of inefficient gas exchange (any one or more of the following):
   a. Hypoxemia without PEEP or CPAP and known Fio_2
      i. Pao_2/Fio_2 ratio
      ii. ≤300 mm Hg for VetALI
      iii. ≤200 mm Hg for VetARDS
      iv. Increased alveolar-arterial oxygen gradient
      v. Venous admixture (noncardiac shunt)
   b. Increased "dead-space" ventilation
5. Evidence of diffuse pulmonary inflammation
   a. Transtracheal wash/bronchoalveolar lavage sample neutrophilia
   b. Transtracheal wash/bronchoalveolar lavage biomarkers of inflammation
   c. Molecular imaging (PET)

[a]No evidence of cardiogenic edema (one or more of the following): PAOP <18 mm Hg (adult horse). No clinical or diagnostic evidence supporting left heart failure, including echocardiography.

CPAP, Continuous positive airway pressure; *CT,* computed tomography; *Fio_2,* fraction inspired oxygen; *PAOP,* pulmonary artery occlusion pressure; *PEEP,* positive end expiratory pressure; *PET,* positron emission tomography; *VetARDS,* veterinary acute respiratory distress syndrome; *VetALI,* veterinary acute lung injury.

From Wilkins PA, Otto CM, Baumgardner JE, et al. Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: the Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine. *J Vet Emerg Crit Care.* 2007;17:333-339.

BOX 20.5 Definition of Equine Neonatal Acute Lung Injury/ Respiratory Distress Syndrome

Postnatal Age	Normal Pao_2 (mm Hg)	Normal Pao_2/Fio_2 Ratio (mm Hg)	NALI Pao_2/Fio_2 Cutoff (mm Hg)	NARDS Pao_2/Fio_2 Cutoff (mm Hg)
60 min	60.9 ± 2.7	>300	<175	<115
12 h	73.5 ± 3.0	>350	<200	<140
24 h	67.6 ± 4.4	>350	<200	<140
48 h	74.9 ± 3.3	>350	<200	<140
4 days	81.2 ± 3.1	>400	<250	<160
7 days	90.0 ± 3.1	>430	<280	<190

This is for VetALI/VetARDS but adheres to the following age-dependent adaptation of the Pao_2/Fio_2 ratio in term foals in lateral recumbency breathing room air (Fio_2 = 0.21) based on age-dependent normal values for Pao_2 under similar conditions.

Fio_2, fraction inspired oxygen; *NALI,* neonatal acute lung injury; *NARDS,* neonatal acute respiratory distress syndromes; *VetALI,* veterinary acute lung injury; *VetARDS,* veterinary acute respiratory distress syndrome.

From Wilkins PA, Otto CM, Baumgardner JE, et al. Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: the Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine. *J Vet Emerg Crit Care.* 2007;17:333-339.

and volutrauma, air leak syndromes (pneumothorax), and hemodynamic complications caused by impaired venous return, whereas the primary long-term complication is bronchopulmonary dysplasia.[301] Because of these concerns noninvasive forms of respiratory support are widely used in human infants with RDS, which include all forms of respiratory support not delivered with an endotracheal tube.[302] The simplest and most readily implemented form of noninvasive respiratory support in foals is the intranasal administration of humidified oxygen via intranasal cannula. Although a single cannula is most often used, this may not provide sufficient oxygen flow rates, in which case a second cannula can be placed in the opposite nostril, and combined flow rates of up to 20 L/minute can be readily delivered.[303] A potential downside to bilateral cannula placement is that this may cause some degree of upper respiratory obstruction in small foals, potentially impairing exhalation and CO_2 elimination, although this effect was not detected when this technique was investigated in healthy foals.[303] If nasal cannulation is not possible or is not achieving adequate flow rates, then an intratracheal catheter can be used for oxygen insufflation, but this rarely represents anything more than a short-term solution.[304]

Although oxygen insufflation can be tremendously helpful, it is unlikely to be sufficient in foals with severe respiratory impairment secondary to surfactant deficiency caused by progressive alveolar collapse and worsening ventilation/perfusion mismatching. In the most severely affected cases mechanical ventilation will represent the only viable means of respiratory support, and this technique is discussed in detail later in this section. However, noninvasive respiratory support strategies that provide continuous positive distending pressure, such as continuous positive airway pressure (CPAP), are widely used in human neonates with RDS and have been shown to reduce respiratory failure and mortality.[305] There are a few older reports of noninvasive ventilatory support techniques for foals that used mechanical ventilators and either nasal prongs or face masks.[306,307] A recent report described the adaptation of a commercial human CPAP device and face mask to provide CPAP to foals.[308] The authors reported that although both CPAP and nonpressurized oxygen supplementation with a face mask normalized pretreatment hypoxemia, oxygen extraction and CO_2 elimination were highest with CPAP at a lower respiratory rate than nonpressurized oxygen administration. Both treatments were associated with the development of modest hypercarbia, but this was not associated with adverse effects. This treatment modality holds promise for foals suffering from NERDS, but further evaluation in affected foals is needed.

The syndromes of EqNALI and EqNARDS represent a subset of ALI and ARDS that occurs in foals in the first week of life. The criteria for EqNALI/EqNARDS differ from those for ALI/ARDS because of the changes that occur in the efficiency of pulmonary gas exchange as foals develop

during this time frame. Diagnosis of these syndromes is fundamentally similar to that of VetALI and VetARDS with the exception of the use of an age-specific scale of Pao_2/Fio_2 ratios based on blood gas values obtained from foals breathing room air and positioned in lateral recumbency, as is typically encountered in clinical practice. It is important to remember that EqNALI/EqNARDS is not a primary diagnosis, and affected foals may be suffering from a broad range of disease processes. There certainly may be overlap with NERDS, but bacterial sepsis and bacterial pneumonia will be the most common disease processes in foals of this age. Other potential etiologies include meconium aspiration, milk aspiration, viral pneumonia, fungal pneumonia, or thoracic trauma, all of which are covered in detail in the following sections.

Treatment of EqNALI/EqNARDS is primarily focused on addressing hypoxemia and hypercapnia while pursuing correction of the primary etiology where possible. Respiratory support may involve the provision of intranasal oxygen, CPAP, or mechanical ventilation, depending on the severity of pulmonary dysfunction. Because of the substantial inflammation present, there may be an indication for antiinflammatory therapy. Nonsteroidal antiinflammatories are unlikely to be sufficient, but there is evidence in adult humans with ARDS[309,310] and in older foals with VetARDS[311,312] that corticosteroid therapy may be beneficial. Although specific therapeutic protocols have not been defined, recent work has suggested that hydrocortisone administration at a dosage of 1 to 4 mg/kg per day IV divided into four to six doses may be appropriate for septic foals with CIRCI, but this approach has not been investigated in septic foals or foals with EqNALI/EqNARDS.[313-315] Because of the likelihood that bacterial infection may be involved in this age group, broad-spectrum antimicrobial therapy is also indicated along with judicious fluid therapy and supportive care.

The most definitive descriptions of acute respiratory distress in foals have been associated with bronchointerstitial pneumonia in foals 1 to 12 months of age.[311,312,316,317] Affected foals often appear clinically normal until they are found in acute respiratory distress or dead.[311] Some cases may have a history of previous respiratory disease associated with sudden clinical deterioration.[293] Physical examination finds affected foals depressed, lethargic, and inappetent, with severe respiratory distress characterized by tachycardia, tachypnea, and nostril flare. A paradoxic breathing pattern may be present, in which the thorax and abdomen move opposite from one another, rather than synchronously, during inspiration and expiration. Auscultation may reveal widespread abnormal sounds, with prominent wheezes and crackles, or lung sounds may be very quiet to absent with only large airway sounds detectable. Fever and injected mucous membranes are common as well. Care should be taken to auscult the heart thoroughly, which may be difficult in the presence of diffuse abnormal respiratory sounds, to rule out a cardiac cause of pulmonary edema. Clinicopathologic evaluation is important both for assessment of pulmonary function and identification of the primary underlying disease process. Arterial blood gas analysis is extremely helpful and should be performed before initiation of intranasal oxygen insufflation, if clinically appropriate. Complete blood count, fibrinogen concentration, and SAA concentration are all helpful in characterizing the severity of systemic inflammation, and very high WBC counts, fibrinogen, or SAA concentrations, although not definitive, may be suggestive of *Rhodococcus equi* infection.[318,319]

Thoracic imaging is extremely helpful in staging the degree of pulmonary inflammation and identifying underlying primary disease processes. Thoracic ultrasonography is readily performed and may provide useful information, such as the presence of severe atelectasis, pleural effusion, or pulmonary abscesses. Diffuse lung inflammation, such as occurs in ALI, will be seen as thickening of the visceral pleura and the appearance of echogenic projections arrayed perpendicular to the surface of the lung (comet-tail artifacts).[320] Thoracic radiographs provide much more detailed information regarding the severity and extent of pulmonary inflammation, and reasonable image quality can be obtained with stall-side digital radiographic equipment.[321] The radiographic abnormalities observed in affected foals may range from a diffuse interstitial pattern to a focal or diffuse coalescing alveolar pattern with multiple air bronchograms, and serial radiography can be very helpful in monitoring the progression of disease and response to treatment.[293,321] The presence of pulmonary abscesses on thoracic ultrasonographic examination or in thoracic radiographs is strongly suggestive of *R. equi* involvement but is not definitive.[318] CT imaging of the thorax for the evaluation of foals with pulmonary disease has been recently reported as well.[321,322] CT imaging provides much more detailed information regarding the nature and degree of pulmonary changes but is only available in a few specialty referral settings at this time.

Foals affected with VetALI/VetARDS most commonly suffer from a primary bacterial pneumonia, but other causes such as viral pneumonia are possible. A transtracheal aspirate should be performed unless the patient is too unstable to undergo the procedure; this sample can provide important cytologic evidence regarding the type and severity of pulmonary inflammation and the presence of extracellular and intracellular bacteria and should also be submitted for bacterial culture and sensitivity. Neutrophilic inflammation is typically present, and the detection of intracellular gram-positive coccobacilli within pulmonary macrophages is strong evidence of the presence of *R. equi.*[318] Polymerase chain reaction (PCR) testing of tracheal aspirates may be helpful in confirming rhodococcal involvement.[323] Treatment of ALI/ARDS-affected foals should focus on addressing the hypoxemia, treating the primary underlying disease process, controlling the excessive inflammatory response, and providing supportive care. Intranasal oxygen insufflation, as described previously, should be initiated as soon as possible in foals suffering from respiratory distress and represents the primary means of respiratory support in these older foals. Antimicrobial therapy should target the most likely bacterial pathogens based on the overall assessment. In younger foals in which sepsis may be playing a primary role, broad-spectrum antimicrobial therapy is recommended. In older foals empiric treatment should address the possible involvement of *R. equi.* Aggressive systemic antiinflammatory therapy using potent corticosteroids, such as dexamethasone and methylprednisolone sodium succinate, has been shown to be the most important intervention in effecting survival of affected foals.[311,312,324] Corticosteroid therapy should be gradually tapered as the clinical condition improves, rather than rapidly withdrawn. Prolonged therapy has been shown to be beneficial in human ARDS patients.[310] Bronchodilator therapy has been used in affected foals because of the severity of

respiratory distress, but bronchoconstriction is not a prominent feature of ARDS, and bronchodilator administration may actually worsen the ventilation/perfusion mismatching and result in clinical deterioration or even death.[293] If used, bronchodilator therapy should only be administered after nasal insufflation of oxygen has been instituted, and the clinician should be prepared to address sudden changes in clinical status. The use of the inhalational route for the administration of corticosteroids and bronchodilators in patients suffering from severe pulmonary dysfunction with substantial ventilation/perfusion mismatching is often unrewarding because of poor pulmonary penetration and delivery, so the systemic route is recommended. The prognosis for survival in affected foals is poor to guarded, with early and aggressive corticosteroid and antimicrobial therapy offering the best chance of survival.[324]

Persistent Pulmonary Hypertension

Persistent pulmonary hypertension of the newborn (PPHN), also known as persistent fetal circulation or reversion to fetal circulation, is a syndrome characterized by sustained increases in pulmonary vascular resistance. Increased pulmonary vascular resistance, possibly combined with decreased right ventricular function, results in right-to-left shunting through the ductus arteriosus and/or foramen ovale.[325] PPHN can be idiopathic, but in human infants it is more commonly associated with pulmonary disease, such as meconium aspiration, perinatal asphyxia, surfactant deficiency, and pneumonia.[326] In foals PPHN may also develop secondary to systemic sepsis, hypoxemia, or acidosis.[327,328] The pathophysiology of PPHN is complex but fundamentally represents dysfunction of the factors that regulate pulmonary vascular tone. PPHN should be suspected in any neonatal foal exhibiting progressive or refractory hypercapnic hypoxemia. Care should be taken to rule out the presence of congenital cardiac anomalies that may be causing extrapulmonary shunting of blood and other causes of hypoxemic respiratory failure, such as sepsis or infectious pneumonia. PPHN should be suspected in cases of hypoxemia that do not show a significant increase in Pao_2 following the institution of intranasal oxygen therapy. Definitive diagnosis can be challenging, but ultrasonography can be very helpful in ruling out congenital cardiac anomalies and detecting primary pulmonary disease.

Treatment of PPHN is challenging but depends on addressing any predisposing or underlying factors while addressing the severe hypoxia. Foals that do not respond well to nasal insufflation of oxygen will require intubation and mechanical ventilation with 100% oxygen.[30] This can be useful both in addressing the hypoxia and in potentially stimulating pulmonary vascular relaxation.[327,328] Following a brief period of hyperoxia, it is recommended to taper the inhaled oxygen concentration to target a Pao_2 of 60 to 100 mm Hg.[325] Therapeutic agents that directly address the pulmonary vasoconstriction are widely used in human neonates, but inhaled nitric oxide (iNO) is the only approved pulmonary vasodilator for human use. The successful use of iNO therapy in foals has been reported,[327] but unfortunately it is impractical in most settings because it requires mechanical ventilation along with specialized equipment for introducing the NO gas into the ventilator circuit.[328] Sildenafil (Viagra, Pfizer Inc., New York), a phosphodiesterase type 5 inhibitor, has been used in humans and is reported to be effective.[326,329] There are anecdotal reports of the use of sildenafil in foals with PPHN, at a dosage rate of 0.5 to 2.5 mg/kg PO, up to every 4 hours, starting at the lower end of the dosage range to avoid systemic hypotension.[330] Although supported by only one case report in humans, the use of pentoxifylline, a nonselective phosphodiesterase inhibitor, as an adjunctive therapy may be worthy of consideration in foals because of availability, low cost, and an accepted safety profile.[331,332]

Congenital Upper Respiratory Tract Disorders

There are a number of congenital upper respiratory tract disorders in foals, although none is common. These can include wry nose, choanal atresia, cleft palate, nasopharyngeal cysts, and subepiglottic cysts.[333] Wry nose involves lateral and rotational deviations in the structure of the nose; in moderate to severe cases it will cause significant upper airway obstruction.[334] Surgical repair is possible, but this must be regarded as a salvage procedure, because the prognosis for athletic function is poor.[334] Choanal atresia is rare in foals but involves unilateral or bilateral soft tissue narrowing or complete obstruction of the caudal aspect of the nasal passages.[335] Foals born with bilateral complete obstruction will die without rapid intervention to establish an airway because of the obligate nasal breathing nature of equines.[333] Foals with unilateral choanal atresia often remain undiagnosed until later in life.[336] Diagnosis is most often made using endoscopy, but CT examinations have been useful in some cases.[336] Surgical correction is feasible, but the prognosis for performance remains guarded because of the persistent airway narrowing in many cases. Cleft palate deformities are rare and are reported in only 0.1% to 0.8% of foals.[337] Most affected foals will show clinical signs of dysphagia when nursing, including coughing or nasal milk drainage, but this is inconsistent.[338] Aspiration pneumonia is a common complication. The primary site of involvement is the soft palate, and the defect can range from a small, focal site to essentially the absence of the entire soft palate. Diagnosis is most readily made endoscopically, although surgical correction is theoretically possible; the approach is difficult and the outcome uncertain, especially with large defects.[337] There is one recent report of successful transoral endoscopically assisted repair in a foal.[339] Subepiglottic cysts are also rare in foals, but when present they can interfere with epiglottal placement, resulting in persistent palate displacement and severe dysphagia and aspiration pneumonia.[333,340] Diagnosis is primarily by endoscopic examination, although visualization may be difficult if the cyst is positioned below the palate. Radiographs or CT may be helpful in detecting these lesions. Treatment is by cyst removal, either via laryngotomy or by nasal or oral endoscopic approaches.[333]

Meconium Aspiration

Meconium aspiration syndrome (MAS) is defined as respiratory distress in a foal born through amniotic fluid stained with meconium in which the symptoms cannot be explained by other etiologies. Meconium staining can occur before, during, or immediately after parturition, and meconium passage in utero is thought to primarily occur in response to fetal hypoxia leading to fetal stress. Fetal hypoxia also may result in fetal gasping, facilitating introduction of meconium into the respiratory tract while in utero. Meconium aspiration may also occur in association with the first few breaths after birth. The presence of meconium-stained amniotic fluid does not guarantee that MAS will occur, however, because only

2% to 9% of human infants born through meconium-stained amniotic fluid develop MAS.[341] When meconium contamination of the lower respiratory tract occurs there are a number of pathophysiologic mechanisms leading to pulmonary dysfunction, including mechanical airway obstruction, regional air trapping, surfactant inactivation, surfactant displacement, chemical pneumonitis and alveolitis, and persistent pulmonary hypertension.[327,341]

If meconium aspiration is suspected then aspiration of the material from the nasal passages and pharynx can be performed, even while the foal is in the birth canal, if the birth is attended. If more severe contamination is suspected then nasotracheal intubation followed by aseptic suctioning is suggested, although care must be taken to avoid contamination of the lower respiratory tract or overly zealous suction. Intranasal oxygen supplementation is recommended in affected foals, but mechanical ventilation will be required in more severely affected cases and is associated with a worsened prognosis. Mechanical ventilation is challenging in these cases because of the degree of pulmonary inflammation and airway compromise as well as the severity of ventilation/perfusion mismatching and strategies to minimize barotrauma, such as CPAP ventilation and synchronized intermittent mandatory ventilation (SIMV), which may be helpful.[342,343] Surfactant administration and lung lavage with dilute surfactant appear to be effective in human neonates with MAS but are not routinely used in foals.[344] Antiinflammatory therapy may be beneficial because of the substantial pulmonary inflammation associated with MAS. Pentoxifylline has shown some promise in animal models, appears safe in foals, and is easily administered.[345,346] Corticosteroids, either inhaled or systemically administered, are commonly used in human infants with MAS.[347,348] Although meconium aspiration is not associated with primary bacterial pneumonia, affected foals are at risk of secondary bacterial infection, and broad-spectrum antimicrobial therapy is recommended.

Milk Aspiration

Neonatal foals may aspirate milk into the lower respiratory tract secondary to a number of conditions, although this is most common secondary to generalized weakness, a poor suckle reflex, or dysphagia related to prematurity or NE.[349] This risk may be exacerbated by attempts at bottle feeding foals affected with these problems. Other potential causes of aspiration include physical abnormalities such as subepiglottic cysts, cleft palate, megaesophagus, esophageal stenosis, esophageal compression by vascular anomalies, or persistent dorsal displacement of the soft palate.[342,349,350] Functional abnormalities of the pharynx, larynx, and esophagus resulting in aspiration have been associated with pharyngeal dysfunction of unknown etiology, botulism, and hyperkalemic periodic paralysis.[342,349,351] Incorrect placement of nasoesophageal feeding tubes has also been associated with direct instillation of milk into the lungs, leading to aspiration pneumonia. Detection of milk aspiration can be difficult because some affected foals may not cough or show nasal milk regurgitation. Diagnosis is based on historic information that may reveal episodes of nasal milk regurgitation, physical examination findings demonstrating abnormal lower respiratory sounds, and clinicopathologic evidence of systemic inflammation (inflammatory leukogram and hyperfibrinogenemia or increased SAA) and pulmonary dysfunction (arterial hypoxemia).[342] Endoscopic examination of the upper respiratory tract may reveal structural abnormalities of the pharynx, larynx, or esophagus suggestive of aspiration, or pharyngeal dysfunction may be observed. Thoracic radiographs typically reveal an alveolar pattern with or without air bronchograms in the caudoventral lung, but this may be localized to the perihilar region.[321] It is important to pursue the identification and correction of the cause of aspiration, if possible, to prevent further aspiration. Placement of a nasoesophageal feeding tube will allow for the safe delivery of milk pending correction of the underlying disorder. Broad-spectrum antimicrobial therapy is indicated to address the bacterial pneumonia accompanying milk aspiration, and successful treatment may require several weeks of treatment.

Transient Tachypnea

Idiopathic or transient tachypnea has been reported in Clydesdale, Thoroughbred, and Arabian foals and is generally seen during hot, humid weather conditions.[352] This condition is believed to be the result of immature or dysfunctional thermoregulatory mechanisms.[327] Affected foals are usually normal at birth and of a normal gestational age, but they develop hyperthermia and tachypnea at variable times following birth.[342] It is critical that other potential causes of respiratory disease are ruled out before making the diagnosis of idiopathic tachypnea, because the consequences of withholding antimicrobial treatment could be severe. Treatment is primarily directed at controlling the hyperthermia and may include body clipping; alcohol baths; and movement to a cool, shady environment.[342] In most foals the condition is self-limiting and will resolve within a few days to a few weeks.

Rib Fractures, Pneumothorax, and Hemothorax

Rib fractures are a fairly common problem, having been reported in 3% to 5% of the general population of neonatal foals and as many as 30% of foals presenting to a neonatal ICU.[353] Fractured ribs can cause a number of traumatic insults to the thoracic viscera, including pulmonary contusions and lacerations of the lungs, major arteries, heart, or diaphragm. Pneumothorax, hemothorax, and diaphragmatic herniation may all occur as a result of these traumatic insults, and myocardial injury is typically fatal. Rib fractures can be single, but are often multiple, most often affecting adjacent ribs on one side of the chest. The most common site of injury is at the costochondral junction or immediately dorsal to it.[354] Flail chest, or paradoxic thoracic wall motion, may occur when multiple ribs are fractured, and the affected region will move inward during inspiration and outward during expiration, counter to the movements of the intact portions of the thoracic wall. Rib fractures are commonly found on physical examination by palpation of the fracture itself or by the detection of crepitus at the site of the fracture. Auscultation may reveal grinding or "clicking" sounds in the area of the fracture as well. Confirmation of the diagnosis is best accomplished ultrasonographically because this modality is much more sensitive than radiography for this purpose.[355] Ultrasonography may also be used to document the presence of air, blood, or abdominal viscera within the thoracic cavity, although radiography may be helpful in this evaluation. Treatment depends on the structures involved and the severity of the complications observed. Most minimally displaced rib fractures, particularly those involving the costochondral junction, can be managed conservatively with stall rest and avoidance of pressure on the affected area when the foal is handled. Mild to moderate pneumothorax may not

require intervention, but if substantial air is presented within the pleural cavity it will cause respiratory distress and should be evacuated. Placement of an indwelling thoracic catheter will facilitate ongoing drainage. If multiple ribs are fractured, and particularly if sharp bony projections are exposed and threatening internal injury, then surgical repair may be indicated.[356] Hemothorax can be life-threatening because of pulmonary compression and/or severe blood loss anemia, and treatment should focus on addressing the primary cause of hemorrhage and patient stabilization and support.[357]

Viral Infections

Viral pneumonia is uncommon in neonatal foals but has been associated with EHV-1, EHV-4, equine influenza virus (EIV), equine arteritis virus (EAV), and equine adenovirus (EAdV). EHV-1 infections in neonatal foals are severe and typically fatal, despite aggressive treatment. One of the challenges associated with these cases is the difficulty of ascertaining EHV-1 involvement, because the presenting signs are very similar to neonatal sepsis. Foals may be delivered somewhat early and with little or no warning of impending parturition, and the placenta is usually grossly normal.[328] Farm outbreaks have been reported.[184,358,359] Clinical signs are of cardiovascular and respiratory insufficiency, and the mucous membranes are severely congested and icteric. Clinicopathologic abnormalities include severe leukopenia with neutropenia, toxic neutrophil morphology, and lymphopenia. The combination of severe leukopenia and icterus may be suggestive of EHV-1 infection.[183] Bone marrow examination will reveal depletion of the myeloid cell lines. Many affected foals will display dilation of the retinal vasculature with reddish discoloration of the optic disk. Diagnostic confirmation is most readily accomplished by PCR testing of nasal secretions or whole blood. Treatment of affected foals with acyclovir has been attempted, and this appeared to have some efficacy in less severely affected foals.[184] Given the superior bioavailability of valacyclovir in adult horses, this drug may represent a more suitable choice for use in EHV-1–infected foals.[328,360] EHV-4 appears to be a rare cause of neonatal disease and is more commonly associated with abortion or stillbirth, but it has been associated with neonatal mortality caused by multisystemic disease.[361,362]

Infections with EIV in neonatal foals are not common, particularly in endemic areas in which mares are routinely vaccinated and foals are typically protected by maternal colostral antibodies.[363-366] Outbreaks have been reported when EIV has been introduced into naïve populations.[364,366] EIV infection in susceptible foals is associated with severe bronchointerstitial pneumonia leading to respiratory distress.[364] Antemortem diagnosis is by PCR of nasal secretions. There is no specific treatment for EIV infection.

Neonatal infections with EAV are associated with severe interstitial pneumonia, which has been reported to be uniformly fatal.[367-369] Both solitary cases and farm outbreaks have been reported.[367,368,370-372] The clinical signs associated with neonatal EAV infection are severe and primarily respiratory and initially include edema, weakness, and depression, ultimately progressing to terminal respiratory distress, although acute death has also been reported.[368,372] Gastrointestinal involvement has been reported in some cases but is not consistently present.[367,369] Clinicopathologic abnormalities are not specific to EAV infection but often include leukopenia and thrombocytopenia.[368] There is no specific antiviral treatment for EAV, and despite attempts at aggressive medical therapy there are no reports of successful treatment of neonatal EAV infections. Diagnostic confirmation of EAV involvement is most readily achieved by PCR testing of blood, respiratory secretions, or tissues (lung, kidney, and spleen).[372]

EAdV infections are rare in immunocompetent foals, and the primary concern is in immunocompromised foals. The best described syndrome associated with EAdV infections is in Arabian foals with severe combined immunodeficiency syndrome, although a similar syndrome may occur in Fell pony foals with an unidentified immunodeficiency.[373-375] Two distinct EAdVs have been identified, with EAdV1 being ubiquitous and readily isolated from normal and diseased foals and horses, whereas EAdV2 is only isolated from foals with upper respiratory tract disease and diarrhea.[373,376,377] Experimental infection of healthy foals with EAdV has been associated with pneumonia regardless of breed.[378,379] PCR testing for EAdV1 and EAdV2 is available, but care must be taken with interpretation because EAdV1 is frequently detected in normal animals. Confirmation of diagnosis may require histopathologic evidence of EAdV infection or virus isolation.[373]

Viral respiratory infections are more common in older foals than in neonatal foals, and respiratory disease in this age group has been associated with EHV-1, EHV-4, EIV, and EAV.[380] The clinical signs associated with EHV and EIV infections in this age group are very similar and are consistent with those reported in adult horses. Clinical signs typically include a dry cough and fever, although a mucopurulent nasal discharge may be present as well. The presence of such a discharge may be suggestive of secondary bacterial involvement, however. EIV and EHV infections in older foals are typically much less severe than in neonates and ultimately self-limiting. A rare, fatal pulmonary vasculotropic form of EHV-1 infection has also been described in young horses.[381] EAV infections typically show similar respiratory signs and fever, but affected individuals often exhibit substantial ventral and limb edema secondary to vasculitis.[369]

The potential role of the gammaherpesviruses, EHV-2 and EHV-5, in foal pneumonia is intriguing but currently unclear. Both of these viruses are ubiquitous in equine populations worldwide, and foals become infected within the first several months of life.[382] Infection in foals is generally considered to occur without clinical signs, but EHV-2 infection has been associated with mild to severe chronic pharyngitis of foals following natural and experimental infection.[383] Other signs of upper respiratory tract disease, such as lymphadenopathy, mild pyrexia, and rhinitis may be associated with natural infections.[384-387] Some intriguing evidence exists that EHV-2 may play a role in potentiating lower respiratory bacterial infections; there are reports that use of an EHV-2 vaccine protected foals from *R. equi* pneumonia.[388,389] Natural infection of foals with EHV-2 has been associated with fever and immunopathologic changes similar to those observed in human adolescents suffering from infectious mononucleosis following infection with Epstein-Barr virus.[390] In addition, the EHV-2 genome contains an IL-10 homolog as well as encoding for several other proteins that may have immunomodulatory effects that could predispose a patient to bacterial infections.[382] The case for a pathogenic role for EHV-5 is stronger, because this virus has been convincingly associated with the syndrome of equine multinodular pulmonary fibrosis.[391-394]

Fungal Diseases

Although fungal pneumonia is very rare in neonatal foals, there are a few conditions to be aware of in this population. In utero infection with *Histoplasma capsulatum* has been associated with placentitis, abortion, and the birth of infected foals.[395,396] Affected foals have multisystemic disease, including granulomatous pneumonia.[395] Antemortem diagnosis is challenging but may be facilitated by tracheal aspirate or bronchoalveolar lavage cytology, in which characteristic yeastlike organisms (3- to 5-μm diameter) may be detected within the macrophages.[342] Serology is useful as well. The mare and foal should be positive for anti-*Histoplasma* antibodies, which can be detected using an agar gel immunodiffusion test.[328] Although successful treatment of infected adults has been reported using amphotericin B, there are no reports of successful treatment in neonatal foals.[328]

Although *Candida* spp. infections are a major problem in human intensive care patients, they appear to be an infrequent problem in foals. Systemic candidiasis has been reported in foals, but superficial infections of the mucous membranes (thrush) appear to be more common.[397-400] The presence of superficial infections may be related to the development of systemic infections, so these lesions should be taken seriously and treatment implemented in a timely manner. This concern is reinforced by the fact that the clinical signs associated with systemic candidiasis are indistinguishable from those seen in bacterial sepsis.[400] Confirmation of the diagnosis of systemic candidiasis is by blood culture of the organism. Successful treatment has been reported with IV amphotericin B and/or oral fluconazole, with fluconazole preferred.[400]

Parasitic Pneumonia

Following ingestion of the larvated eggs of *Parascaris equorum* the infective larvae emerge in the intestinal lumen and migrate through the liver and lungs before being coughed up and reingested, returning to the small intestine in which they mature into adults.[401] Passage through the lungs is associated with substantial inflammation, and infected foals may present with clinical signs of lower respiratory disease when the larvae are migrating through the lungs.[402] Infestation is ultimately self-limiting, and the pulmonary signs rarely require medical treatment. Because of concerns regarding possible colic secondary to intestinal obstruction by the adult parasites, it is recommended that foals suspected of parasitic pneumonia be dewormed. Ivermectin has been recommended traditionally, but the widespread emergence of macrocyclic lactone–resistant strains has led to the recommendation that benzimidazole or pyrimidine anthelmintics should be used.[401] Resistance has been demonstrated in these classes as well, unfortunately, requiring individuals to be monitored with fecal egg counts to ensure efficacy of anthelmintic therapy.[403]

Bacterial Infections

Neonatal Foals

Bacterial pneumonia in neonates is most often associated with hematogenous spread secondary to bacteremia, but it may also occur secondary to infection in utero or meconium or milk aspiration. The bacteria associated with neonatal pneumonia are typically the same as those involved in neonatal sepsis, and gram-negative bacteria are the organisms most commonly involved. Gram-positive infections appear to be increasing in prevalence, however, and mixed infections occur as well.[404] The most common isolate is *E. coli,* with *Klebsiella* spp., *Actinobacillus* spp., *Pasteurella* spp. *Salmonella* spp., *Streptococcus* spp., *Enterococcus* spp., and *Staphylococcus* spp. also occurring with some frequency.[25,171,176,178,180,181] Successful treatment depends on early and effective support of respiratory function with correction of hypoxemia, control of systemic and pulmonary inflammation, and appropriate antimicrobial therapy. Unfortunately antimicrobial selection is almost always empiric initially, but collection of blood culture samples before initiation of antimicrobial therapy is encouraged to provide confirmation of bacterial involvement and to guide future antimicrobial therapy on the basis of antimicrobial sensitivity patterns. Transtracheal aspirates are not commonly performed in neonatal foals because they can be technically challenging and may worsen the foal's respiratory distress. They can be very useful diagnostically, especially when the respiratory infection is secondary to aspiration.[404] Because of the possibility of polymicrobial and mixed infections, broad-spectrum therapy is recommended initially. This often consists of a β-lactam (penicillin) in combination with an aminoglycoside, but a third-generation cephalosporin, such as ceftiofur, may represent a better choice because of its superior pulmonary penetration.[328]

Older Foals

Pneumonia is common in foals from 1 to 6 months of age and is the most common cause of death in this age group.[405] The most common etiologic agent of bacterial pneumonia in these older foals is *Streptococcus equi* subsp. *zooepidemicus,* which is a normal upper respiratory commensal organism. This age group of foals may be at risk for the development of respiratory infections caused by decaying levels of maternal immunoglobulins in conjunction with delayed endogenous immunoglobulin production and possibly impaired immunologic responses to pathogen exposure. Additional risk factors in older foals include the stresses of weaning and sales preparation and transport, as well as confinement in crowded or dusty conditions that result in heavy exposure to potential respiratory pathogens. Secondary infection with gram-negative organisms is not uncommon, and foals in which this occurs may exhibit a poor response to treatment or deteriorate clinically in the face of treatment. Viral infections such as EHV-1, EHV-4, and EIA may cause pulmonary inflammation and injury, whereas other viral infections such as EHV-2 may directly impair pulmonary immune responses, facilitating the development of secondary bacterial pneumonia.

The second most common agent of pneumonia in this age group is *R. equi,* which is a facultative, intracellular gram-positive coccobacillus. This organism was first isolated from foals with pyogranulomatous pneumonia in Sweden in 1923 and was originally named *Corynebacterium equi.*[406] Although it has been known as *R. equi* for several decades, the taxonomic nomenclature for this organism is a matter of ongoing debate, and the alternative names *Prescottella equi* and *Prescottia equi* have been recently proposed.[407,408] The conventional terminology *R. equi* will be used here. *R. equi* is considered to be a ubiquitous bacterium with a worldwide distribution,[409] although a recent study suggests that it may not be present in Iceland.[410] All isolates capable of causing disease in foals carry a plasmid encoding a virulence-associated protein (VapA). Although VapA is required for virulence, it alone is not sufficient, and other plasmid-encoded genes also influence virulence.[349] Rhodococcal pneumonia is occasionally seen as a

sporadic disease but is more common on endemic farms, on which there is often substantial variation in the incidence of disease on an annual basis.[411] On endemic farms as many as one third of the foals are affected with clinical disease, and up to 50% of affected foals may die.[412] The most likely route of infection in foals is by inhalation, and increased airborne concentrations of virulent *R. equi* are positively associated with the development of pneumonia.[413,414] High stocking densities of mares and foals have also been associated with an increased incidence of rhodococcal pneumonia.[415,416] Higher concentrations of *R. equi* have been detected in stalls and barns, as opposed to pastures and paddocks,[417,418] and this could lend support to the suggestion that dusty conditions are associated with an increased incidence of rhodococcal infection.[419]

R. equi infections are rare in adult horses unless they are suffering from some form of immunodeficiency. Given the ubiquitous nature of *R. equi* in the environment, this suggests that foals are in some way uniquely susceptible to infection by this organism. Several studies have investigated the immune responses of foals, but the results have been inconclusive and there is no clear evidence of an age-related immunodeficiency that renders them susceptible.[420,421] Recent studies have investigated the potential for genetic predispositions to rhodococcal infections, with some intriguing findings. Polymorphisms in the transferrin and *SLC11A1* genes have been associated with rhodococcal pneumonia in Thoroughbred and Arabian foals, respectively.[422,423] More recently a genetic region on chromosome 26 that contains the *TRPM2* gene, which is associated with neutrophil function, was found to be positively associated with rhodococcal pneumonia, and foals with a single nucleotide polymorphism in this region were three to four times more likely to be clinically affected than their herdmates.[424]

Because of the occult nature of this disease, there has been tremendous interest in identifying infected foals as early as possible so that treatment can be implemented early in the disease process. To this end a number of screening programs for early detection of infected foals have been investigated, including serial monitoring of physical examinations, WBC concentration, fibrinogen assays, SAA concentration, and quantitative fecal VapA PCR testing, but none has proven to be clinically effective.[349,425] Serology has been unrewarding as well,[426] although there are recent reports that VapA-specific serum IgG(T) measurement may be useful in identifying infected foals, although this requires further validation in the field setting.[410,427] Ultrasonographic screening programs were developed, and these demonstrated that large numbers of foals had pulmonary lesions in the absence of clinical signs.[428] Because of the widespread implementation of these ultrasonographic screening protocols on endemic farms, subclinical *R. equi* infections have become the most common form of this disease.[429] This approach has also resulted in the treatment of many foals in which the pulmonary lesions would likely have resolved spontaneously, contributing to the development of macrolide resistance.[430,431]

Clinically evident rhodococcal pneumonia is often insidious, ultimately presenting with signs consistent with lower respiratory tract infection, and fever, lethargy, coughing, tachypnea, and dyspnea are common clinical signs. Dyspnea can be severe, with nostril flaring and prominent abdominal expiratory effort. Although relatively rare, some foals may present with a subacute, severe form of respiratory disease, consistent with ARDS, and severely affected foals may be found dead.[429] Auscultation typically reveals diffuse crackles and wheezes, with prominent large airway sounds (rattles) caused by the accumulation of exudate in the cranial thoracic region. Rebreathing examination is typically not necessary because of the prominence of the abnormal lung sounds, and it is contraindicated in animals in respiratory distress. It is important to perform a thorough examination in affected foals, because extrapulmonary disorders are common.[432] The most common of these are diarrhea, ulcerative enterotyphlocolitis, presumed immunomediated synovitis, intraabdominal lymphadenitis, or abscessation and uveitis.[432] Arterial blood gas analysis is extremely helpful in assessing the degree of pulmonary dysfunction and should be performed before initiation of intranasal oxygen insufflation if clinically appropriate. Complete blood count, fibrinogen concentration, and SAA concentration are all helpful in characterizing the severity of systemic inflammation, and very high WBC counts, fibrinogen, or SAA concentrations, although not definitive, may be suggestive of *R. equi* infection.[318,319] Serial monitoring of these values can be helpful in assessing the response to treatment and in determining the duration of therapy.

Thoracic imaging is extremely helpful in staging the degree of pulmonary inflammation and supporting the diagnosis of rhodococcal involvement, and serial imaging studies can be very helpful in monitoring the progression of disease and response to treatment. Thoracic ultrasonography is readily performed and is very effective for the detection of peripheral pulmonary consolidation or abscesses, but it is unable to detect axial lesions unless peripheral lesions are present.[349] Despite these limitations ultrasonography is the most widely used imaging technique in evaluating foals suspected to have rhodococcal pneumonia because of the combination of ready availability, ease of performance, and diagnostic utility. Abdominal ultrasonography should also be performed in foals with suspected rhodococcal pneumonia because of the frequency of abdominal extrapulmonary disorders. Thoracic radiographs provide more detailed information regarding the severity and extent of pulmonary disease, however, and should be considered in more severely affected cases, particularly given that reasonable image quality can be obtained with stall-side digital radiographic equipment.[321] The radiographic abnormalities observed in affected foals may include a diffuse interstitial or alveolar pattern, tracheobronchial lymphadenopathy, intrapulmonary abscesses, and pleural effusion. A scoring system has been developed to assess the severity of alveolar pattern, interstitial pattern, tracheobronchial lymphadenopathy, pleural effusion, and the number of nodular opacities and cavitary lesions in affected foals.[433] Foals with higher median scores (≥15) were less likely to survive (odds ratio [OR] 6.15, 95% confidence interval [CI]: 1.35–28.2) than foals with a lower score, with only the severity of the alveolar pattern and number of cavitary lesions being associated with decreased survival. Care should be taken to avoid overinterpretation of imaging studies, especially thoracic ultrasonography, because many of the lesions detected may resolve without therapeutic intervention. A recent study on an endemic farm found that 80% of foals developed ultrasonographic evidence of pulmonary consolidation or abscess formation, but only 21% developed clinically apparent *R. equi* pneumonia.[434] As a result of this concern a thoracic ultrasonographic scoring system has been used in several prospective studies of rhodococcal pneumonia therapies in an effort to more effectively identify foals that require treatment.[431,435-438] This scoring

system defines a pulmonary abscess as a focal hypoechoic area with a diameter of ≥1.0 cm, and the number of abscesses identified is recorded along with the diameter of each abscess. The diameter of each individual abscess is totaled to generate a total abscess score in centimeters, with foals that have a total score less than 8 cm or 10 cm typically not receiving treatment.

Following the completion of any imaging studies a transtracheal aspirate should be performed unless the patient is too unstable to undergo the procedure; this sample can provide important cytologic evidence regarding the type and severity of pulmonary inflammation and presence of extracellular and intracellular bacteria. This sample should also be submitted for bacterial culture and sensitivity. Profound neutrophilic inflammation with degranulation of neutrophils is typically present, and the detection of intracellular gram-positive coccobacilli within pulmonary macrophages is strong evidence of the presence of *R. equi*.[318] PCR testing of tracheal aspirates may also be helpful in confirming rhodococcal involvement, because the culture is frequently negative even when intracellular bacteria are seen on cytologic examination.[323] Quantitative PCR testing of feces was recently investigated on an endemic farm and was found to be useful in diagnosing *R. equi* in foals with clinical signs of pneumonia and, although these results are preliminary, this technique may prove useful in situations where tracheal aspirates cannot be collected.[439]

Treatment of foals with rhodococcal pneumonia should focus on addressing respiratory distress, if present, and treatment of the infection. Oxygen insufflation should be provided, if possible, to animals with dyspnea. Nonsteroidal antiinflammatory therapy may be helpful in controlling the fever, and affected animals should be kept in a cool, shaded area if possible because of the risk of exacerbation of physiologic hyperthermia. Antimicrobial therapy of rhodococcal pneumonia has been based on the combination of a macrolide and rifampin for over 30 years, which is an approach that was validated by a recent ACVIM consensus statement.[440] Although erythromycin was initially the primary macrolide used, it has been supplanted by azithromycin and clarithromycin for a variety of reasons, including less frequent administration, superior drug distribution, and pharmacokinetics as well as evidence of superior efficacy in a retrospective study.[420,441,442] There has been interest in the use of gamithromycin for the treatment of *R. equi* infections in foals because the pharmacokinetics support once-weekly intramuscular administration.[443] A recent study reported that gamithromycin therapy was noninferior to the combination of azithromycin and rifampin, although they also reported that 58% of foals treated with gamithromycin showed adverse reactions consisting of either colic or hindlimb lameness following drug administration, which is likely caused by tissue irritation from the drug.[435] The potential efficacy of the macrolide tulathromycin has been investigated, but despite early reports of efficacy[437] it has unacceptable pharmacokinetics and has subsequently been demonstrated to be ineffective.[436]

Rifampin has been used in combination with macrolide therapy on the basis of in vitro evidence of synergistic effects with erythromycin and limited evidence of enhanced treatment efficacy.[440] A recent study compared the efficacy of an azithromycin-rifampin combination to azithromycin alone and found that both treatments were superior to placebo, but there was no difference in efficacy between treatments.[436] Despite this evidence of efficacy the combination has been called into question because of the interference of rifampin with macrolide absorption after coadministration.[444,445] It is still recommended to use rifampin in combination with a macrolide to aid in minimizing the development of resistant strains, because these combinations have been shown to have lower mutant prevention concentrations than any of the individual macrolides or rifampin alone.[440,446] Reports of the emergence of macrolide-resistant and rifampin-resistant strains of *R. equi,* especially on endemic farms in which large numbers of foals have received treatment for subclinical pulmonary lesions identified on survey ultrasonographic examination, reinforce the need for this approach.[430,447,448] Indeed, one can reasonably question the need to treat foals that are not suffering from more severe forms of the clinical disease; recent studies examining treatment efficacy have also reported that 78% to 88% of foals in the untreated control groups recovered without intervention.[431,435] The prognosis for survival and athletic function in foals with *R. equi* pneumonia are good, at 60% and 54%, respectively.[349] Unfortunately the odds of survival are approximately sevenfold lower in foals infected with macrolide-resistant strains.[448]

There has been tremendous interest in reducing the incidence of rhodococcal infections on endemic farms for many years, but no highly effective approaches have been identified. The mainstay of prevention on many farms has been the administration of hyperimmune plasma, despite some conflicting evidence regarding efficacy, and widespread acceptance that even in the best-case scenario protection is incomplete.[449-453] Despite the expense, difficulty of administration, and potential for complications, the administration of hyperimmune plasma will likely continue to be used in prevention efforts until better approaches become available. Chemoprophylactic strategies have been investigated using azithromycin and gallium maltolate, with azithromycin yielding conflicting results and gallium showing no evidence of efficacy.[438,454,455] The prophylactic use of macrolides should be discouraged, however, because of the emergence of resistant strains on farms in which large numbers of foals receive these drugs.[430] Ultimately vaccination represents the ideal prevention strategy, but despite intensive investigation no effective vaccine is yet available.[420,456]

Respiratory Therapeutics

Bronchodilators

In foals suffering from respiratory dysfunction or respiratory distress there may be some utility in using bronchodilators to increase the airway diameter, decreasing the work of breathing and improving ventilation. The clinical utility of this approach is limited, however, because bronchoconstriction does not appear to play a prominent role in ARDS.[457] The other factor limiting the utility of bronchodilator therapy is the risk that the resulting increase in ventilation may actually worsen the degree of ventilation/perfusion mismatching caused by increased ventilation of areas of the lung that are poorly perfused. To determine whether bronchodilator therapy may be beneficial, one can perform a bronchodilator response test under close clinical monitoring. Because of the risk of worsening hypoxemia, it is best if the foal is already receiving oxygen by nasal insufflation, but at the very least oxygen should be readily available in case of clinical deterioration. Administer a single dose of a short-acting bronchodilator, preferably by inhalation rather than systemically, and then monitor the response using clinical assessment and ideally with repeated arterial blood gas analysis.[324] If the patient responds favorably,

TABLE **20.10 Inhaled Drugs Used for Treating the Respiratory Tract**

Class	Drug	Dose	Route	Frequency (h)
Bronchodilator	Albuterol	90–180 μg (young foals) 360 μg (weanlings)	MDI, Neb	2–6
	Ipratropium bromide	18–36 μg	MDI, Neb	8–12
	Ipratropium bromide with albuterol	18–36 μg ipratropium, 90–180 μg albuterol	MDI, Neb	8–12
Aerosolized antimicrobial	Ceftiofur	2.2 mg/kg	Neb	24
	Gentamicin	2.2 mg/kg	Neb	24

MDI, Metered dose inhaler; *Neb,* nebulization.
Adapted from Wilkins PA, Lascola KM: Update on interstitial pneumonia. *Vet Clin North Am Equine Pract*. 2015;31:137-157; Mckenzie HC: Treating foal pneumonia. *Comp Equine*. 2006;47-53.

with decreased respiratory effort and improved arterial oxygenation, then it may be reasonable to continue bronchodilator therapy. Regarding the choice of bronchodilator, the methylxanthines (aminophylline and theophylline), although readily available, are not recommended because of their systemic effects and narrow therapeutic index.[458] Generally, the use of the aerosol route is preferred; this targeted application allows for the use of smaller dosages, reducing the risk of systemic toxicity. β_2-Adrenergic agonists (albuterol and clenbuterol) are easily administered and may have additional benefits including enhancement of mucociliary clearance. Albuterol is inexpensive and the metered dose inhaler (MDI) formulation is most often used (Table 20.10). This drug has a fairly short duration of action of 1 to 2 hours. The anticholinergic bronchodilator ipratropium bromide (Atrovent, Boehringer Ingelheim) has a longer duration of action than albuterol (6–8 hours) and can be used alone or in combination with a β_2-agonist (Combivent, Boehringer Ingelheim). Ipratropium is only available as an aerosol preparation, either as an MDI or a solution for nebulization.

Aerosolized Antimicrobials

The targeted administration of antimicrobial drugs to the respiratory tract is of interest because it achieves very high local drug concentrations, which may allow for a more rapid response while minimizing the risk of systemic toxicity.[459] Although controlled studies in horses are lacking, there is evidence in human medicine that the use of aerosolized antimicrobials as an adjunct to systemic therapy is well tolerated and may improve outcomes in certain subsets of patients.[460,461] Although a number of antimicrobial drugs have been administered via nebulization empirically in the clinical setting, only a few drugs have been investigated for aerosolized administration in horses, including ceftiofur, cefquinome, gentamicin, and marbofloxacin.[459,462-466] Aerosol administration of these drugs to horses has been shown to achieve high respiratory drug concentrations, is well tolerated, and appears safe. Anecdotally, the two most widely used inhaled antimicrobials in horses are ceftiofur and gentamicin[458] (Table 20.10). A variety of devices have been used to aerosolize these drugs, including jet and ultrasonic nebulizers, but the recently developed vibrating mesh nebulizers yield the most uniform and appropriately sized aerosols with a wide variety of drugs. The availability of a vibrating mesh nebulizer that is integrated into a face mask device specifically designed for horses (Flexineb, Nortev, Galway, Ireland) has greatly facilitated the ability to routinely deliver aerosolized medications in the clinical or field setting.

Mechanical Ventilation

The goals of mechanical ventilatory support are to achieve and maintain adequate pulmonary gas exchange, reduce the work of breathing, and minimize patient discomfort and distress.[467,468] Mechanical ventilation provides pressure and volume support to ensure that adequate minute ventilation is achieved and also provides control over the composition of the inspired gases to provide sufficient oxygen to support arterial oxygenation. Patients requiring mechanical ventilation typically are suffering from arterial hypercapnia and/or arterial hypoxemia. Treatment of hypercapnia, defined as a $Paco_2$ of greater than 60 mm Hg, is fundamentally to increase the patient's alveolar ventilation by increasing the rate and/or depth of breathing. For initial therapy some clinicians will use respiratory stimulants to increase the patient's ventilatory efforts and try to avoid the need for mechanical ventilation, but if respiratory stimulant therapy is unsuccessful at resolving the hypercapnia, or if the hypercapnia is more severe ($Paco_2$ > 70 mm Hg) one should consider instituting mechanical ventilation. Early intervention is preferable, because there is no benefit to the patient from prolonged hypercapnia and the duration of the requirement for mechanical ventilation is usually shorter with early intervention.

Treatment of hypoxemia, defined here as a Pao_2 of less than 60 mm Hg, is initially by increasing the fraction of inspired oxygen (Fio_2) through the provision of supplemental oxygen by intranasal insufflation, but this will be inadequate in patients with significant hypoventilation or ventilation/perfusion mismatching. Mechanical ventilation allows for much higher Fio_2 than can be achieved with insufflation, up to 100%, dramatically increasing alveolar oxygen tension. Mechanical ventilation is also useful in terms of increasing minute ventilation through controlled respiratory rate and volume and in recruitment of alveoli for participation in gas exchange. An additional benefit is the decrease in the effort required for respiration, which can be dramatically increased in the face of pulmonary disease, which allows for a substantial decrease in the patient's energy and oxygen needs. This can also ease patient distress and increase patient comfort.

In equine patients the provision of mechanical ventilatory support is indicated in only a few basic situations. The first of these is the patient lacking normal respiratory drive, such as the obtunded or comatose neonatal foal, or the patient with impaired ventilatory effort, such as a patient with botulism. These types of patients are fairly easy to ventilate because the lungs are not diseased and pulmonary function is relatively normal. The prognosis for survival of these foals is excellent if

mechanical ventilation is instituted early.[469,470] A fundamentally different situation is present in the patient with severe pulmonary disease resulting in respiratory failure, such as a foal with severe sepsis, ARDS, meconium aspiration, or severe pneumonia. In these patients the presence of pulmonary disease results in profound alterations in pulmonary function, primarily in the form of increased pulmonary resistance and decreased dynamic compliance, making these patients much more challenging to ventilate. The prognosis for survival in this population of foals is much more guarded. The decision to initiate mechanical ventilation can be an agonizing one because of concerns regarding prognosis, client cost, potential complications, and the intimidation factor associated with managing the ventilator. Unfortunately this can result in delays in the initiation of therapy that dramatically decrease the likelihood of a successful outcome. The development of some familiarity with the process of mechanical ventilation on the part of the neonatal intensive care team often results in a willingness to use mechanical ventilation earlier. Training sessions that provide familiarity with ventilator setup and initial settings are extremely useful, and so is a pictorial guide to setting up a circuit and attaching it to the patient.

PPV functions by generating a positive pressure within the patient's airways, which is used to overcome the resistance to airflow arising from the airways themselves, the lungs, and the thoracic wall. Invasive PPV relies on intubation for the establishment of an airway for gas exchange and aids in preventing the aspiration of upper respiratory secretions or refluxed stomach contents. Intubation is best achieved in the conscious patient by the nasal route, and this is easiest to do with the head fully extended. Nasotracheal tubes in the range of 7 to 10 mm outside diameter will accommodate most horse foals, and these tubes should be cuffed. The largest tube that can be passed through the upper respiratory tract without trauma should be used. Care should be taken to ensure that the tip of the tube is located in the cervical portion of the trachea, because it is possible to insert the tube too deeply, resulting in placement within a mainstem bronchus and ventilation of only one lung. After final positioning of the tube the cuff should be inflated with only enough pressure to maintain a seal during PPV, because excessive cuff pressure can cause tracheal injury and necrosis. The tube should be anchored to the patient's head to prevent inadvertent removal resulting from patient movement, and this can be done by tying a section of umbilical tape to the hub of the tube and anchoring the ends of the tape to an elastic tape bandage placed around the muzzle or to a soft cotton halter around the patient's head. Endotracheal tubes should be changed at least every 12 to 24 hours, because respiratory secretions and exudate will accumulate within the lumen of the tube, impeding gas flow and potentially causing obstruction of the tube. The presence of large amounts of pulmonary exudate may require even more frequent changing of the tube.

The ventilator gases must be appropriately pretreated before delivery to the patient to ensure that the gases are humidified and warmed and avoid injury to the respiratory mucosa. This can be achieved with an active humidifier, which is typically a component of the mechanical ventilator, and these devices are very effective in humidifying and warming the large volumes of gases involved. Unfortunately the gases tend to cool as they pass through the tubing from the ventilator to the patient, resulting in substantial condensation (rain out) within the circuit that must be periodically drained. This effect is accentuated if the hospital environmental temperature is low. Alternatively a passive humidifier can be used, which consists of a heat–moisture exchange (HME) filter device placed in between the ventilator circuit and the patient.[469] These devices are effective with small foals but may not be adequate for foals over 70 kg and may need to be supplemented with a cold active humidifier in the ventilator circuit.[469] The primary limitation to HME filters is that they tend to clog with airway discharge, which can result in obstruction and failure of mechanical ventilation.[470,471] For these reasons the author typically uses HME filters only for short periods of time, such as when first initiating mechanical ventilation, and relies on active humidification for the duration of ventilation.

The settings on the ventilator should be established before attaching the patient to the ventilator to avoid inadvertent overinflation of the lungs. Although there are several different ventilator modes to select from, on most ventilators there are some basic settings that are fairly universal including Fio_2, tidal volume, peak flow, and breath rate. Fio_2 should be set to the minimum level required to maintain an adequate Pao_2 but no lower than atmospheric O_2 (0.21% or 21%). The tidal volume is the volume of gas delivered with each machine-controlled breath, and this should be set such that the peak inspiratory pressure (PIP) does not exceed 25 to 35 cm H_2O to avoid trauma to the pulmonary tissues. Peak flow is the maximal gas flow rate delivered by the ventilator during the inspiratory phase of ventilation. Excessive peak flow rates will result in overly rapid inflation of the lungs and high peak airway pressures. Low peak flow rates will result in an overly long inspiratory phase, resulting in a loss of synchrony with the ventilator, especially at high respiratory rates. Reasonable initial settings for these parameters are an Fio_2 of 0.5 (0.3–1.0), a tidal volume of 5 mL/kg (up to 8 mL/kg), a peak flow of 70 L/min (60–80 L/min) and a breath rate of 20 to 30 breaths/min.[469] These values may require adjustment once ventilation is instituted, and the response to ventilation should be closely monitored. Additional variables that may be controlled with the ventilator are positive end-expiratory pressure (PEEP), which should be set at 3 to 5 cm H_2O, trigger sensitivity (−2 cm H_2O), pressure support (8–10 cm H_2O), and inspiration:expiration ratio (I:E ratio = 1:2).

When considering mechanical ventilation one encounters a bewildering array of modes of ventilation, but the ideal mode is one that maintains consistent and adequate tidal volume and minute ventilation at moderate airway pressures, is synchronized to the patient's respiratory efforts, responds to patient demands, and allows for the lowest possible work of breathing.[468] This discussion will be limited to the most commonly used modes of mechanical ventilation. SIMV is a modification of assist-control ventilation that still delivers a set minimum rate of mandatory breaths, which are rigidly controlled; however, the ventilator attempts to synchronize these breaths with the patient's inspiratory efforts if possible. The primary advantage of this mode is that it is well tolerated by the patient because of the synchronization of mandatory breaths with patient effort. In addition, SIMV ensures a minimum breath rate in patients with variable respiratory efforts or that are exhibiting periods of apnea. The limitation of SIMV is that the spontaneous breaths are not supported by the ventilator and require a large degree of patient inspiratory effort. Pressure support ventilation (PSV) allows the patient complete control over all aspects of the ventilatory cycle except for the pressure limit. In this mode each patient breath is supported by a preset assist pressure, which is stopped when the flow rate decreases below a set fraction of peak flow at end inspiration. This allows

the patient to determine the size of the breath and the inspiratory flow rate, substantially decreasing the work of breathing. The risk of PSV is that there is no mandatory minimal breath rate guaranteed by the ventilator. The limitations of SIMV and PSV can be overcome by using SIMV with pressure support. SIMV provides a guaranteed minimal breath rate, and the PS provides pressure support of the patient-initiated breaths to overcome the inherent resistance of the ventilator circuit and endotracheal tube. CPAP is used to provide for a positive airway pressure throughout the ventilatory cycle. The pressure provided is typically the clinician-selected PEEP level. CPAP is often combined with PS to aid in overcoming the resistance of the circuit and decreasing the work of breathing.

It is generally desirable when ventilating a patient to not only provide for the minimal ventilatory needs of the patient but to use the ventilator to recruit poorly ventilated regions of the lung back into participating in gas exchange. The most commonly utilized recruitment maneuver is PEEP, which functions to maintain positive pressure within the ventilatory circuit during exhalation and between breaths to prevent alveolar collapse that might result during periods of negative pressure. Over time the presence of PEEP will keep open the alveoli that are "recruited" during the inspiratory cycle, and this allows for gradual improvement in the functional capacity of the lungs. This can result in substantial increases in Pao_2 and may allow for a decrease in the Fio_2.[472] By preventing cyclical alveolar collapse and reopening PEEP, the amount of shear stress-induced pulmonary injury may also decreased.[472] The use of PEEP is not always benign, however, because it can cause compression of the intrathoracic venous system and impair cardiac return with detrimental effects on cardiac output. When first initiating mechanical ventilation it is reasonable to use PEEP in most patients, especially at moderate settings, because the benefits appear to outweigh the potential negative effects.

The provision of mechanical ventilation is a very dynamic process requiring substantial involvement of the clinician in the supervision of ventilator setup and adjustment. Appropriate monitoring is critical to effective mechanical ventilation, and this cannot be overemphasized. The two most important aspects of monitoring are the assessment of pulmonary mechanics and pulmonary function. When considering the assessment of pulmonary mechanics one is really analyzing the interaction of the mechanical ventilator and the patient, and the three most important parameters are the driving pressure, the tidal volume, and the tidal airflow. The primary parameters of ventilator function and ventilator/patient interaction are the PIP and tidal volume (V_T). These parameters are interrelated, because increasing pressures will be associated with increasing tidal volume in normal lungs within normal physiologic limits. In ventilated patients, especially those with substantial pulmonary disease, one will often find that this relationship is abnormal, with normal pressures resulting in inadequate tidal volumes, or excessively high pressures being required to achieve a desired V_T. Continuous monitoring of PIP is extremely important, because sudden decreases may indicate a circuit leak, ventilator failure, inadequate gas supply, or a leak in the endotracheal tube cuff.[469] Increases in PIP may indicate obstruction of the endotracheal tube caused by kinking or accumulation of exudate, bronchospasm, or pneumothorax.[469]

The other critical aspect of monitoring involves monitoring pulmonary function, which fundamentally consists of the evaluation of pulmonary ventilation, in the form of elimination of CO_2, and pulmonary oxygenation, in the form of arterial oxygen tension. Assessment of pulmonary oxygenation relies primarily on the measured Pao_2, because the Fio_2 is known. In the patient with normal pulmonary function there should be a linear increase in Pao_2 with increasing Fio_2, but this relationship breaks down in the presence of pulmonary disease caused by ventilation/perfusion mismatching. The presence of intrapulmonary shunts, resulting from the perfusion of poorly ventilated regions of the lungs, will cause the Pao_2 to be lower than expected. A reasonable target for Pao_2 is 80 to 100 mm Hg or slightly higher, because values above 150 mm Hg are not beneficial and are an indication to decrease the Fio_2. The goal is to use the Fio_2 closest to room air (0.21) that achieves the desired Pao_2, and Fio_2 values above 50% are associated with oxygen toxicity to the respiratory mucosa. Additional information can be derived from knowledge of the exhaled $EtCO_2$ concentration, which is measured using capnography. The $EtCO_2$ is representative of the $Paco_2$ in patients with normal pulmonary function, usually with a value 2 to 5 mm Hg less than the $Paco_2$.[469] Decreases in $EtCO_2$ indicate decreased pulmonary perfusion secondary to decreases in cardiac output or increases in pulmonary vascular resistance.[469]

An important aspect of clinical monitoring is to check the endotracheal tube for exudate accumulation when the tube is changed, which should be done at least daily (more often if copious exudate is present). An increase in the amount of exudate within the tube, or a change in the character of the exudate to a more purulent appearance, may be an early indication of ventilator-associated pneumonia (VAP). A hemorrhagic appearance to the tube exudate may suggest ventilator-associated lung injury (VILI) or worsening of pulmonary inflammation caused by other insults.

The administration of mechanical ventilation is inherently unnatural and unphysiologic and has the potential to disrupt the normal functioning of many body systems. The provision of PPV, especially in the form of excess PEEP, has the potential to substantially decrease venous return, leading to impaired cardiac output. This is a serious concern, especially in the critical patient where cardiac output is often already impaired. The presence of an endotracheal tube has a number of potential adverse effects. First, the tube causes an increase in airway resistance because of its long narrow lumen and increases the work of breathing associated with spontaneous respirations. Second, the presence of the endotracheal tube results in a bypass of the normal protective functions of the upper respiratory tract and can allow access to the respiratory tract for pathogenic organisms. Infections arising by this route are termed *VAP*, and the likelihood of VAP developing is increased with prolonged duration of mechanical ventilation. The presence of inflammation secondary to the process of mechanical ventilation itself will also increase the likelihood of VAP, as will impairment of the patient's immune function associated with systemic illness. The organisms involved in VAP are often nosocomial in nature, which can be associated with a pattern of increased resistance to antimicrobials, complicating treatment of the condition. Aerosolized ceftazidime has been shown to be effective in the prevention of VAP in human patients, while also attenuating the proinflammatory response in the lung.[473] The author has subjectively observed a decreased rate of VAP in mechanically ventilated foals when aerosolized amikacin is nebulized into the ventilator circuit starting within 24 hours of the initiation of mechanical ventilation.

Ventilator-induced lung injury (VILI) should be considered to be inevitable, and the clinician's goal is fundamentally

to minimize the severity of this effect. There are three fundamental types of VILIs: barotrauma, volutrauma, and atelectotrauma.[474] In patients with poor pulmonary compliance and areas of pulmonary atelectasis, high positive inspiratory pressure may be required to achieve adequate ventilation, and this causes overdistention of the ventilated regions of the lung (local volutrauma).[475] Volutrauma results from exceeding the normal physiologic functional residual capacity of the ventilated regions of the lung, resulting in the development of pulmonary edema and initiation/amplification of the local inflammatory response. PEEP is somewhat protective in that it appears to slow the development of pulmonary edema unless it too is excessive, at which point it contributes to overinflation and causes further harm.[476] Atelectotrauma is caused by the repeated opening and closing of lung units during tidal ventilation and essentially represents a syndrome of low-volume injury resulting in the initiation of an inflammatory response.[474] By appreciating that the lungs are susceptible to both high- and low-volume injury it is apparent that optimal mechanical ventilation is achieved within a fairly narrow range of tidal volumes and that this range may vary dramatically from patient to patient.

The discontinuation of mechanical ventilation *(weaning)* can be the most challenging part of the entire process, and in human patients this phase may constitute as much as 50% of the time the patient is being mechanically ventilated.[477] Arguably the process or weaning begins as soon as the patient is placed on the ventilator, because the clinician constantly strives to identify the minimum level of support required to maintain adequate ventilation and oxygenation. By minimizing the degree of support, one can accelerate the patient's recovery of strength and stamina in the muscles of respiration (or minimize its loss) while also increasing the clinician's ability to identify when the patient no longer requires ventilatory support. Gradually decreasing the level of pressure support provided and increasing the trigger sensitivity level can accomplish progressive challenge of the patient's ability to ventilate on its own. Ultimately, however, the determination of readiness to be removed from the ventilator is a subjective one, and the question can only be answered by an extubation challenge. This is preferable to simply removing the patient from the ventilator while leaving the endotracheal tube in place, because the tube causes significant resistance to airflow and increases the patient's work of breathing. Intranasal oxygen insufflation should be provided immediately following tube removal in most cases, unless the patient has been maintaining normal oxygenation at an Fio_2 of 0.21 while on the ventilator. Care must also be taken so that one is fully prepared to immediately reintubate the patient if the challenge is not successful and mechanical ventilation must be reinstituted. The primary endpoints of the challenge are respiratory rate, respiratory effort, and arterial blood gas evaluation, and some patients may fail within minutes while others fail over several hours. Several challenges may be required over a period of hours to days before one is certain that the patient is able be maintained without ventilatory support.

GASTROINTESTINAL DISORDERS

Colic

Colic is a common presenting complaint in foals.[478,479] Unfortunately the evaluation of foals with colic can be frustrating because of the common clinical presentation associated with acute abdominal pain, despite the many possible underlying etiologies. Foals are typically more demonstrative of abdominal pain than adult horses, and signs of colic in foals may range from very nonspecific signs such as tachycardia, tachypnea, anorexia, agitation, and bruxism to more classic signs such as abdominal distention, recumbency, rolling, and lying in dorsal recumbency.[480] Causes of colic in neonatal foals can include meconium impaction, infectious and noninfectious enterocolitis, dysmotility associated with other disease processes, small intestinal strangulating obstructions, congenital abnormalities, intussusceptions, hernias, gastric or duodenal ulceration, aerophagia, foreign body obstructions, lactose intolerance, hypoxic injury, and ovarian or testicular torsion.[480] Causes of colic in older foals are similar but also include conditions such as ascarid impactions, displacements, pyloric or duodenal strictures, abdominal adhesions, and nonstrangulating obstructions such as fecaliths. Nonintestinal pain may cause clinical signs indistinguishable from true colic in foals, and this may result from pain in the thorax, liver, or urogenital tract; distention associated with uroperitoneum; or nongastrointestinal inflammation such as peritonitis.

Examination of foals with colic is somewhat facilitated by their small size, which allows for repositioning and external abdominal palpation, as well as thorough ultrasonographic examination. The inability to perform a rectal examination beyond digital palpation can be a frustrating limitation, however. Just as in adults the initial goals of colic evaluation are stabilization of the patient and differentiation of cases requiring surgical versus medical management. Although most cases of colic in foals can be successfully managed medically, there are cases in which prompt surgical intervention will be required, and small intestinal strangulating obstruction is the most common.[479] The presence of diarrhea is usually an indication that medical management will be sufficient, but this may be present in association with a surgical problem. Unrelenting pain that is poorly controlled with analgesics is a strong indication of a surgical problem, just as in adults. Severe intestinal distention on ultrasonographic examination, particularly caused by fluid or mixed fluid and gas rather than gas alone, may also suggest the presence of a surgical lesion.

The most common cause of intestinal obstruction in neonatal foals is meconium impaction.[480,481] Meconium is a mixture of glandular secretions, mucus, bile, digested amniotic fluid, and epithelial cells and should normally be expelled within the first few hours of life following the foal's first feedings. Colostrum feeding may be helpful in the expulsion of meconium because of the laxative effects of colostrum, but the lack of colostrum intake in a recent study had no effect on meconium release compared with foals fed milk replacer.[482] If the meconium is not passed by 12 hours of age it will likely cause intestinal obstruction, typically at the level of the small colon or the pelvic inlet.[481,483] Progressive intestinal and abdominal distention will develop over the next several hours secondary to gas accumulation orad to the obstruction. Identification of the mass of meconium may be possible on manual palpation of the abdomen, but ultrasonography is a more sensitive and specific means of identifying meconium obstructions. In some cases retrograde contrast radiography may be helpful in confirming the presence and level of the obstruction and in ruling out other causes of obstruction such as congenital defects. Administration of an enema can be useful both as a therapeutic intervention and a diagnostic test and is indicated in all cases of suspected meconium impaction. Sodium phosphate

enemas are widely used because of their ready availability in a premixed human preparation that is easily administered. Care must be taken to avoid hyperphosphatemia caused by excessive administration, however, and for this reason this type of enema should be administered no more than twice in the first 24 hours of life. Soapy water enemas given by gravity flow have also been frequently used, but because of the likelihood of rectal irritation and limited efficacy they should not be used repeatedly.

The most effective type of enema for the treatment of meconium impaction is the acetylcysteine retention enema.[481] These enemas can be prepared using commercially available acetylcysteine (*N*-acetyl-L-cysteine powder, Sigma-Aldrich, St. Louis, MO) by adding 8 g of acetylcysteine to a solution of 20 g of baking soda in 200 mL of water. Commercially prepared acetylcysteine enemas for foals are also available (http://www.scahealth.com/e-z-pass-foal-enema-kit.html). The foal is placed in lateral recumbency and restrained and sedated, if necessary. A 30-Fr Foley catheter with a 30-mL balloon is placed 2.5 to 5 cm into the rectum, and the balloon is filled, taking care not to overinflate. The acetylcysteine solution is infused using gravity flow to a volume of 100 to 200 mL and left within the rectum for 30 to 45 minutes.[481] Because this type of enema does not seem to be highly irritating, this procedure can be repeated as many as three times, usually at 12- to 24-hour intervals. Additional treatments that are helpful in managing affected foals include IV fluid therapy to address any deficits and ongoing maintenance needs, as well as analgesic therapy. Butorphanol administration may be sufficient to control discomfort in many foals, but individuals with more pain may require flunixin administration to control their pain while medical management is pursued. Cases refractory to medical management may require surgical correction of the meconium impaction, but this is uncommon since the introduction of acetylcysteine enemas.[481]

Roundworm *(P. equorum)* infestation is a common condition among foals, with a reported prevalence around 40%.[484] Most foals will not show evidence of infestation, but the clinical signs associated with the presence of this parasite may include lethargy, anorexia, decreased weight gain, coughing, hypoproteinemia, nasal discharge, colic from gastrointestinal impaction, and occasionally rupture or perforation of the small intestine.[485,486] The colic signs result from acute small intestinal obstruction caused by a large burden of the parasite, and in most cases the colic is associated with recent administration of anthelmintic medications but may be associated with a stressor such as transportation or weaning.[485] Horses with impaction of the small intestine caused by *P. equorum* commonly suffer from secondary intestinal abnormalities caused by luminal obstruction, including small intestinal volvulus or intussusception, and surgical intervention is typically required to prevent intestinal rupture.[486,487] As a result of the increasing resistance of *P. equorum* to commonly used anthelmintics, especially the macrocyclic lactones, it seems likely that the prevalence of this condition will increase.[403,488-490]

Although congenital defects of the gastrointestinal tract are rare, they must be ruled out when evaluating the neonatal foal with colic because of the similarities in clinical presentation with meconium impaction. The most common congenital defects are atresia of the colon, rectum, or anus. Affected foals typically present within the first 2 to 48 hours of life and exhibit signs of acute, progressive colic and abdominal distention.[338] In addition to signs of colic (tachycardia, tachypnea, recumbency, rolling, and anorexia), tenesmus may be noted. No fecal material will have been passed, and there will be no meconium staining noted in enema fluids that have been administered. Atresia ani is readily diagnosed on visual examination and digital palpation, whereas rectal and colonic lesions are more challenging to identify.[491] Ultrasonography may be useful in demonstrating distention orad to the site of the lesion but rarely is able to characterize the lesion. Retrograde contrast radiography can be helpful in further characterizing the lesion and differentiating atresia from meconium impaction. Colonoscopy may aid in diagnosing lesions in the terminal colon and rectum. This procedure can be performed under standing sedation, and the use of *n*-butyl scopolamine bromide (Buscopan, Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO) has been shown to aid visualization.[492] Ultimately surgical exploration may be the only way a definitive diagnosis of atresia coli can be made. Surgical correction of atresia ani is straightforward and typically successful, although anal sphincter function may not be normal.[491] Atresia ani may be accompanied by penile malformations (hypospadias) that will also require surgical correction.[493] Surgical resection and anastomosis has been attempted in some cases of atresia coli in which the lesion was accessible, but outcomes have been poor.[491] This is likely caused by additional underlying neurologic and motility disorders and means that this condition should be considered typically fatal.

Congenital aganglionosis, or overo lethal white syndrome, is a syndrome that affects white American Paint Horse foals born from overo-overo matings, although it has been reported in one foal with one solid color Quarter Horse parent.[494] This syndrome occurs when foals receive one copy of the mutated endothelin receptor B gene (*EDNRB,* overo lethal white gene) from each parent.[495,496] Affected foals suffer from aganglionosis of the distal small intestine and large intestine, which results in a lack of intestinal motility leading to colic.[494] Recent work suggests that the extrinsic innervation may be affected as well.[497] Not all foals born from overo-overo matings will be affected, so care should be taken to ensure that the foal is not simply suffering from meconium impaction before making a potentially terminal decision. A mutagenically separated PCR was recently developed for the detection of the *EDNRB* genotype in horses.[498]

Diarrhea

Diarrhea is a common problem in foals, with substantial morbidity and mortality.[405] It is associated with a number of potential pathophysiologic mechanisms and many etiologies, making diagnosis and management challenging. Syndromes involving noninfectious etiologies as well as bacterial, viral, protozoal, and parasitic etiologies are all reported in foals. Although many of the conditions associated with diarrhea can affect foals of any age, some conditions, such as necrotizing enterocolitis (NEC) and asphyxia-associated enteric dysfunction, are primarily seen in neonates, whereas others, such as proliferative enteropathy, are seen in older, weanling age foals.

Foal heat diarrhea is a mild, self-limiting condition seen in foals from 5 to 15 days of age, and is temporally associated with the occurrence of the mare's first heat following parturition. This temporal association has implied causation, but this is not the case. Foals raised on milk replacer also exhibit diarrhea during this time frame, and analysis of the composition of mares' milk has not revealed any changes that might precipitate the development of foal diarrhea.[499] Affected foals are

clinically normal with the exception of diarrhea and remain bright with good appetites. It appears more likely that changes occurring within the gastrointestinal tract in relation to solid feed ingestion and development of the fecal microbiota are responsible.[500,501] Additionally there may be hypersecretion of the small intestinal mucosa that is inadequately compensated for by immature colonic absorption that contributes to foal heat diarrhea.[502] Diarrhea in a foal of this age should not be taken lightly, however, because rapid clinical progression is possible. Any sign of systemic illness, dullness, or inappetence should prompt rapid assessment for a more severe condition than foal heat diarrhea that may warrant medical intervention.

A common cause of diarrhea in hospitalized neonatal foals is perinatal asphyxia-associated gastrointestinal dysfunction. Affected foals typically have associated risk factors such as dystocia, delivery by cesarean section, umbilical problems during delivery, or some cause of inadequate oxygenation immediately postpartum.[503] These foals may exhibit dysmotilities leading to ileus, gastroduodenal reflux, intolerance of enteral feeding, abdominal distention, colic, and diarrhea.[503] Evidence of perinatal asphyxia syndrome may be observed in other body systems, especially the neurologic system. Affected foals should be considered at risk for developing sepsis, and a similar presentation may be observed in foals suffering from sepsis, likely caused by the presence of severe systemic inflammation. For these reasons appropriate broad-spectrum antimicrobial therapy is indicated in these cases.

Another condition affecting hospitalized neonatal foals is NEC. This syndrome is the most frequent and lethal disorder affecting preterm human infants and is associated with disruption of the intestinal barrier leading to intestinal necrosis, multiorgan failure, and death.[504] NEC has been sporadically reported in foals for many years, but it appears likely that it represents an underdiagnosed condition.[505-511] A broad variety of infectious agents, including not only bacteria but also viruses and fungal species, have been associated with NEC in humans.[512] Although most of the cases reported in foals have been linked to the presence of a variety of pathogenic bacteria, the cause of NEC remains the subject of much discussion in human literature, and it is not clear if it is primarily an infectious condition. It appears likely that the pathophysiology is truly multifactorial, involving a complex interplay between intestinal immaturity, hemodynamic instability, inflammation, genetic factors, formula feeding, and dysbiosis.[513-515] The clinical presentation may be similar to that described for the asphyxia-associated disorders mentioned previously, and certainly those foals may be considered at risk for NEC. In a recent report foals diagnosed with NEC presented most commonly with colic or diarrhea, but these signs were absent in the majority of affected foals.[511] Other abnormalities observed in association with NEC included prematurity, gastric reflux, abdominal distention, bloody feces, and pneumonia.[511] Interestingly, the authors of that report found no evidence of an association of *C. difficile, C. perfringens,* or *Salmonella* species with NEC.

The diagnosis of NEC is made through radiographic or ultrasonographic evidence of intramural gas in the intestinal wall (pneumatosis intestinalis) or surgical or postmortem evidence of gastrointestinal necrosis.[511] Although as many as 80% of affected human neonates are reported to survive, the presence of NEC is associated with a poor prognosis for survival in foals.[511,513] Treatment of foals with NEC will be as for any critically ill foal and will likely include IV fluid therapy and broad-spectrum antimicrobial therapy. Because of concerns that enteral feeding may precipitate or worsen NEC, it has been recommended that enteral feeding should be avoided, which is generally recommended in the foal with colic, ileus, or reflux. Parenteral nutrition will be required until enteral feeding can be gradually reintroduced. Human studies have suggested that a minimal enteral nutrition approach, rather than complete withdrawal of enteral feeding, using less than 20 mL/kg per day for the first several days, then gradually advancing to normal intake levels over several days, appears to be well tolerated and safe.[516,517] Human studies have shown that breast milk is protective against NEC in low-birth-weight infants, and for this reason it makes sense to use the mare's milk for feeding the foal if possible.[503,518] Metronidazole therapy may be indicated because of the reported association of NEC with clostridial infection in foals, although a recent human report found that metronidazole therapy may not prevent clinical deterioration in cases of NEC.[519]

Other causes of noninfectious diarrhea can include dietary intolerance, particularly when milk replacers are fed rather than mare's milk.[503,520] This can be the result of products used in the milk replacers that are poorly digested by foals, such as maltodextrins, corn syrup, oligosaccharides, or glucose polymers.[520] Gastrointestinal irritation secondary to ingestion of sand, grit, or dirt may also result in diarrhea caused by mechanical irritation of the mucosa.[521]

Infectious Causes of Diarrhea

The most common cause of infectious diarrhea in foals is rotavirus, which is detected in the feces of foals with diarrhea in 20% to 77% of cases.[522-524] Equine coronavirus has been associated with clinical disease in adult horses[525] and has been detected in the feces of diarrheic foals, but the role of this virus in foal disease is unclear.[524,526-528] EAdV2 has also been detected in the feces of foals with diarrhea, but the actual involvement of adenovirus in the development of disease is unclear, especially in the immunocompetent individual.[529-532] There are older reports of parvovirus-like particles identified in foals with diarrhea, but no further evidence has emerged regarding the potential pathogenic role of such organisms in the foal.[533,534]

The pathogenesis of rotaviral diarrhea is multifactorial, and this organism is frequently detected in combination with other potential gastrointestinal pathogens. Rotavirus infects the epithelial tips of the villi of the duodenum, jejunum, and ileum, but it does not affect the crypt epithelium.[523] The virus replicates within the villous epithelium and is released following cell lysis, which results in destruction of the infected cell and desquamation of the villous tips. This leads to a loss of the normal absorptive capacity of the villi, but the secretory crypt epithelium is unharmed, resulting in malabsorption that likely contributes to the development of diarrhea. Villous injury also results in the decreased production of disaccharidases, particularly lactase, which may impair the digestion of lactose and contribute to the development of diarrhea by osmotic mechanisms. Other factors contributing to the development of rotaviral diarrhea may be the activity of viral enterotoxins, inhibition of sodium-glucose cotransport, dysregulation of calcium homeostasis, and activation of the enteric nervous system.[523]

Clinically rotaviral diarrhea often occurs in large, comingled groups of mares and foals, and affected foals are typically from 5 to 35 days of age.[535] Foals initially exhibit anorexia and

depression, which quickly progresses to acute, profuse watery diarrhea. Affected foals may become rapidly dehydrated and frequently develop electrolyte abnormalities and metabolic acidosis. Although the morbidity associated with rotavirus infections is high, which is caused by the highly contagious nature of the virus, the prognosis for survival is good. Treatment is generally supportive and symptomatic, but IV fluid therapy is often needed to effectively address the fluid and electrolyte deficits. Balanced electrolyte replacement solutions are most effective given the frequent involvement of hyponatremia and hypochloremia. Severely affected foals may also benefit from a brief period of enteral rest (1–2 days), which necessitates the provision of parenteral nutrition until feeding can be reintroduced. Supplementation with lactase enzymes (Lactaid, McNeil Nutritionals, LLC, Ft. Washington, PA) at 9000 U (one tablet) PO every 3 to 8 hours may be helpful in improving milk digestion in foals that remain on the mare, or when nursing is reintroduced.[503] The diagnosis of rotaviral diarrhea is by detection of viral particles using electron microscopy, virus isolation, enzyme-linked immunosorbent assay (ELISA), immunochromatography tests, and real-time reverse-transcriptase PCR (RT-PCR). Of these the immunochromatography tests and RT-PCR are the most rapid and simplest to perform and provide high sensitivity and specificity.[523,536] Control of rotaviral diarrheal outbreaks can be challenging, especially in crowded environments because of the highly contagious nature of the virus, its persistence in the environment, and the resistance to disinfectants.[523] Prevention can be facilitated by the use of maternal vaccination, which has been associated with a reduction in the frequency and severity of rotaviral diarrhea on endemic farms, and a conditionally licensed commercial vaccine is available for provisional use (equine rotavirus vaccine, Zoetis, Kalamazoo, MI).

The primary bacterial agents of concern in foal diarrhea are *C. difficile* and *C. perfringens*. Discerning the relationship between these organisms and clinical disease has been challenging because either or both organisms can be identified in normal animals as well as diseased animals, but both organisms are isolated significantly more frequently from foals with enterocolitis than from healthy foals.[506,509,522,537-540] *C. difficile*–associated diarrhea (CDAD) is commonly associated with a history of antimicrobial therapy and likely represents the primary agent of antimicrobial-associated diarrhea (AAD) in foals.[541] Spontaneous cases of CDAD can occur without exposure to antimicrobials, however, both sporadically and in outbreaks.[509,537,542,543] Additional risk factors that may predispose foals to CDAD include hospitalization, stress, dietary alterations or starvation, transportation, nasogastric intubation, and surgical or medical treatment.[544] Clinically CDAD can be quite variable both in terms of the clinical signs and the severity of the disease. The primary clinical sign of CDAD is diarrhea, which may be watery or bloody, typically accompanied by signs of systemic inflammation and hypovolemia (hyperemic mucous membranes, prolonged capillary refill time, pyrexia, tachycardia, and tachypnea) and occasionally by abdominal distention and colic.[545] Unfortunately these signs are nonspecific, and although CDAD may be suspected on the basis of history and clinical presentation, diagnostic testing is required for confirmation of the diagnosis. Because normal animals may carry the organism and these often represent nonpathogenic strains, culture is not useful for diagnosis of CDAD. Virulence of *C. difficile* depends on the elaboration of toxin A (TcdA) and toxin B (TcdB), and there is evidence to suggest that both toxins are important in the development of clinical disease.[546,547] An additional toxin, termed *C. difficile transferase* (CDT), appears to play a role in virulence as well; CDT-producing strains have been associated with increased mortality in human patients.[547] Confirmation of a diagnosis of CDAD is based on the detection of TcdA and/or TcdB in the feces of the affected individual, and this is most often performed using a commercial ELISA (*C. difficile* Tox A/B II, Techlab, Inc., Blacksburg, VA) or RT-PCR.[524,541]

C. perfringens has also been associated with enterocolitis in foals, and this syndrome is typically quite severe in nature, with high mortality rates.[508] Both type A and type C *C. perfringens* have been implicated in these cases, but the more severe form of the disease is typically associated with type C, and affected foals do not typically respond to treatment.[508] *C. perfringens* produces four major toxins, but the β-toxin appears to be the primary one responsible for intestinal injury.[509] A novel β-pore-forming toxin, NetF, has recently been described and has been associated with severe NEC in dogs and foals.[548,549] Risk factors may include birth on dirt, sand, or gravel and housing in stalls or dry lots in the first few days of life. Clinical signs are similar to CDAD, but because of enterotoxemia affected foals may show more pronounced signs of systemic inflammation and shock. Hemorrhagic diarrhea has been reported in some cases but may be transient in nature. Diagnosis of *C. perfringens* enterocolitis can be challenging, because the organism may be present in the feces of healthy foals. A positive fecal culture in combination with appropriate signalment and clinical presentation may be supportive, however, because healthy foals will generally shed very low numbers of the organism. Fecal Gram stain may also be supportive if it demonstrates large numbers of large gram-positive rods or spores. Commercial assays are available for detection of fecal enterotoxin, but they lack sensitivity.

Treatment of CDAD and *C. perfringens* enterocolitis is primarily supportive in nature, similar to other causes of enterocolitis. Broad-spectrum antimicrobial coverage is indicated, even in situations in which AAD is suspected, because of the risk of bacteremia secondary to bowel wall inflammation and injury. Metronidazole therapy represents the primary specific therapy for clostridial infections, but metronidazole-resistant strains of *C. difficile* have been reported.[550] A recent pharmacokinetic study suggests that the metronidazole dosing regimens used in foals should be revised to 10 mg/kg orally every 12 hours for newborn foals and 15 mg/kg orally every 12 hours for the 10- to 12-day-old foal.[551] After that age the current recommendation of 15 mg/kg orally every 8 hours remains unchanged. Additional therapies that may be of some benefit in CDAD include enterally administered adsorbents, such as di-tri-octahedral smectite.[552] Probiotic therapy is of interest because of the positive results reported in human patients, but the limited studies do not support the efficacy of probiotics in foal diarrhea at this time.[553,554]

A number of other bacteria have been associated with diarrhea in foals, including *Salmonella* spp., *E. coli, Enterococcus* spp., *Aeromonas* spp., and *Bacteroides fragilis,* although causation can be difficult to establish.[531,555-558] Given that diarrhea is a common clinical abnormality associated with sepsis in foals, it is important to be aware that bacterial involvement may be present, even if not in the form of a primary enteric pathogen. One retrospective study found that of foals less than 30 days of age presenting with diarrhea, 50% were bacteremic at admission, further reinforcing this concern.[120] Blood cultures

should be collected routinely at admission in this population, not only to confirm bacteremia but also to yield information regarding antimicrobial sensitivities.

R. equi, although primarily a respiratory pathogen, commonly exhibits extrapulmonary involvement and has been associated with enteric disease, primarily in older foals.[558] Diarrhea, ulcerative enterotyphlocolitis, abdominal abscessation, mesenteric lymphadenitis, and peritonitis have all been reported.[432] In one study 33% of foals with *R. equi* infections were reported to have diarrhea, and in half of those foals diarrhea only began following the initiation of treatment for the primary infection.[432]

Equine proliferative enteropathy (EPE) is an infectious disease affecting young horses, primarily foals from 2 to 8 months in age.[559,560] EPE is caused by the obligate intracellular bacterium *Lawsonia intracellularis.* This disease causes dramatic structural changes in the mucosal epithelium of the small intestine caused by proliferation of the crypt epithelial cells. These alterations lead to a protein-losing enteropathy that can result in variable degrees of hypoalbuminemia, hypoproteinemia, ventral edema, lethargy, diarrhea, fever, weight loss, and colic.[561,562] Diagnosis of proliferative enteropathy is by a combination of clinical signs (ventral edema), clinicopathologic abnormalities (hypoalbuminemia), abdominal ultrasonographic examination, immunoperoxidase monolayer assay serology, and fecal PCR testing for *Lawsonia* DNA.[563] Treatment is best accomplished using lipophilic antimicrobials administered for 3 weeks, such as tetracyclines (oxytetracycline, doxycycline, or minocycline), macrolides (azithromycin and clarithromycin), or chloramphenicol.[564] Rifampin has been used in combination with macrolides but does not appear necessary to achieve a positive clinical response. Regarding prevention, unfortunately passively acquired antibodies have been demonstrated to have no effect on the occurrence of subclinical or clinical EPE.[565] Promising results regarding prevention have been seen with the intrarectal administration of a commercial avirulent porcine vaccine against *L. intracellularis,* which has been demonstrated to result in complete protection against EPE and reduces fecal shedding.[566] The prognosis for survival with appropriate treatment is good, but affected animals often exhibit a decrease in growth rate and as a result may be at a slight disadvantage relative to their peers for several months.[560] Recent reports have detailed a more severe form of EPE that is associated with fatal outcomes, but these cases appear to be unusual.[567,568]

The pathogenic role of *Cryptosporidium* spp. in foal diarrhea has been the subject of debate because normal foals have been shown to shed the organism, but there have been several studies that implicate this organism in both sporadic and outbreak situations.[569-572] Although the most commonly identified species has been *C. parvum,* another *Cryptosporidium* (the horse genotype) has been identified in horses, humans, and a calf.[573,574] Affected foals usually do not exhibit substantial systemic inflammation, and the disease is typically self-limiting. Profuse watery diarrhea may necessitate IV fluid therapy in addition to routine supportive therapy. This disease has clear zoonotic potential, so appropriate biosecurity precautions are indicated to protect in-contact individuals. Indeed, a recent report detailed an outbreak of human cryptosporidiosis in veterinary students associated with exposure to infected foals in an equine perinatology unit.[575] Diagnosis has traditionally relied on the identification of oocysts in the feces using acid-fast staining techniques, but RT-PCR testing can be performed, and rapid and easily performed immunofluorescence assays are commercially available (Xpect Giardia/Cryptosporidium Test, Thermo Scientific, Waltham, MA; Merifluor Cryptosporidium/Giardia, Meridian Bioscience, Inc., Cincinnati, OH).

Strongyloides westeri is a nematode primarily transmitted to foals by the transmammary route. Although this organism has been suspected as a cause of diarrhea in young foals, it appears likely that clinical disease would only be present when the parasite is present in very high numbers.[503,569] Control is typically by means of ivermectin administration to the mare shortly after delivery, but the prevalence of this parasite appears to be increasing, perhaps related to the decrease in ivermectin administration to foals because of concerns for ivermectin resistance in *P. equorum.*[576]

Gastric Ulceration

Gastric ulceration has been frequently reported in foals, with prevalence ranging from 22% to 57%.[577-580] The clinical signs associated with gastric ulceration in foals are often nonspecific and may include diarrhea, colic, rolling, restlessness, lying in dorsal recumbency, excessive salivation, bruxism, and anorexia.[581] For this reason diagnosis should not be made on clinical grounds alone but should rely on gastroscopic examination. In addition to confirming the presence of gastric ulceration, gastroscopic examination allows for thorough characterization of the site(s) involved and the severity of the lesions present. Noninvasive techniques for diagnosing gastric ulceration in foals are of interest but are not well validated and would not provide detailed information regarding the extent and severity of gastric ulceration.

The greatest challenge associated with the diagnosis and treatment of gastric ulceration in foals is the fact that many of the animals with endoscopically evident ulceration do not show any clinical signs suggesting that the ulcers are causing dysfunction or discomfort.[580] Therefore the clinical significance of gastric ulceration in some foals, and the need for treatment, is unclear. Despite this fact there has been substantial concern related to the risk of intestinal perforation secondary to the progression of clinically silent gastric ulcers, because this condition is fatal when it occurs.[582] For this reason prophylactic antiulcer therapy has often been administered to clinically ill foals or those receiving nonsteroidal therapies. The efficacy of these prophylactic approaches has not been confirmed in clinically ill foals, however, and the response of sick foals to acid-suppressive therapy is less consistent than in healthy foals.[583] Indeed, two large retrospective studies reported that the prevalence of gastric ulceration on postmortem examination of hospitalized foals was not related to whether or not prophylactic treatments were administered.[578,584] Unfortunately prophylactic acid suppression may be associated with some risks, and human studies have documented an increased risk of pneumonia and CDAD in non-ICU hospitalized patients treated with acid-suppressive drugs.[585,586] Proton-pump inhibitors (PPIs) are more potent inhibitors of acid suppression than histamine 2-receptor antagonists (H2RAs), and for this reason PPIs appear to be associated with a greater risk of these complications.[587,588] In human ICU patients there does not appear to be an increased risk of pneumonia or differences in overall mortality associated with acid suppression, but the use of PPIs is associated with an increased risk of CDAD.[586] A recent multicenter study found that the use of acid-suppressive therapy in hospitalized foals was associated with an increased risk of

undifferentiated diarrhea but not of CDAD.[589] Together these concerns suggest that such use should be avoided and that treatment be limited to those foals with documented disease requiring treatment.

The pathophysiology of gastric ulceration in the foal is likely complex and multifactorial and may differ between the squamous and glandular mucosal regions of the stomach. Within the stomach there is a constant interplay between protective factors and aggressive factors. The protective factors maintain a healthy gastric mucosa by promotion of mucosal blood flow, mucus and bicarbonate production, prostaglandin E2 production, promotion of epithelial growth factors, epithelial cell restitution, gastric afferent innervation, and gastroduodenal motility. The aggressive factors, which include gastric acid, bile salts, pepsin, and numerous enzymes, act to induce and potentiate gastric epithelial injury. As gastric acid production is highly variable in neonatal foals and the intragastric environment is often alkaline,[583] it seems likely that ulceration results most commonly from suppression of the protective factors rather than from excess acid production. Perinatal hypoxia, systemic illness, or the administration of nonsteroidal antiinflammatory medications may lead to gastric mucosal hypoxia or ischemia, impairing the local protective factors and predisposing the patient to mucosal ulceration. Ulceration may occur in the squamous mucosa, the glandular mucosa, or both, and may extend to involve the duodenum and/or the esophagus. The clinical syndromes associated with ulceration include subclinical, clinically significant ulceration, perforating ulceration, and gastroduodenal ulcer syndrome (GDUS). This scheme should perhaps be expanded to include gastroesophageal ulceration, although this is most commonly associated with reflux esophagitis secondary to GDUS-induced delayed gastric emptying. The classification of ulceration as subclinical or clinical may be challenging and cannot be based solely on the number and severity of lesions identified on gastroscopic evaluation. Instead, it must involve consideration of the history and clinical signs associated with those findings. The diagnosis of perforation may also be difficult and cannot be based on gastroscopic assessment alone because of the sometimes benign surface appearance of these lesions. For this reason abdominal ultrasonography and abdominocentesis are important in confirming the presence of perforation. The diagnosis of GDUS is based on gastroscopic evaluation combined with the presence of one or more of the signs of gastric ulceration listed previously, although signs of gastric-outflow obstruction, such as ptyalism and bruxism, are typically more common with this diagnosis.

GDUS is most commonly seen in foals 2 to 6 months of age and is often associated with an unthrifty, pot-bellied appearance and foals being small relative to their peers.[590] Ultrasonographic examination is indicated in foals suspected to be suffering from GDUS because it allows for noninvasive assessment for gastric and duodenal distention. When gastric distention is present a nasogastric tube should be passed to extract the fluid and facilitate gastroscopic evaluation. Gastroscopic abnormalities commonly observed with GDUS include esophagitis, gastric squamous and glandular ulceration, pyloric ulceration, and pyloric stricture. Examination of the duodenum is usually not possible because of the presence of pyloric stricture. Treatment of affected foals is challenging and requires intensive management. Frequent gastric decompression is required, and parenteral nutrition is typically necessary because of the inability of the foal to eat. Supportive care including IV fluids, antimicrobials, and analgesics is also indicated. Acid-suppressive therapy is required, and this is usually accompanied by gastroprotectants and prokinetics. Although medical management may be helpful in resolving delayed gastric emptying, many affected foals will have severe fibrosis and constriction of the pylorus and duodenum, necessitating surgical correction. The goal of surgical correction is to bypass the pylorus and proximal duodenum, which typically involves gastrojejunostomy. Surgery is challenging, and success likely depends on early intervention, surgical expertise, and appropriate postoperative care.[590] Reported surgical outcomes have improved over time, with the most recent report demonstrating 100% survival to hospital discharge and 50% long-term survival.[591]

The cornerstones of treatment of gastric ulceration in foals are acid-suppressive drugs, primarily the H2RA drugs cimetidine and ranitidine and the PPI omeprazole (Table 20.11). The acid-suppressive effects of the H2RAs are variable and less dramatic than those seen with PPIs, but these drugs may suppress acid production sufficiently to facilitate ulcer healing.[592] Because of the more consistent and pronounced acid-suppressive effects of the PPI omeprazole, this drug has become the mainstay of gastric ulcer therapy in horses.[593] Dosing for foals can be challenging, because there is no labeled form specifically designed for use in foals, but the product marketed for use in adults can be measured out on a volume basis and administered orally at a body weight–appropriate dosage to foals. An IV formulation of omeprazole is not readily available for administration to foals that cannot take medications orally, but the IV pharmacokinetics of the PPI pantoprazole have been determined in foals.[594] Other treatments include

TABLE **20.11** **Drugs Used in the Prophylaxis and Treatment of Gastric Disorders in Foals**

Drug Class	Drug	Dosage (mg/kg)	Route	Frequency (h)
H2RA	Ranitidine	6.6	PO	8
		1.5–2.0	IV	6
PPI	Omeprazole—treatment	4	PO	24
	Omeprazole—prevention	1	PO	24
	Pantoprazole	1.5	IV	24
Mucosal protectant	Sucralfate	20–80	PO	6–12
Prostaglandin E1 analog	Misoprostol	2–5 μg/kg	PO	8–12
Antacids	Aluminum/magnesium hydroxide	120–240 mL	PO	4–8

H2RA, Histamine 2-receptor antagonists; *IV,* intravenously; *PO,* orally; *PPI,* proton pump inhibitor.

mucosal adherents, such as sucralfate, and oral antacids, such as aluminum hydroxide and magnesium. Sucralfate dissociates in the acidic environment of the stomach to sucrose octasulfate and aluminum hydroxide. Sucrose octasulfate binds to the ulcerated mucosa and decreases tissue exposure to hydrochloric acid and may also interfere with the activity of peptic enzymes.[595] Sucralfate appears safe and is well tolerated and likely represents a safer approach for ulcer prevention in hospitalized neonatal foals compared with the use of a PPI. The prostaglandin E1 analog misoprostol has been used in an effort to enhance ulcer healing by increasing epithelial mucous secretion, bicarbonate secretion, and mucosal blood flow.[596] Misoprostol may also enhance epithelial repair via closure of tight junctions following epithelial restitution of denuded regions of the mucosa.[597]

UROGENITAL DISORDERS

Abnormalities involving the urogenital tract are common in foals and can be congenital or acquired in nature. Acquired conditions may occur secondary to infectious, toxic, traumatic, or iatrogenic causes. The presence of urogenital disorders may represent the primary disease process or may occur secondary to other disease processes. In some cases the presenting signs may be directly associated with the urogenital disorder, but often these cases present with nonspecific signs such as depression and poor body condition. Clinicopathologic evaluation may be normal, but cases involving impaired renal function or urine retention are typically associated with azotemia and electrolyte abnormalities. Azotemia most often presents as an elevation in serum creatinine concentration, but with more chronic or insidious conditions an elevation in blood urea nitrogen (BUN) may be more prominent. Serum electrolyte abnormalities may include hyponatremia, hypochloremia, and hyperkalemia. Metabolic acidosis is also common. Urinalysis in normal foals will demonstrate hyposthenuria, because they produce dilute urine with a specific gravity 1.010 or less. Foals with renal dysfunction may have hyposthenuric, isosthenuric (specific gravity of 1.010), or concentrated, hypersthenuric urine (specific gravity >1.010), depending on the nature of dysfunction. Transient proteinuria is typical at birth, but this should resolve in the first few days of life in normal foals, and casts should not be present.

Congenital Disorders

Congenital urinary tract disorders are quite rare in foals, but of these renal dysplasia or hypoplasia is the most commonly reported.[598-604] No familial or breed predisposition has been demonstrated for this condition in horses. In utero exposure to therapeutic drugs or toxins may cause renal dysplasia, and there are reports of renal dysplasia in foals born to mares treated for equine protozoal myeloencephalitis with pyrimethamine, trimethoprim, sulfonamides, folic acid, and vitamin E.[605] Renal dysplasia or hypoplasia may represent an incidental finding in a foal or young adult horse presented for evaluation of other problems. Azotemia is typically not present unless renal function has been impaired by at least 65% to 75%, because of the substantial reserves of renal function that are normally present. Cases with bilateral renal involvement, urine retention, or suffering from acute-on-chronic disease are more likely to be associated with clinical and clinicopathologic findings consistent with renal insufficiency. Patients with unilateral involvement often remain asymptomatic, whereas treatment of renal dysplasia or hypoplasia is usually unrewarding if bilateral renal involvement is present.

Pollakiuria, dysuria, stranguria, and incontinence may be observed with renal dysplasia/hypoplasia, but these are more commonly associated with conditions such as ectopic ureters.[606-608] Ectopic ureters may be associated with urine scald caused by urinary incontinence. Surgical intervention, while often challenging, is the only option for addressing cases of ectopic ureter, with relocation of the ureteral opening being the primary intervention. Hematuria is uncommonly associated with congenital urogenital disorders but may be present in association with renal arteriovenous malformations.[609] Congenital abnormalities of the bladder have been suspected in some cases of uroperitoneum,[610,611] but evidence of a true congenital origin is lacking in horses or other species.[612] Umbilical hernias may be present at birth but are usually small and will resolve without intervention. Larger hernias, typically over 3 cm in size, may require surgical repair, but there is no rush to perform this procedure as long as the hernia remains easily reducible. Inguinal hernias may also be present at birth but are also typically small and easily reducible. Conservative medical management consisting of frequent, repeated reduction, or bandaging to maintain reduction, is often successful in resolving small hernias. Larger inguinal hernias may allow for substantial herniation of the small intestine and often require surgical repair.

Uroperitoneum

Accumulations of urine within the peritoneal cavity represent one of the most common urogenital conditions in young foals, involving as many as 2.5% of hospitalized neonates.[613] Most cases are observed within the first few days of life and are associated with bladder wall rupture.[614,615] The most common site of bladder wall failure is the dorsal wall, and it is believed that most cases occur during parturition. The proposed etiology is that the fetus has a very full bladder, which ruptures under the intense pressures occurring during transit through the birth canal. Obstruction of urine outflow via the urachus during delivery may contribute to high intravesicular pressures. This theory is supported by anecdotal reports of bladder distention identified on fetal ultrasonographic examination in foals that subsequently developed bladder rupture after birth. There may be some sex predilection for bladder rupture, with colts being overrepresented in cases presenting shortly after birth, but in cases developing later there does not seem to be a difference between the sexes.[612] Not all cases of uroperitoneum are associated with primary bladder rupture, however, because ureteral tears and urachal rupture can also result in uroperitoneum. Although ureteral tears initially result in urine accumulation in the retroperitoneal space, this typically progresses to uroperitoneum after several days. Urachal rupture may be associated with infection and necrosis of the umbilical remnant, and for this reason these foals may present slightly later than foals with bladder rupture.

Diagnosis of uroperitoneum is made on the basis of history, physical examination, clinical pathology, and ultrasound examination. The clinical signs associated with uroperitoneum may vary based on the site of leakage, but affected foals most often present with depression and weakness and signs of hypovolemia. It can be difficult to differentiate these foals from those suffering from neonatal sepsis, and indeed many affected foals may be suffering from sepsis in addition to uroperitoneum.[613] The rate at which clinical signs develop is often

associated with the size of the defect and the associated rate of urine leakage into the peritoneal space, with small defects in the bladder or retroperitoneal ureteral leakage often not becoming clinically obvious for several days to a week post foaling. Some foals with uroperitoneum will present with ventral edema, although this is most dramatic in foals with umbilical trauma and associated subcutaneous urine leakage. Foals with retroperitoneal urine accumulation may present with stranguria before the development of uroperitoneum, and foals with urethral defects most often demonstrate substantial subcutaneous edema in the perineal region. Some foals with uroperitoneum will present with abdominal distention or abdominal discomfort but will otherwise be in good physical condition. Palpation or ballottement of the abdomen may aid in detecting fluid accumulation within the peritoneal cavity.

The classic clinicopathologic presentation of the foal with uroperitoneum is that of azotemia, with increases in serum creatinine and (less reliably) BUN. Azotemia is typically accompanied by hyperkalemia, hyponatremia, hypochloremia, and metabolic acidosis. Hyperkalemia is caused by the reabsorption of substantial amounts of potassium, whereas hyponatremia and hypochloremia are caused by reabsorption of water from the urine within the abdomen. These changes are likely more pronounced because of the milk-based diet of foals; milk contains relatively high concentrations of potassium (25 mEq/L) and is relatively low in sodium (12 mEq/L).[616] Hyperkalemia is potentially life-threatening because of the possibility of fatal bradyarrhythmias. An electrocardiogram (ECG) should be performed in all foals with uroperitoneum or hyperkalemia of any cause. Typical ECG findings in hyperkalemia will progress from peaked T waves and a shortened QT interval to lengthening PR interval and loss of P waves, followed by widening of the QRS complex, and potentially leading to cardiac arrest and death.[617] Other potential cardiac sequelae associated with hyperkalemia include third-degree atrioventricular block, ventricular fibrillation, and ventricular premature contractions. This classic pattern of electrolyte abnormalities is not typically observed, however, in hospitalized foals that develop uroperitoneum while being treated with IV fluid therapy with balanced electrolyte solutions.[612,613]

Ultrasonographic examination is the most useful ancillary diagnostic test in the evaluation of uroperitoneum. Not only can one confirm the presence of free fluid within the peritoneal space, but one can also assess the degree of fluid accumulation and investigate possible sites of urine leakage. The free fluid within the abdomen is typically hypoechoic to mildly hyperechoic, and numerous loops of small intestine or other intraabdominal structures may be suspended in the free fluid contained within the abdomen. The dorsal bladder wall is the most common site of bladder rupture, and this area should be thoroughly investigated because in some cases the free margins of the defect can be readily observed. It is important to remember that there may be more than one site of urine leakage, however, either from the bladder itself or potentially involving the urachus, ureters, or urethra. Although ultrasound examination is typically less useful when evaluating ureteral or urethral defects, it is important to perform a complete examination of the urinary tract to detect any defects in the kidneys or ureters that might be missed if only the bladder and urachus are examined. Contrast radiography may be required to identify sites of leakage other than the bladder or urachus.

Definitive confirmation of uroperitoneum requires abdominocentesis. Creatinine diffuses poorly across the semipermeable peritoneal membrane, so the creatinine concentration in the peritoneal fluid will be at least twofold higher than the creatinine concentration in the serum. Abdominocentesis is both a diagnostically important technique and a therapeutic technique, because it allows for the drainage of accumulated urine from the peritoneal cavity. Removal of this fluid will aid in controlling hyperkalemia, and it will minimize further potassium absorption from the peritoneal cavity. Drainage will also decrease the pressure being exerted on the diaphragm and thoracic cavity, aiding in the resolution of any tachypnea, dyspnea, or respiratory distress. Abdominocentesis should be performed with a teat cannula or stainless bitch catheter or with an indwelling type of catheter such as a Foley or mushroom-tip peritoneal catheter. This approach minimizes the risk of trauma to the abdominal viscera and allows for safe manipulation and maintenance of the catheter while the abdomen is being drained. Care should be taken to administer appropriate fluid therapy before and during the drainage of the abdomen to avoid hypovolemia resulting from the removal of this third-space fluid. Drainage should be continued until surgical repair is performed, because premature discontinuation will simply allow for reaccumulation of urine within the abdomen.

Although medical management has been described, the treatment of uroperitoneum is primarily surgical because the site of urine leakage must be identified and addressed by surgical repair or removal. Correction of hypovolemia and electrolyte disturbances before surgery is important in minimizing the risk of anesthetic complications. The most critical of these disturbances is hyperkalemia because of the risk of cardiac disturbances. Hyperkalemia is addressed by the administration of IV fluids that do not contain potassium, and isotonic (0.9%) or hypotonic (0.45%) saline solutions are most commonly used. Dextrose is typically added to the fluids at a rate of 5%, and this will aid in lowering serum potassium concentrations by encouraging movement of potassium from the extracellular to the intracellular compartment, but in severe cases the administration of exogenous insulin (0.1 U/kg) may be necessary to substantially reduce serum potassium concentrations. Sodium bicarbonate therapy may aid in lowering serum potassium concentrations and may be helpful in addressing the concurrent hyponatremic metabolic acidosis.[617] Administration of calcium gluconate may also be helpful in decreasing the negative effects of hyperkalemia.[617] Recent reports have suggested that the frequency of anesthetic complications during surgical correction of uroperitoneum is less common than previously reported, perhaps because of less severe electrolyte disturbances, better preoperative stabilization, or the use of safer inhalant anesthetics (primarily isoflurane).[612]

The prognosis for survival in foals with uncomplicated uroperitoneum secondary to bladder rupture is good, whereas the prognosis for foals suffering from ureteral or urethral disorders is less favorable. Delays in the identification of affected foals and the presence of concurrent disease, especially sepsis, will result in worsening of the prognosis for survival.[612,613]

Umbilical Disorders

The umbilicus represents the primary channel for exchange of nutrients and oxygen between the dam and the fetus and the primary outlet for fetal urine. The umbilical cord consists of two arteries carrying poorly oxygenated blood away from the fetal heart and one vein carrying relatively better oxygenated blood from the placenta toward the fetal heart and the

urachus, which connects the fetal urinary bladder to the allantoic cavity.[618] Following second-stage parturition the umbilicus will narrow and separate at a point 2 to 3 cm from the body wall, typically within about 10 minutes if the mare and foal are undisturbed.[619] A small amount of neonatal blood loss may occur normally following separation of the cord, but it should be of minimal volume and should cease within a few minutes. If the mare stands too soon, then premature separation of the umbilical cord or umbilical cord damage may occur. Subcutaneous rupture of the urachus can result in substantial accumulation of urine in the tissues of the abdominal wall, which will likely require surgical resection of the umbilical remnants. Following separation from the placenta the umbilical structures immediately become vestigial, and in the normal foal the umbilical remnants will atrophy over the first few months of life.

One of the most common umbilical disorders is patent urachus, in which the urachal remnant is open and urine drains to the external environment. Although this may occur immediately following cord separation, it is more typically seen several days after birth and is most often associated with umbilical infections. Systemic illness and the associated stress of handling involved in the management of sick foals may also predispose the patient to the resumption of patency. Patent urachus may present simply as moistness of the external umbilical remnant or may be associated with a streaming flow of urine. Urine scald of the abdominal wall and the medial aspect of the hindlimbs may occur secondarily. It is important that an ultrasound examination be performed in these cases to determine whether there are internal abnormalities, such as umbilical remnant infections, associated with a patent urachus. Conservative management consisting of topical cleansing of the external umbilicus and close monitoring for the development of infection is often sufficient, although complete resolution may take days to weeks in some cases. If any infectious component is suspected then appropriate systemic antimicrobial therapy is indicated. Chemical cautery using silver nitrate sticks is often used and may accelerate closure of the urachal remnant, especially in early, mild cases. Excessive use of silver nitrate may result in local tissue necrosis, however, and may precipitate the development of infection. If conservative management fails then surgical excision of the umbilical remnants is indicated, but this is rarely a problem that needs to be addressed urgently, especially in a foal suffering from systemic illness or other disease processes.

Umbilical remnant infections are also common and can take several forms. Affected foals may appear clinically normal or they may exhibit signs of systemic inflammation (fever, leukocytosis, hyperfibrinogenemia, and elevated SAA). Infection of the external umbilical structures will result in local abscess formation, which presents as swelling, inflammation, and often discharge from the area of the external umbilicus, but it can become more locally invasive, involving the body wall. External umbilical abscesses can often be treated with the establishment of drainage combined with appropriate systemic antimicrobial therapy. Internal umbilical remnant infections can occur in all three of the distinct umbilical structures: the urachus (infection of the urachus is called *urachitis*), the umbilical arteries (infection of the umbilical arteries is called *omphaloarteritis*), and the umbilical vein (infection of the umbilical vein is called *omphalophlebitis*). It has traditionally been thought that umbilical remnant infections occurred secondary to external contamination of the umbilicus, with ascending migration of bacteria. This is likely true in some cases, and for this reason it is important to practice appropriate routine cleaning and disinfection of the external remnant. Excessive cleansing or treatment with caustic agents may actually increase the risk of ascending infection, so moderation is key. It is very possible that bacteremia occurs secondary to umbilical infections, resulting in seeding of other sites. Infection of remote structures, especially synovial structures and growth plates, has been frequently associated with the presence of umbilical remnant infections. Although the umbilical structures may represent the primary site of infection, it is also possible that some umbilical remnant infections actually develop secondary to systemic illness and bacteremia, rather than secondary to external contamination.

Ultrasonographic examination of the umbilical remnants is well described and can be performed readily with either a linear or curved probe using a frequency of 5 to 7.5 MHz, although higher quality imaging can be obtained with a linear 10- to 12-MHz probe.[620] All four umbilical structures (urachus, vein, and paired arteries) can be readily imaged in the external remnant as it courses out of the body wall. Internally the paired umbilical arteries are found ventral and lateral to the urachus and bladder, and they course caudally and deep toward their origins from the iliac arteries. They are thick-walled structures and should have a diameter of less than 13 mm.[621] Although the arteries may still be observed to pulsate in very young foals, they should contract down and be immobile by 24 hours of age. The lumen may be filled with clotted blood in some cases. The urachus extends from the apex of the bladder outward to the umbilical stump, and the lumen is typically collapsed and difficult to appreciate. A transverse view of the urachus and umbilical arteries taken at the apex of the bladder should normally measure less than 25 mm in total diameter.[621] The umbilical vein courses cranially from the site of the external umbilicus to the liver and is located along the midline very close to the abdominal wall. The vein is a thin-walled structure and may contain anechoic fluid within its lumen. The vein should measure less than 5 to 10 mm in diameter.[621] Infection involving these structures will typically manifest as filling of the lumen with material of variable echogenicity, thickening of the wall, and an increase in the overall size of the structure.[622,623] Thorough assessment is important, because multiple structures may be involved in the infectious process.

Treatment of umbilical remnant infections can be medical or surgical in nature. Medical management is generally preferred, and treatment with appropriate broad-spectrum antimicrobials is often successful in resolving the infection. Prolonged treatment of several weeks' duration and ongoing ultrasonographic monitoring is required to ensure complete resolution. In cases suffering from a combination of umbilical remnant infection and infections in other sites the clinician may feel a sense of urgency to surgically remove the umbilical remnants, but the stress of general anesthesia and abdominal surgery may be counterproductive. Stabilization of the patient and the institution of antimicrobial therapy before surgery may be beneficial in these cases. Broad-spectrum antimicrobial therapy is indicated, preferably using oral medications because of the need for prolonged therapy in most cases. The presence of gas within the internal structures on ultrasonographic examination or a fetid order represents an indication for the addition of metronidazole to the treatment regimen. In cases refractory to medical therapy, surgical excision of the affected

internal umbilical remnants is indicated. Thorough ultrasonographic examination preoperatively is helpful in developing the surgical plan and may reveal areas of infection deep in the umbilical arteries or vein that may not be able to be surgically removed. Continued medical management may be indicated in such a situation, but marsupialization of the umbilical vein or arteries can be performed to allow for external drainage and possible lavage of the infected structures.[624-626]

Acute Kidney Injury and Acute Renal Failure

Acute kidney injury can occur in foals secondary to systemic disease, toxin exposure, or postrenal obstruction. The most common of these etiologies is systemic disease, which has previously been termed *vasomotor nephropathy*, although the actual pathophysiology involved in these cases is not well understood.[627] It appears likely that there is a complex interaction among systemic cardiovascular responses, local vasomotor tone, systemic and local inflammatory mediators, microvascular dysfunction, and local renal tissue responses that result in decreased renal function. This decrease in renal function may represent a self-protective response by the kidneys in which decreased energy and oxygen demands within the kidney may help to improve tissue survival and recovery.[628] The most common toxic causes of renal injury in foals are iatrogenic in nature—namely, aminoglycoside antimicrobials and oxytetracycline (administered as a treatment for tendon contracture).[629] Nonsteroidal-associated renal injury is relatively uncommon in foals and is likely because these drugs are not commonly used in foals at this time, although this may change with increasing use of COX-2–specific NSAIDs in foals. Other causes of toxin-induced renal injury are hemoglobin released because of NI and myoglobin released because of myopathies, most commonly white muscle disease. Postrenal obstruction is very rare in foals and is primarily associated with congenital abnormalities.

Diagnosis of acute kidney injury is complicated by the poor sensitivity of the commonly used biomarkers of renal function—namely, serum creatinine and BUN. Because of the substantial renal reserve, it is likely that substantial injury has occurred by the time changes in these markers are detected clinically. BUN is so insensitive that it is of limited use in evaluation of acute kidney injury in foals, but one should be concerned when substantial simultaneous increases in BUN and serum creatinine are observed. Serum creatinine, despite its poor sensitivity, remains the best biomarker for renal function in foals. Although there is tremendous interest in identifying more sensitive biomarkers of renal function, none has yet been characterized in foals. Interpretation of serum creatinine concentrations in neonatal foals is complicated by spurious hypercreatininemia, which can be caused by placental insufficiency or neonatal hypoxia.[166] Although foals presenting with spurious hypercreatininemia had similar elevations of serum creatinine concentration compared with foals presenting with acute renal failure, serum creatinine concentrations in foals with spurious hypercreatininemia typically decrease by 50% within 24 hours of initiation of treatment and normalize by 72 hours.[166] The most effective way of improving the sensitivity of serum creatinine is to become more critical about evaluation of changes in the serum concentration. Even though the values may remain within the published normal range, an elevation of as little as 0.3 mg/dL above baseline may be indicative of decreased renal function. Because serum creatinine may be elevated from prerenal causes at presentation, it is important to evaluate the serum creatinine concentration frequently to assess the response to therapy and detect upward trends as early as possible.

Given the limitations of serum creatinine concentration as a marker of renal function, and more specifically glomerular filtration rate (GFR), it may be helpful in some cases to obtain a more accurate assessment of GFR. The exogenous marker iohexol has been validated in foals, but iohexol assays are not readily available.[630] Endogenous creatinine clearance is actually fairly simple to perform in foals with an indwelling urinary catheter and urine collection system. This involves obtaining a baseline serum sample for creatinine determination and simultaneous emptying of the urine collection bag, followed by a timed urine collection over at least several hours, but ideally over 24 hours. At the end of that time a second serum sample is obtained for serum creatinine measurement. The volume of urine collected is accurately measured, and a representative sample of urine is collected for creatinine determination. The endogenous creatinine clearance is calculated using the formula[631]:

$$\text{endogenous creatinine clearance (mL/min/kg)} = (\text{urine [creatinine]/plasma [creatinine]}) \times (\text{urine output [mL]/time [minutes]})/\text{body weight [kg]}$$

Reported values for endogenous creatinine clearance in normal foals are 1.78 to 2.17 mL/min per kilogram.[630,632,633]

Urinalysis can be helpful in detecting acute kidney injury, but interpretation can be challenging because of temporal changes in the composition of neonatal urine and the influences of fluid therapy and other treatments on urine constituents. Urine specific gravity is normally hyposthenuric (<1.010) in foals that are well hydrated and should increase appropriately (>1.012) in foals that are dehydrated. Isosthenuria (specific gravity of 1.010) may indicate a loss of renal function, but serial determination may be required to confirm the inability of the kidneys to dilute or concentrate the urine with changes in hydration status. Proteinuria is normally present in the first 24 hours of life but should then be absent unless there is renal injury. If the urine is alkaline, then mild spurious proteinuria (1+) may be observed on dipstick examination. Sick foals often will have acidic urine, making this less of an issue of interpretation than in adults. Examination for enzymuria has been advocated as an early indicator of renal injury in foals, primarily regarding urine γ-glutamyl transferase (GGT). This is assessed using the GGT-to-creatinine ratio (urine GGT/urine creatinine × 100), which corrects for dilutional effects. Elevations of the urine GGT:creatinine ratio above 25 are suggestive of proximal tubular injury, but this test does not have good specificity. Unfortunately elevations of the GGT:creatinine ratio are to be expected in foals receiving systemic aminoglycoside therapy, and the magnitude of the increase is not well correlated with the degree of renal injury.[634]

Treatment of acute renal failure is primarily supportive in nature. All efforts should be made to remove exposure to the potential initiating cause of acute kidney injury, if possible. Fluid therapy is typically indicated, both to correct any existing dehydration or hypovolemia and to induce diuresis. Carefully monitoring of urine output is indicated to be sure that the patient is not oliguric or anuric, and placement of a urinary catheter and urine collection system is extremely helpful in this regard. This may be difficult to achieve in the ambulatory

patient but is readily accomplished in recumbent foals. Urine output in a normal 4-day-old foal is approximately 6 mL/kg per hour, but this value should increase in response to fluid therapy.[632] Monitoring of "ins" versus "outs" should be routinely performed, with the goal of at least two thirds of fluid intake being excreted. If this is not achieved, then fluid overload is likely to develop. If urine output is inadequate after restoration of normovolemia and correction of systemic hypotension, then diuretic therapy is indicated. Furosemide appears safe and is well tolerated. In addition to its loop diuretic effects, furosemide may actually lessen renal metabolic demands by suppression of tubuloglomerular feedback. Recommended dosing of furosemide ranges from 0.5 to 1.0 mg/kg IV q 8–12 h to 1 to 2 mg/kg every 30 to 120 minutes over 6 hours.[185,635] CRIs have also been used in foals based on dosing regimens developed for adult horses, starting with a loading dose of 0.12 mg/kg IV, followed by 0.12 mg/kg per hour CRI.[636] If furosemide is ineffective, then osmotic diuretics can be used. DMSO is commonly administered to foals suspected of suffering from NE, and in addition to its free radical scavenging effects it does have some osmotic diuretic effects. Mannitol can be used as a more potent osmotic diuretic, at a dosage of 0.5 to 1.0 g/kg IV as a 20% solution over 20 minutes.[185] If medical therapy is not effective, then renal replacement therapy (dialysis) can be considered. Hemodialysis is the gold standard therapy and has been performed in foals, but it is rarely available for equine patients because of the expense and lack of access to the appropriate equipment.[629] Although typically less effective than hemodialysis, peritoneal dialysis and thoracic dialysis have been performed in foals and are much more feasible in most clinical settings.[635]

ENDOCRINE DISORDERS

The critically ill foal undergoes severe physiologic stress, and the body responds to this stress with a complex, integrated series of neuroendocrine and humoral adaptations that are directed toward support of critical hemodynamic, immune, and metabolic functions. The HPA axis, sympathetic-adrenomedullary axis, hypothalamic-pituitary-thyroid (HPT) axis, and the somatotropic axis are all of critical importance in this response.

Hypothalamic-Pituitary-Adrenal Axis Function and Dysfunction

Activation of the HPA axis leads to increased secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus of the hypothalamus. CRH is the primary stimulus for the production and secretion of ACTH by the anterior pituitary, whereas AVP acts synergistically with CRH to increase ACTH secretion. ACTH is secreted into the systemic circulation and interacts with the cells of the zona fasciculata of the adrenal glands, which subsequently produce cortisol. Cortisol is not stored in the adrenal glands; it is released into the systemic circulation immediately after it is produced. Only the unbound, or "free," cortisol is biologically active, and in the normal adult state the vast majority of the cortisol in circulation is bound to cortisol binding globulin (CBG), with much smaller amounts bound to albumin.[637] Foals have been shown to have a much greater free cortisol fraction (58 ± 8 at birth to 33 ± 6 at 7 days of age) than adult horses (7 ± 3) or human infants (32% at birth to 19% by 3 months of age).[638] Increases in the free cortisol fraction can be associated with localized or systemic inflammation, because bound cortisol can be released from CBG by the neutrophil elastase.[639] The concentration of active cortisol is also regulated at the tissue level by the action of two isoforms of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD). 11β-HSD1 primarily generates active cortisol from inactive cortisone, whereas 11β-HSD2 primarily converts active cortisol to inactive cortisone.[640] Unbound cortisol reaches the tissues by diffusion and enters the cell, in which it binds to the intracellular glucocorticoid receptor (GR). The cortisol–GR complex then translocates to the nucleus in which it is able to exert both genomic (regulation of gene transcription) and nongenomic (protein–protein) effects.[309] In critical illness cortisol is important in supporting cardiovascular function, regulating immune responses, and increasing the availability of glucose as an energy source.

A variety of approaches has been used to assess the function of the HPA axis in both health and disease. These include the determination of neutrophil:lymphocyte ratios, basal serum cortisol concentrations, basal serum ACTH concentrations, ACTH/cortisol ratios, and ACTH stimulation tests that measure the ability of the adrenal glands to produce cortisol (delta cortisol). There are a number of challenges associated with HPA axis assessment, however.[641] The first is that the activation and response of the HPA axis are highly dynamic, with rapid changes in a short period of time and substantial variation even on an hour-to-hour basis. The second challenge is that measurement of total serum cortisol concentrations does not reflect the biologically active free portion, and determination of the active, free cortisol fraction is technically challenging, time-consuming, and not readily available in the clinical setting. The third is that the concentration of cortisol in the circulation provides no information related to the concentration of cortisol at the tissue or intracellular levels, in which it is active. The fourth challenge is that ACTH stimulation testing, either high or low dose, may not represent an accurate assessment of HPA axis function in critical illness. Finally, there may be substantial variation among cortisol assays, rendering it extremely difficult to compare the results of studies using different assays[114] and calling into question the use of specific values of serum cortisol as indicators of HPA axis function or dysfunction.

The maturation of HPA axis function in the equine fetus occurs very late in gestation, in the last few days before birth, and continues for the first several weeks of life.[64,92,93,642] As a result, foals delivered prematurely often suffer from inadequate HPA axis function, manifested by inappropriately low serum cortisol concentrations despite increased serum ACTH concentrations. These findings are indicative of a decreased response to ACTH at the level of the adrenal gland, and this is supported by the fact that these premature foals also show impaired responses to ACTH stimulation testing.[64,91,92] The neutrophil:lymphocyte ratio was noted by Rossdale et al. to be an easily determined surrogate marker for basal cortisol concentration in foals, with a ratio of <1.0 suggestive of impaired HPA axis function in premature foals, whereas a ratio of >2.0 was associated with adequate HPA function in term foals.[92] Normal term foals also show some evidence of incomplete HPA axis development, however, because they exhibit impaired responses to endogenous ACTH and both low- and high-dose ACTH stimulation tests, compared with adult horses.[64,642] Following birth the serum cortisol and

ACTH concentrations peak in the first hour of life and then gradually decline over 6 to 12 hours to levels lower than normally seen in adult horses.[638,643]

The correlation between HPA axis dysfunction and equine prematurity led to an early interest in this area of equine medicine, but little work was done in this area until the past decade. This renewal of interest was primarily the result of extensive work done in humans regarding the role of the HPA axis in critical illness.[644] The concept of relative adrenocortical insufficiency (RAI) was developed and defined as an inadequate cortisol response for the degree of illness.[645] RAI is considered to be a transient, reversible condition and has been associated with exaggerated proinflammatory responses in conditions such as sepsis, ARDS, and severe trauma. Potential mechanisms of RAI include suppression of the HPA axis at the level of the hypothalamus, the pituitary, or the adrenal gland.[646] RAI has been associated in a number of studies with an increase in the risk of death in critically ill human patients.[647] Subsequent studies using corticosteroid supplementation demonstrated a trend toward decreased mortality and improved vasopressor responsiveness, which further supported the concept of RAI in critical illness.[648-650] The diagnosis of RAI remained challenging, however, because of the wide range of diagnostic criteria used in different studies. The most widely accepted criteria was a random total serum cortisol of <10 mg/dL or a delta cortisol of <9 mg/dL following ACTH stimulation.[651]

Several studies have been performed in healthy foals to characterize normal HPA axis function in this population.[95,642,652] Substantial age-related changes in basal cortisol concentrations were found, and normal age-based ranges were reported. Unfortunately the rapid changes over time and the high variability of a single cortisol measurement mean that the application of basal cortisol concentration as a clinical marker of RAI cannot be recommended at this time.[315] The response to both low- and high-dose ACTH stimulation testing has also been examined, and although the dosages of ACTH varied among some studies there was a consistent pattern of age-related differences in the response to ACTH, with the most profound responses observed immediately after birth.[95,642,653] Age-related reference ranges for both low-dose and paired low- and high-dose ACTH stimulation testing have been reported.[95,642]

Several studies have been performed in clinically ill foals to determine whether RAI occurs in the septic foal. The first report of transient adrenal insufficiency in a septic foal was published in 1998, and the foal in that report had a low basal serum cortisol concentration and an inadequate response to high-dose ACTH stimulation testing.[654] Gold et al. reported that septic foals had higher mean cortisol and ACTH concentrations than normal foals, and the septic foals also had higher ACTH/cortisol ratios than normal foals.[655] Castagnetti et al. reported that nonsurviving septic foals had higher ACTH and ACTH/cortisol ratios at admission than healthy foals or surviving septic foals.[656] Interestingly, Wong et al. reported no difference in baseline cortisol or ACTH concentrations or ACTH/cortisol ratios between normal and clinically ill foals.[96] A small number of foals in that study did exhibit low baseline cortisol and ACTH concentrations or inadequate responses to ACTH stimulation suggestive of RAI, however. Hurcombe et al. reported that ACTH, cortisol, and AVP concentrations were increased in septic foals, compared with sick, nonseptic foals and normal foals.[121] They also found that ACTH, cortisol, and AVP concentrations were higher in sick, nonseptic foals than in healthy foals. Some septic foals in that study exhibited low or normal serum cortisol concentrations despite an increased ACTH concentration, which was considered to be suggestive of RAI.[657] Hart et al. examined a population of hospitalized foals and an age-matched population of healthy foals.[97] They found that 46% of hospitalized foals had an inappropriately low baseline cortisol concentration, and 52% had an inadequate response to high-dose ACTH stimulation. A significant correlation was observed between an inadequate response to high-dose ACTH stimulation and both shock and MODS in hospitalized foals as well as a correlation with decreased survival in a subset of septic foals. Armengou et al. reported that nonsurviving septic foals have higher cortisol concentrations and ACTH/cortisol ratios than surviving foals.[114] Although there are no reports examining the role of peripheral tissue corticosteroid resistance in the development of CIRCI in foals, a recent study performed in adult horses with SIRS found that decreased GR binding affinity was associated with nonsurvival and a trend toward an increased ACTH:cortisol ratio.[658] Investigation of the role of peripheral tissue corticosteroid resistance in foals may be warranted.

The variability seen in these equine studies mirrors the challenges observed in human medicine in applying basal cortisol concentrations and the results of high- and low-dose ACTH stimulation testing in the diagnosis of RAI. The use of baseline cortisol concentrations and ACTH stimulation testing is no longer recommended in human critical care patients.[659-661] Similarly, there is currently no consensus regarding the appropriate diagnostic features of this condition in foals.[662] Because of these difficulties and the increasing appreciation that it is not possible to determine the actual activity of cortisol at the tissue level, a new term was developed in human medicine: CIRCI. CIRCI is inadequate cellular corticosteroid activity for the severity of the patient's illness.[309] The current recommendations in human medicine regarding the diagnosis of CIRCI are based on clinical criteria rather than diagnostic testing. Patients with hypotension refractory to fluid replacement and vasopressor therapy should be suspected of suffering from CIRCI, and they should be treated with hydrocortisone. The positive response to hydrocortisone therapy is potentially supportive of a diagnosis of CIRCI.[309,660]

There is very little information available regarding the treatment of foals that may be suffering from CIRCI. The results of multiple studies in human patients have demonstrated that low-dose corticosteroid therapy in septic shock is associated with improved hemodynamics and a decreased requirement for vasopressor therapy, but it is not clear that there is a survival benefit associated with this intervention.[663] Based on the experience in human medicine, it appears reasonable to reserve corticosteroid therapy for those foals in which CIRCI is suspected and that demonstrate fluid-refractory, vasopressor-resistant hypotension.[190,662,664,665] The potential role of corticosteroid replacement therapy may be supported by the recent study regarding factors associated with nonsurvival in foals with NE. This study reported that persistent hypotension requiring vasopressor and/or inotrope therapy was significantly associated with nonsurvival.[666] Recommendations for corticosteroid therapy in foals are by necessity based primarily on the recommendations derived from human medicine, because no specific therapeutic protocols have been investigated in the foal.[667] Current human recommendations are for the use of physiologic dosages of hydrocortisone. This approach most closely mimics normal corticosteroid

dynamics rather than using high supraphysiologic dosages or long-acting drugs like prednisolone or dexamethasone.[315] A 3.5-day course of tapering dosages of hydrocortisone (1.3 mg/kg/day divided q 4 h IV) in healthy 2- to 6-day-old foals was reported to potentially have beneficial antiinflammatory effects without any apparent adverse effect on innate immunity.[313] The daily endogenous production of cortisol and the pharmacokinetics of hydrocortisone have been studied in neonatal foals, and it was determined that an appropriate dosage of hydrocortisone for foals suspected to have CIRCI might be in the range of 1 to 3 mg/kg per day.[314] This is slightly lower than the 2- to 4-mg/kg-per-day dosage (divided into two to four IV boluses per day) currently recommended in human medicine,[309] and it has since been suggested that a reasonable hydrocortisone dosage for foals may be 1 to 4 mg/kg per day divided into four to six IV boluses per day.[315] The appropriate duration of therapy is unknown in foals, but in humans it has been shown that early withdrawal of hydrocortisone therapy is deleterious, and prolonged treatment (7–10 days) with subsequent tapering of dosages is recommended.[646,668]

Hypothalamic-Pituitary-Thyroid Axis Function and Dysfunction

The production of thyroid hormones is regulated by the hypothalamus, which releases thyrotropin-releasing hormone (TRH) into the pituitary portal system. TRH then stimulates the thyrotropes of the anterior pituitary to release thyroid-stimulating hormone (TSH) into the systemic circulation. TSH regulates the synthesis and release of thyroid hormones by the thyroid gland. The thyroid hormones are stored within the thyroid gland as the precursor thyroglobulin, which is cleaved to produce triiodothyronine (T_3) and thyroxine (T_4) under the influence of TSH. T_3 and T_4 then enter the systemic circulation. In the circulation the thyroid hormones are bound to thyroid binding globulin and other proteins, including albumin. T_4 has minimal activity and essentially serves as a prohormone. It is converted to T_3, the primary active form of thyroid hormone, at the tissue level. Only the unbound, free thyroid hormones can be transported into the cell, in which they bind to thyroid hormone receptors in the nucleus and subsequently influence gene transcription. The effects of thyroid hormones are extensive but primarily involve increasing metabolic rate, enhancing cardiovascular function, and thermogenesis.[643]

The assessment of HPT function relies primarily on the measurement of TSH and/or the measurement of basal thyroid hormone concentrations (T_3, T_4, free T_3, free T_4, and reverse T_3). This approach is complicated by the age-related changes in these hormone concentrations that occur in newborn foals, as well as the myriad of influences of other nonthyroidal factors. The measurement of circulating concentrations is also poorly reflective of the activity of these hormones at the tissue level. Stimulation testing is difficult because of the lack of ready availability of TRH or TSH and is not practical in the clinical setting. In newborn foals thyroid hormone concentrations are substantially higher at birth than in adult horses.[669-674] These elevated concentrations gradually decrease to adult levels over several months' time. Only a few studies have measured TSH in neonatal foals, and they found that the concentrations were not elevated; instead, they were similar to the levels seen in adult horses.[674,675] This suggests that the HPT axis is different in foals, perhaps because of increased activity of TSH or increased receptor sensitivity to TSH. This alteration in the HPT axis may account for the rapid growth of foals in the first few months of life and their high neonatal thermogenic capacity.[669,674]

Dysfunction of the HPT axis has been described in neonatal foals and is caused by congenital hypothyroidism, prematurity, and systemic illness. A syndrome of congenital hypothyroidism and dysmaturity syndrome was first described in neonatal foals in Western Canada in 1981.[676,677] This syndrome is associated with thyroid hyperplasia (goiter), increased gestational length, dysmaturity, and numerous musculoskeletal abnormalities, including flexural limb deformities, rupture of the common digital extensor tendon, incomplete ossification of the cuboidal bones, mandibular prognathism, and incomplete closure of the abdominal wall.[676,678-684] This syndrome is also suspected to be associated with abortion in some cases.[685] Thyroid hormone levels in affected foals may be low or normal, but the response to TSH stimulation is consistently decreased.[686,687] Although the etiology is unknown, this syndrome is suspected to be associated with exposure to some causative agent, and epidemiologic investigations have suggested increased dietary nitrate intake or exposure to mustard plants could be involved.[643,678,682] Other potential risk factors could include inadequate iodine or selenium intake.[682,688] The prognosis for survival in affected foals is poor, and those that do survive are likely to suffer a variety of orthopedic abnormalities that render them unsound.[680] Congenital hypothyroidism has also been reported in foals whose dams suffered dietary iodine deficiency or excess, and affected foals typically exhibit prominent goiter.[689-691] In utero exposure of foals to endophyte *(A. coenophialum)*-infected fescue has been associated with clinical signs of hypothyroidism after birth and with decreased circulating concentrations of T_3.[32,692]

Premature foals exhibit hypothyroidism because they have substantially lower thyroid hormone concentrations compared with healthy, full-term foals.[82,671] This may be analogous to the syndrome of transient hypothyroxinemia of prematurity that has been described in premature human infants.[693,694] One report described that both premature and term hospitalized foals had lower T_3 concentrations compared with healthy term foals, whereas the premature foals had lower T_4 concentrations than either group of term foals.[674] The presence of systemic illness is also associated with hypothyroidism in both premature and term foals, and this has been termed the *sick euthyroid syndrome* or the *nonthyroidal illness syndrome* (NTIS). NTIS is well described in humans, dogs, and cats, and there is increasing evidence that it occurs in adult horses and foals.[671-674,695,696] NTIS in sick foals is characterized primarily by low T_3 concentrations.[674] The mechanisms underlying NTIS are thought to be associated with the proinflammatory state associated with illness, but they may also be related to decreased feed intake, because fasting induces NTIS in healthy humans.[697,698] It has been proposed that this phenomenon may represent an appropriate and beneficial response to critical illness, at least in the acute stages, and may not require any therapeutic intervention beyond addressing the primary disease.[697,699]

Dysfunction of the Somatotropic Axis and Energy Regulation

As previously discussed the maturation of the endocrine system of the foal is incomplete at birth, and development

continues for weeks to months after parturition. This is also the case for the systems regulating energy metabolism in foals.[700] These systems are very complex, involving neuroendocrine (cortisol, vasopressin, and thyroid hormone), somatotropic (growth hormone [GH] and insulin-like growth factor-1 [IGF-1]), sympathoadrenal (epinephrine and norepinephrine), and pancreatic (insulin and glucagon) responses, as well as signals derived from fat stores (leptin and adiponectin) and the gastrointestinal tract (ghrelin).[701] The somatotropic axis is stimulated by hypothalamic release of growth hormone-releasing hormone and inhibited by the release of somatostatin.[702] The somatotropic cells of the anterior pituitary respond to these signals by increasing or decreasing the release of GH. The effects of GH are primarily mediated by IGF-1, which is produced by the liver and has similar effects on insulin when regulating blood glucose concentrations by decreasing hepatic gluconeogenesis and stimulating the uptake, utilization, and storage of glucose.[703] The secretion of GH is stimulated by ghrelin and under negative feedback control of IGF-1 and leptin.

The sympathoadrenal response is stimulated by physiologic stress and hypoglycemia, leading to the release of epinephrine from the adrenal gland.[704] The metabolic effect of epinephrine is to increase energy substrate availability by inhibiting pancreatic insulin secretion and increasing glucagon secretion, interfering with the effects of insulin on the tissues, stimulating hepatic glycogenolysis, and increasing lipolysis. The pancreatic hormones insulin and glucagon are critical mediators of blood glucose concentrations, with insulin being produced by β cells in response to hyperglycemia and glucagon produced by α cells in response to hypoglycemia. Insulin has a multitude of effects, primarily focused on lowering blood glucose concentrations, and these include increasing glucose uptake in insulin-dependent tissues such as muscle and adipose tissue, increasing glycogen synthesis, increasing fat synthesis, and decreasing gluconeogenesis and lipolysis. Glucagon acts in opposition to insulin, primarily functioning to increase blood glucose concentrations by increasing glycogenolysis and gluconeogenesis, as well as by increasing lipolysis. The adipokine leptin is involved in the control of appetite, with increases seen following ingestion of a meal and with increasing total body fat, whereas adiponectin is negatively correlated with total body fat and has some activities similar to glucagon. Ghrelin mainly acts to increase feed intake and to stimulate GH secretion.

Hypoglycemia is a common finding in critically ill equine neonates, perhaps because of limited endogenous energy stores and decreased enteral intake.[131,705,706] Care should be taken in interpreting blood glucose concentrations in neonatal foals, however, because they typically have relatively low blood glucose concentrations (50–60% of maternal blood glucose) in the immediate postpartum period, especially before their first nursing.[707] Hypoglycemia has been repeatedly associated with an increased risk of nonsurvival in critically ill foals, although different diagnostic criteria have been used to define hypoglycemia.[118,131,708,709] In the study reported by Hollis et al. there was an association between the severity of hypoglycemia and the risk of nonsurvival, with each increase of 18 mg/dL from a cutoff of 50 mg/dL being associated with an increase of the odds of survival to discharge of 3.4 times (95% CI 2.1–5.4).[131] In one study the percentage of survivors was lower among foals with blood glucose values ≤120 mg/dL (31%) compared with foals with blood glucose concentrations >120 mg/dL (55.6%).[708] A second study, however, found no clinically relevant pattern of alteration in blood glucose concentration when comparing septic and sick, nonseptic neonatal foals to healthy controls.[114] Septic foals had slightly lower median blood glucose concentrations than controls, but this remained within the normal reference range. The treatment of hypoglycemia in sick foals is of critical importance when it is documented and should be addressed by the immediate provision of nutritional support, either enterally and/or parenterally, as is appropriate to the individual case (see the later section Nutritional Support for the Foal).

Hyperglycemia is common in critically ill foals as well, with one study reporting that 36.5% of foals demonstrated hyperglycemia at admission, which was similar to the rate of hypoglycemia (34.4%).[131] That study reported that extreme hyperglycemia (>180 mg/dL) was associated with an increased risk of nonsurvival, which is similar to the situation reported in human neonates and adult horses with acute abdominal disease.[710-713] Interestingly, Barsnick et al. reported different findings, because the septic foals with the highest blood glucose concentrations (up to 329 mg/dL) in their study all survived.[709] Insulin resistance may play a role in the development of hyperglycemia, although there are many other factors that may contribute to the development of hyperglycemia, as discussed previously. Increased insulin concentrations have been associated with mortality in critically ill foals, which might be an indication of insulin resistance in the most severely affected individuals.[709] Insulin resistance does not appear to be a common feature of critical illness in foals, however, because both sick nonseptic and septic foals have exhibited normal insulin sensitivity in the studies that have investigated this phenomenon.[114,709]

There has been tremendous interest and debate in human medicine regarding therapeutic interventions to control hyperglycemia in the critically ill. Tight regulation of blood glucose concentrations (between 80 and 110 mg/dL) was initially advocated in human medicine,[714] but this approach has been shown to be deleterious because of frequent hypoglycemia resulting from insulin administration. A more permissive approach is now recommended, in which blood glucose concentrations are maintained between 145 to 180 mg/dL.[715] This approach attempts to avoid the requirement for aggressive insulin therapy, minimizing hypoglycemic episodes, while also recognizing that stress hyperglycemia is a normal physiologic response that is important for maximizing energy delivery to noninsulin-dependent tissues, such as the brain, intestine, red blood cells, and kidney.[716,717] The primary goal should be the avoidance of severe hypoglycemia that exceeds the renal threshold, which in foals is likely to be above 180 mg/dL.[718] Insulin therapy may be required to accomplish this goal, and various regimens have been described, including intermittent bolus administration or continuous rate IV infusions[30,643,718-720] (see the later section Nutritional Support for the Foal). The institution of insulin therapy is not to be taken lightly, because it requires frequent monitoring of blood glucose concentrations and rapid intervention to avoid hypoglycemia until a stable blood glucose level is achieved, which may take several hours of fine-tuning.[720]

Other indicators of alterations of energy regulation that have been investigated in foals include triglycerides (TG), nonesterified fatty acids (NEFAs), GH, IGF-1, leptin, and glucagon. Although our understanding of the role of these factors in equine neonatal critical illness is still developing, these studies

give valuable insight into the complexities involved and provide some indication of the potential benefits of assaying these variables. Barsnick et al. reported that septic foals had higher glucagon and TG concentrations than healthy foals but found no difference in leptin concentrations between groups.[709] Lower leptin concentrations were associated with mortality in that study, however. In a later study Barsnick et al. found that septic foals had higher ghrelin, GH, and TG concentrations and lower IGF-1 and glucose concentrations compared with healthy foals, and these findings are likely related to inanition and a negative energy balance.[721] Sick, nonseptic foals in that study had higher GH and TG and lower IGF-1 concentrations than were observed in healthy foals. The GH:IGF-1 ratio was higher in septic and sick, nonseptic foals than healthy foals and was highest in nonsurvivors. This finding was indicative of somatotropic axis resistance in clinically ill foals.[721] Panzani et al. reported that IGF-1 concentrations did not differ between healthy and sick foals but increased over time in all groups, whereas NEFA concentrations were higher in sick foals at some time points.[672] Armengou et al. also reported that NEFA concentrations were higher in sick foals than in healthy foals but found no differences in TG concentrations between groups.[114] Although direct intervention in the somatotropic axis does not appear to be indicated, [722] these findings support the importance of correcting the negative energy balance that exists in many critically ill foals.

IMMUNOLOGIC DISORDERS

Failure of Transfer of Passive Immunity

The most common type of immunodeficiency disorder in horses is FTPI, which is the failure of the foal to ingest or absorb adequate immunoglobulin from colostrum.[723,724] This is critically important because foals are essentially agammaglobulinemic at birth from the inability of macromolecules to transfer across the diffuse epitheliochorial equine placenta from the dam to the fetus.[725] FTPI is regarded as the most important risk factor for the development of infection and death for foals within the first month of life, and the incidence of FTPI has been estimated at 3% to 24%.[726] FTPI can occur by several mechanisms, including failure of the foal to ingest adequate volumes of colostrum in the early neonatal period, loss of colostrum before ingestion because of premature lactation, low colostral immunoglobulin concentration, and inadequate absorption of colostrum by the neonatal gastrointestinal tract.[725,727] The timing of colostrum ingestion is critically important, because the ability of the neonatal gastrointestinal tract to absorb macromolecules is maximal at birth but rapidly declines over the first 24 hours of life.

The diagnosis of FTPI cannot be made on clinical grounds and requires determination of the foal's serum IgG concentration within the first 18 to 24 hours of life. The gold standard assay for the quantification of immunoglobulin quantification is the single radial immunodiffusion assay, but this test requires a prolonged incubation period, rendering it of little utility in the clinical setting. A number of types of rapid screening tests are available for estimating foal IgG concentrations, including glutaraldehyde coagulation, zinc sulfate turbidity, turbidimetric immunoassay, latex agglutination, and enzyme immunoassay tests, as well as serum globulin or TP concentrations.[727-735] The ultimate decision regarding which test to use is based on the consideration of each test's accuracy, time requirement, cost, and ease of implementation.[733] Several studies have indicated that serum globulin concentrations can be used to estimate the IgG concentration, but it appears that the cutoff points must be established in each individual clinical laboratory because of the variations in testing methodology.[733,736,737] The enzyme immunoassay test is widely used because of its acceptable diagnostic performance as a screening test (high sensitivity), combined with simple performance and rapid results.[733] The interpretation of the results of IgG testing has been the subject of tremendous interest over the past 40 years and can be a point of confusion because of the different diagnostic criteria and different test methodologies used over time. A recent report supported the traditional cutoff value of >800 mg/dL as indicative of adequate transfer of passive immunity (ATPI) and found that in a large population of hospitalized foals values <800 mg/dL were proportionally associated with mortality.[165] This study also reported a regression equation that could be used to estimate serum IgG concentration from serum TP, albumin, and globulin concentrations with good diagnostic performance (IgG = −241.4 × [albumin] + 462 × [globulin] + 222.8 × [TP] − 370.3).[165] This estimation may be helpful in situations where specific testing for serum IgG concentration is not readily available.

Treatment of FTPI depends to some extent on the clinical status of the foal and the foal's environment. If the foal is known or suspected to have ingested inadequate amounts of colostrum, then early enteral administration of maternal or banked colostrum may be effective; however, such treatment should not be assumed to result in ATPI, and monitoring of serum IgG is still indicated.[738] A clinically normal foal examined in the home farm environment may not require treatment if the IgG value is between 400 and 800 mg/dL (partial FTPI), whereas a value of less than 400 mg/dL (complete FTPI) represents grounds for treatment. If the foal shows any signs of clinical illness or is being examined in a hospital environment, then any IgG value of less than 800 mg/dL is an indication for treatment. Treatment consists of providing IgG supplementation, which most often is accomplished by IV administration of equine plasma, because test results are typically not available until after the time period in which enteral supplementation would likely be effective. The dosage for IV plasma administration is based on the severity of the foal's deficit, but it is not precise because of the tremendous variability in IgG content in commercial equine plasma.[724] In clinical practice the administration of 1 L of plasma can reasonably be expected to provide an approximately 200-mg/dL increase in serum IgG.[739] Unless plasma with a higher IgG concentration is used, it can be difficult to administer enough plasma to completely normalize serum IgG in severely affected foals because of the risk of volume overload as well as the expense of treatment, so the maximum initial dosage of plasma is typically 2 L.[740] It is important to monitor the effect of treatment by repeated measurement of serum IgG to ensure that further treatment is not required, especially in severely affected clinically ill foals that may have ongoing catabolism of IgG associated with their systemic illness.[740]

Neonatal Isoerythrolysis

NI is the most common cause of icterus in newborn foals. It is an immunogenetic disorder in which the foal's red blood cells are destroyed by preformed maternal anti–red blood cell antibodies ingested in the colostrum. These maternal antibodies are produced in response to exposure of the mare to "foreign"

red blood cell antigens by several possible routes, including placental pathology allowing exposure to fetal red blood cells during gestation, exposure to foal red blood cells during parturition, or blood transfusions administered to the mare.[741] Blood group incompatibilities between the mare and the foal are caused by the foal inheriting a blood group antigen from the sire that the mare does not possess. These incompatibilities are likely commonly caused by the multitude of equine blood group antigens, with an estimated incidence of 14%, yet the reported incidence of NI is only 1% in Thoroughbreds and 2% in Standardbreds.[122,742,743] This is because the majority of blood group antigens are not strongly immunogenic under these conditions of exposure. Some blood group factors are strongly immunogenic, and factor Aa in the A system and factor Qa in the Q system have historically been the factors associated with the majority of cases of NI.[742] More recent reports have documented the involvement of other alloantigens, perhaps as a result of an enhanced ability to detect these other factors or because of differences in the breed composition of the local horse population.[119,744] The incidence of NI in mules is much higher than in horses, with estimates as high as 10% because of the presence in these foals of a donkey-specific red blood cell antigen ("donkey factor") that horses lack.[745,746]

Foals affected with NI are typically born clinically normal and begin to show clinical signs within 2 to 5 days of birth, although intervals of as long as 12 days have been reported.[119] The clinical signs of NI result from anemia and tissue hypoxia and include progressive lethargy, weakness, tachypnea, and tachycardia. Affected foals will initially have pale mucous membranes but subsequently develop icterus, although in peracute cases foals may die before exhibiting icterus.[741] As the disease progresses foals will become dyspneic, and seizure-like activity may occur, potentially caused by kernicterus in cases with severe hyperbilirubinemia. Pigmenturia may be present, which is caused by severe hemolysis. Affected foals are anemic, although the magnitude of the anemia may be masked by concurrent hemoconcentration at presentation.[119] Although most foals will present with hematocrits between 10% and 20%, the anemia can be severe, with hematocrits as low as 5% reported.[119,741] Thrombocytopenia may be present as well, and this finding appears to be more common in mule foals.[741,747] Venous blood gas analysis reveals decreased venous oxygen concentration and saturation caused by increased oxygen extraction at the tissue level. There is metabolic acidosis caused by lactic acidosis, which is caused by anaerobic tissue metabolism, resulting in increased lactate production. Hyperbilirubinemia, primarily caused by increased indirect bilirubin concentrations, is a consistent feature, although increased direct bilirubin concentration is seen in some affected animals, potentially caused by hepatic injury secondary to hypoxia or iron toxicity associated with bilirubin accumulation.[119,122] Increased SDH concentrations have also been associated with severe anemia (hematocrit <11%) in foals with NI, further supporting that hepatocellular injury occurs in severely affected foals.[119] Hemoglobinemia and hemoglobinuria can be pronounced, and pigment nephropathy resulting in acute renal failure can occur in severely affected cases.

Diagnosis is often made based on the signalment, history, and clinical signs, but confirmation is important because there are other causes of hemolytic anemia in neonatal foals, including DIC associated with sepsis, bacteria-induced hemolysis, and iatrogenic causes such as incompatible transfusion of blood or plasma.[119] A definitive diagnosis is made by demonstrating the presence of antibodies in the mare's colostrum or serum directed against the foal's red blood cell antigens. This can be done using agglutination or lytic tests, with lytic tests regarded as more reliable.[743] The hemolytic crossmatch of mare serum with foal red blood cells using exogenous complement is considered the test of choice. Identification of the specific red blood cell factors involved can also be accomplished by testing panels of red cells that represent all the known blood groups.[741] Despite their limitations, agglutination tests are commonly used because they are more readily performed and provide more rapid results. A crossmatch of mare serum with foal red blood cells without the addition of exogenous complement has agglutination rather than hemolysis as the endpoint and is less sensitive than the hemolytic crossmatch. The direct antiglobulin (Coombs) test can be used to demonstrate the presence of antibodies on the surface of the foal's red blood cells, but this test can lack sensitivity. The most readily performed test is the jaundiced foal agglutination (JFA) test, which is simple and provides rapid results. The JFA test is performed using red blood cells from the foal and colostrum from the mare, with agglutination as the endpoint. Unfortunately the JFA test can lack both sensitivity and specificity and is most useful in prevention of NI rather than diagnosis of an affected foal.

The treatment for NI will be dictated by the severity of the anemia and the associated clinical signs. Moderately affected foals primarily require supportive care, exercise restriction, and close monitoring. Stress should be avoided in handling the foal. If the foal presents at less than 24 hours of age then it should be withheld from nursing until the risk of further antibody ingestion has passed. This time interval can be difficult to assess accurately, but it should not exceed 24 hours because of waning maternal antibody content in the milk and decreased gastrointestinal absorption in the foal. Serial monitoring of the JFA test can be used, if desired, to assess the decline of maternal alloantibodies in the milk and confirm that the introduction of nursing should be safe.[748] The foal will need to be provided with nutritional support during this time period, which is most readily performed using an indwelling feeding tube. IgG supplementation with colostrum from another mare or with frozen plasma will be necessary to ensure adequate passive transfer. Despite some concerns in the literature, withholding colostrum does not appear to have any deleterious effects on gastrointestinal development in foals.[749] IV fluid therapy is helpful in supporting cardiovascular function and tissue perfusion as well as ensuring diuresis, minimizing the potential nephrotoxic effects of hemoglobin. Fluid therapy should be administered conservatively, however, to avoid hemodilution, particularly in more severely affected foals. Plasma exchange has been successfully used to treat foals affected with severe hyperbilirubinemia secondary to NI.[258]

Further treatment is indicated if the affected foal shows evidence of shock caused by tissue hypoxia, which becomes more likely in foals with profoundly low hematocrits (<10–12%), but it should not be based on the hematocrit reading alone. The decision to treat in these cases may be supported by findings of persistent or progressive tachycardia and tachypnea and demonstration of decreased mixed venous oxygen tension.[750,751] Treatment in these foals is directed at the restoration of the oxygen-carrying capacity of the blood and improving tissue oxygen delivery. Intranasal oxygen insufflation is readily performed but may be of limited benefit because oxygen saturation is typically not adversely affected. The only other way to improve oxygen

delivery is by transfusion of red blood cells that will not be damaged by the maternal alloantibodies. The transfused red blood cells will likely only persist in the foal's circulation for a few days, but the goal of the transfusion is to provide support while the foal produces sufficient red blood cells to support itself. In the ideal situation a known Aa and Qa negative "universal" donor could be used, but these are very difficult to identify and not commonly available. In most cases the mare represents the most logical donor, and once her red blood cells have been washed to remove the alloantibodies present in her serum they can be transfused to the foal. The most effective way to wash the maternal red blood cells is by centrifugation, but this is often not readily available. Serial gravity sedimentations of anticoagulated maternal red blood cells using sterile isotonic saline to remove and discard the supernatant is readily performed and reasonably effective, but it does require a substantial period of time (several hours) during which the foal's clinical status may deteriorate. There are reports of the administration of polymerized bovine hemoglobin (Oxyglobin, Biopure Corporation, Cambridge, MA) as an alternative form of bolstering oxygen transport capacity. This is appealing because the product is shelf-stable and requires no delay in administration.[119,750,752] These reports provide some conflicting evidence regarding the potential safety of this approach because the administration of bovine hemoglobin was associated with poor outcomes in some instances. It is unclear if this is the result of the product administered or a result of case selection, in which the most severely affected foals were likely selected to receive this therapy.[752] When blood transfusions are used the volume of blood to be administered to the foal should be kept to a minimum; administration of greater than 4 L of blood is associated with the development of hepatic failure (OR 19.5).[122] Reinforcing this concern is the finding that the administration of each additional unit of blood was shown to increase the odds of nonsurvival 8.4 times.[122]

The most effective treatment for NI is prevention. Blood typing of the mare can be performed before breeding to fully characterize the mare's blood group, and if the mare lacks factors Aa and/or Qa she would be considered at risk for becoming sensitized in the future.[741] Testing to identify the specific alloantibodies produced by a mare that has produced an NI-affected foal can be used in combination with blood typing of the sire to predict future risk.[753] This is rarely done, however, and it is simpler to perform the JFA test at the time the foal is born and before the foal is allowed to nurse. When performed in this manner the JFA test is reasonably diagnostic, and a negative result supports allowing the foal to nurse.[748,754] In the absence of JFA test results, any foal born to a mare that has had a previous foal affected by NI should be considered at high risk, and the foal should be muzzled at birth and not allowed to nurse for the first 24 hours of life. Although clinically affected foals have likely received adequate passive transfer of immunoglobulins, any foals that are deprived of maternal colostrum as a preventive measure must receive immunoglobulins in the form of pooled colostrum administered enterally or fresh frozen plasma administered intravenously.

Neonatal Alloimmune Thrombocytopenia and Neutropenia

Neonatal alloimmune thrombocytopenia (NAIT) and neonatal alloimmune neutropenia (NAN) appear to be rare in the equine, but they have been reported in horse and mule foals.[747,755-759] A syndrome of ulcerative dermatitis, thrombocytopenia, and neutropenia has also been described in foals.[760] It is possible that the incidence of these conditions is underappreciated, however, because neutropenia and thrombocytopenia are common findings in critically ill patients secondary to a number of other mechanisms.[761] The pathophysiology of NAIT and NAN is very similar to that of NI: affected foals ingest maternal alloantibodies directed against antigens on platelets or neutrophils, resulting in their destruction or removal from circulation. Diagnosis of these conditions is based on the demonstration of persistent thrombocytopenia or neutropenia in the absence of other disease processes that might cause these abnormalities, such as bacterial sepsis. Foals affected by NAIT may appear clinically normal or they may exhibit petechial hemorrhages or prolonged bleeding from venipuncture sites. Foals with NAN are typically clinically normal, but they are predisposed to secondary bacterial infections that may lead them to exhibit clinical signs of local or systemic inflammation. Confirmation of the clinical diagnosis requires the demonstration of antibodies bound to the patient's platelets (NAIT) or neutrophils (NAN). Direct fluorescent antibody tests, ELISA, immunoradiometric tests, and flow cytometry have been used to confirm the diagnosis.[747,755-759,762]

Treatment of NAIT is supportive in most cases, although whole blood or platelet-rich plasma transfusions can be administered to foals exhibiting clinical bleeding diathesis.[763] Supportive care is indicated in foals with NAN, although recombinant human granulocyte colony-stimulating factor can be administered in an effort to increase endogenous neutrophil production.[758,759] Foals affected by NAIT and especially NAN appear to be at increased risk for secondary bacterial infections, so appropriate broad-spectrum antimicrobial therapy is indicated. Both conditions are ultimately self-limiting because the offending alloantibodies are consumed and eliminated from circulation. The use of immunosuppressive therapy has been proposed but does not appear to be indicated in these conditions.

HEPATIC DISORDERS

Hepatic disorders are uncommon in foals, but there are a wide range of possible etiologies. True hepatic failure is rare, and hepatic dysfunction is the most common disorder. Detection and diagnosis of hepatic disease in foals are challenging because the clinical signs are nonspecific and often related to a primary disease process. These nonspecific signs can include anorexia, depression, fever, weight loss, and abdominal pain. Icterus may be present but is not specific for hepatic dysfunction, and it may be secondary to anorexia, intravascular or extravascular hemolysis, sepsis, or severe systemic illness. With more severe hepatic involvement one may observe any or all of the following: CNS signs, bleeding disorders, edema, ascites, diarrhea, or dermatitis. A definitive diagnosis requires clinicopathologic examination consisting of serum enzyme activities and conjugated and unconjugated bilirubin at a minimum but potentially including serum bile acids, serum ammonia, and prothrombin time. Additional biochemical abnormalities that may be supportive of, but not specific for, hepatic disease include hypoglycemia, metabolic acidosis, low BUN, and polycythemia. Ultrasonographic examination also can be very helpful because it allows for the assessment of the hepatic parenchyma and may allow for the detection of structural abnormalities. Hepatic biopsy, although rarely performed

TABLE **20.12 Biochemical Parameters in Foals over the First Month of Life**

Biochemical Parameters	Units	1 Day	7 Days	1 Month
Alkaline phosphatase	IU/L	<2670	<1170	<866
γ-Glutamyl transferase	IU/L	<33	<98	<44
Sorbitol dehydrogenase	IU/L	<21	<18	<6
Aspartate aminotransferase	IU/L	<340	<620	<440
Glutamate dehydrogenase	IU/L	<27.5	<17	—
Total bilirubin	mg/dL	<4.5	<3.3	<1.7
Direct bilirubin	mg/dL	<0.35	<0.7	<0.6
Ammonia	μg/dL	—	<60	—
Bile acids	μmol/L	<82	<30	<17

Adapted from Axon JE, Palmer JE. Clinical pathology of the foal. *Vet Clin North Am Equine Pract*. 2008;24:357-385, vii; Divers TJ, Byars TD: Hepatic disease. In: McKinnon AO, Squires EL, Vaala WE, et al., eds. *Equine Reproduction*. West Sussex, UK: Wiley-Blackwell; 2011:409-415; Barton MH, LeRoy BE. Serum bile acids concentrations in healthy and clinically ill neonatal foals. *J Vet Intern Med*. 2007;21:508-513; Armengou L, Jose-Cunilleras E, Rios J, et al. Metabolic and endocrine profiles in sick neonatal foals are related to survival. *J Vet Intern Med*. 2013;27:567-575.

in foals, may be useful in diagnosis, treatment planning, and prognostication.

The interpretation of the biochemistry profile can be challenging in young foals because the activities of some hepatic enzymes and other parameters are substantially different from those normally seen in adult horses (Table 20.12). Serum alkaline phosphatase (ALP) activity shows the most striking elevations compared with adults, with values as much as 10-fold greater in the first week of life. This is primarily caused by bone metabolism, which rapidly declines over the first month of life and then gradually decreases to the adult range by 6 months of age.[707,764,765] Serum GGT activity transiently increases during the second week of life and then returns to the normal adult range by 1 month of age.[766,767] AST concentrations increase slightly after the first week of life but then remain similar to adult values.[707,764] SDH and glutamate dehydrogenase (GLDH) values do not differ significantly with age.[707,768] Serum bile acid concentrations are also increased at birth but gradually decrease to normal adult ranges over the first 6 weeks of life.[769] Neonatal hyperbilirubinemia is well documented in foals and is primarily associated with increased total bilirubin concentration.[707] This elevation gradually resolves, and values are typically within normal adult ranges after the first week of life. Direct bilirubin concentrations are low at birth but increase to normal adult ranges after the first few days of life.[769] The serum enzymes that are liver specific—namely, SDH, GLDH, and GGT—are of greatest utility in evaluating the foal with hepatic dysfunction compared with the nonspecific enzymes ALP and AST. GGT is liver and biliary tract specific, whereas SDH and GLDH are of hepatocellular origin.

Acquired Disorders

Tyzzer's Disease

Tyzzer's disease is an enterohepatic syndrome affecting foals from 7 to 42 days of age that is associated with the rapid onset of septic shock and death, usually within 2 to 48 hours from the onset of clinical signs.[770,771] The primary manifestation of this disease is a peracute bacterial hepatitis. This disease is well described in foals, with numerous cases documented in the United States and other countries over the past 40 years.[772-778] The causative agent of Tyzzer's disease is *C. piliforme,* a soil- and manure-borne gram-negative, pleomorphic, motile, spore-forming, rod-shaped obligate intracellular bacterium.[779] The epidemiology is poorly understood, but as the disease does not affect adult horses it is likely that adult carriers contaminate the environment with subsequent fecal-oral transmission.[770] Risk factors for this disease include seasonality, with a 7.2 times greater risk between March 13 and April 13.[770] Foals born to young mares (<6 years of age) and nonresident mares are also at increased risk, possibly because of lack of previous exposure leading to poor colostral antibody production resulting in inadequate passive immunity in their foals.[770]

Tyzzer's disease often affects otherwise healthy foals, and affected individuals, especially younger foals, may simply be found dead. In foals presenting alive the clinical signs are often nonspecific, including lethargy, anorexia, dehydration, icterus, fever, colic, diarrhea, and seizures followed by the rapid onset of recumbency, weakness, coma, and death.[771,776] Antemortem diagnosis is difficult and is typically based on the signalment, history, clinical signs, and clinicopathologic findings. PCR testing may be useful for early and specific diagnosis,[771] but the results may not be available within a useful time frame because of the rapid progression of disease. Clinicopathologic examination typically demonstrates severe leukopenia with a left shift; thrombocytopenia; marked hypoglycemia; severe metabolic acidosis; elevated serum fibrinogen; and elevated total, indirect, and direct bilirubin concentrations.[771,779] The hepatocellular enzymes AST and SDH are markedly increased, but GGT and ALP are typically within normal limits.[768,771] Ultrasonographic examination of the liver reveals marked hepatomegaly with increased echogenicity of the hepatic parenchyma, or possibly an enhanced vascular pattern.[623,771] Treatment is extremely difficult because of the severe, acute nature of the disease, and the prognosis should be regarded as grave. There are, however, reports of successful treatment of three suspected and one confirmed case of the disease.[770,771,780] Treatment consists of antimicrobial therapy with penicillin or ampicillin in combination with an aminoglycoside, as well as fluid therapy, correction of electrolyte and acid-base disorders, parenteral nutritional support, and appropriate supportive care.[771,780]

Bacterial Hepatitis

Bacteria other than *C. piliforme* can cause hepatic disease, and are commonly associated with severe systemic inflammation and bacteremia, but these cases do not typically present with primary hepatic disease. These foals typically present as septic, critically ill foals, and the finding of hepatic involvement is secondary.[781] *Actinobacillus* spp. and *S. equi* subsp. *zooepidemicus* have been reported to be involved in acute bacterial hepatitis of young foals.[768,781] The spirochete *Bartonella henselae* was recently associated with severe suppurative cholangiohepatitis in a foal, which was successfully treated with trimethoprim-sulfamethoxazole and rifampin along with *S*-adenosylmethionine and pentoxifylline for their potential antifibrotic and antioxidant effects.[782] Leptospirosis has been associated with jaundice and death in a 10-day-old foal,[783] and *Leptospira interrogans* serovar Pomona appears to be a rare cause of hepatic disease in neonatal foals.[784] Ascending cholangiohepatitis and bile duct obstruction have been associated

with duodenal stenosis resulting from severe gastroduodenal ulcer disease (GDUD).[785-787] Effective surgical bypass procedures have been described for foals suffering from delayed gastric emptying associated with GDUD, but the prognosis for foals with hepatic involvement appears to be guarded.[591,787]

Equine Herpesvirus 1

EHV-1 infection of the near-term fetus can result in the delivery of a nonviable foal suffering from hepatic, respiratory, and/or gastrointestinal disease.[358,788] Most affected foals will be born premature and will be severely icteric on initial examination. Clinicopathologic examination typically demonstrates severe leukopenia caused by neutropenia and lymphopenia, which may be more severe than seen in septic foals.[183] Hyperbilirubinemia may be present, although the magnitude of hyperbilirubinemia may be less than one might expect based on the profound icterus observed clinically.[183,184] No increase is usually observed in the serum activity of the hepatic enzymes, which is surprising given the severity of the hepatic necrosis detected on postmortem examination.[183] Although hepatic involvement is prominent in most affected foals, death is usually caused by overwhelming respiratory disease within 1 to 5 days of birth.[184] Treatment with acyclovir was associated with an improvement in survival in one report, although valacyclovir may represent a superior choice given the superior bioavailability of that drug in adult horses after oral administration.[184,789]

Hepatic Lipidosis

Hepatic lipidosis can occur secondary to hyperlipemia in neonatal foals, but this appears to be most common in Miniature breeds.[790-792] Hypertriglyceridemia (>500 mg/dL) typically develops as a consequence of a negative energy balance resulting from inanition or anorexia caused by some other primary disease process and, if unresolved may progress to hyperlipemia, with characteristic grossly lipemic serum.[709,793] Fat accumulation in the liver can proceed rapidly, resulting in hepatic lipidosis. Hepatic enzyme activities may be increased, but this is not consistently observed.[790,791] Clinical signs of hepatic lipidosis may be referable to the primary disease process but can include severe depression, seizures, blindness, and ventral edema.[768] Treatment should be directed toward resolving any primary disease process and correction of the negative energy balance with parenteral nutrition. Insulin therapy is often critical in facilitating the resolution of the hyperlipemia and allowing for the administration of adequate amounts of parenteral nutrition.

Neonatal Isoerythrolysis

NI is the most common cause of hyperbilirubinemia in foals, and hepatic disease may develop because of hepatocellular injury resulting from excessive bilirubin accumulation, anemic hypoxia, and/or iron toxicosis.[119,122] Total and direct bilirubin, AST, ALP, and SDH activities may be increased in foals with NI. Foals with the lowest presenting packed cell volumes tend to have the highest SDH values, suggesting that hepatic injury was present at the time of presentation.[119] One study reported that foals receiving multiple blood transfusions (4 L or more) were 19.5 times more likely to develop hepatic failure than those receiving smaller volumes of blood products.[122] It is thought that multiple blood transfusions may cause iron overload leading to iron toxicity.[122,794] The administration of deferoxamine mesylate, an iron chelator, has been shown to decrease hepatic iron accumulation in healthy foals receiving blood transfusions.[794] Although the use of this drug in foals with NI has not been reported, the results of this study suggest that the administration of deferoxamine to foals with NI starting before blood administration may be beneficial in decreasing iron-associated hepatic injury.[784,794]

Iron Toxicity

The oral administration of iron fumarate is a very well-described cause of hepatic injury in foals. The greatest risk of toxicity is associated with iron administration before the foals first suckle, presumably caused by the presence of protective factors in colostrum or milk that decrease the hepatotoxicity of iron when administered after nursing has begun.[795-797] When iron is administered at birth and before colostrum ingestion, clinical signs will typically manifest within 2 to 5 days and are primarily associated with hepatoencephalopathy. Seizures, profound depression, head pressing, ataxia, and abnormal behavior are common. Icterus is usually present at the time of onset of neurologic signs. Clinicopathologic examination typically reveals elevated bilirubin, GGT, ALP, and SDH, as well as increased ammonia concentrations.

Inherited or Congenital Disorders

Glycogen Storage Disease Type IV

Glycogen storage disease type IV, a fatal recessive inherited deficiency of the glycogen branching enzyme, has been described in Quarter Horse foals.[798] The clinical signs associated with this disease are variable, ranging from stillbirth to progressive weakness, transient flexural limb deformities, persistent recumbency, seizures, and respiratory or cardiac failure.[798] Affected foals are leukopenic and typically have elevated AST and GGT activities, in addition to elevated creatine kinase (CK) caused by muscle pathology. The genetic lesion is a single base nonsense mutation in the glycogen branching enzyme encoded by the GBE1 gene.[799,800] One study reported that approximately 2.5% of fetal and early neonatal deaths in Quarter Horse–related breeds were homozygous for the mutant GBE1 allele, suggesting that this syndrome has a clinically relevant impact on the reproductive efficiency of these breeds.[801]

Persistent Hyperammonemia

Persistent hyperammonemia associated with encephalopathy has been described in Morgan foals 4 to 7 months of age.[263,802] Affected foals exhibit acute onset of clinical signs shortly after weaning, which can include coma, blindness, and seizures. Hepatic enzymes may be mildly elevated, but hepatic pathology is modest. Blood ammonia levels are extremely high in affected foals (300–600 μmol/L), and this syndrome is thought to be related to an inherited disorder of hepatic ammonia metabolism and possibly other amino acids.[803] The metabolic defect may resemble HHH syndrome in humans.[263] Although some foals may survive the first encephalopathic crisis, the syndrome is considered to be fatal and may end with a terminal hemolytic crisis.[768]

Congenital Fibrosis

A syndrome of congenital hepatic fibrosis has been described in the Swiss Franches-Montagnes and Swiss Frieberger breeds.[804,805] The onset of clinical signs is sudden, and affected foals are jaundiced and encephalopathic, with abdominal

distention and colic. Fever and tachypnea are also common. Leukocytosis caused by neutrophilia and increased GGT, ALP, and serum bile acid values are reported. Histopathology demonstrates diffuse bridging portal fibrosis with numerous small and irregular bile ducts, which are sometimes cystic.[805]

Portosystemic Shunts

Portosystemic shunts are an infrequent congenital anomaly in foals that allow for shunting of blood directly from the portal circulation to the systemic circulation.[806-808] The shunts can be located intra- or extrahepatic and may be single or multiple in number.[807] Clinical signs of encephalopathy often do not develop until foals are 6 to 12 weeks of age. The diagnosis is based on the signalment, particularly age of onset, and presence of encephalopathic signs with normal serum hepatic enzyme activities but marked elevations of serum ammonia. Confirmation of the diagnosis may be possible using hepatic ultrasonography, or by a "bubblegram" study involving the injection of 10 mL of agitated saline into the spleen while monitoring for the rapid appearance of bubbles via simultaneous echocardiography.[808] CT, positive contrast portography, and transrectal portoscintigraphy may also be useful in confirmation of the diagnosis.[784] Successful surgical repair using banding techniques that provide progressive occlusion has been described.[807,808]

MUSCULAR DISORDERS

Polysaccharide Storage Myopathy

Polysaccharide storage myopathy (PSSM) was first described in Quarter Horses and related breeds, such as Paint and Appaloosa horses, but is now recognized in some draft, Warmblood, and light horse breeds as well.[809-813] PSSM is characterized by abnormal glycogen accumulation in skeletal muscle associated with muscle damage following exertional exercise. This syndrome has been associated with an incompletely penetrant autosomal dominant mutation in the *GYS1* gene, which encodes the skeletal muscle glycogen synthase enzyme.[814] This mutation has been identified in more than 30 horse breeds, although at highly variable frequencies, with Quarter Horses and Belgians having the highest reported prevalences.[814-819] PSSM is rarely reported in foals because it remains subclinical, especially if foals are stall confined.[820] The only indication of the presence of the syndrome may be increased serum CK activity, unless the foals undergo a period of exertional activity or are affected by concurrent disease. Typically the disease is not recognized until affected individuals are mature enough to be put into training or work.[820] The clinical signs may range from muscle soreness and gait abnormalities in Warmbloods to progressive weakness and muscle atrophy in draft breeds, whereas Quarter Horses may suffer from acute exertional rhabdomyolysis.[815,821] Diagnosis in adults depends on muscle biopsy, but this may not be diagnostically useful in foals, and genetic testing is preferred.[822] Daily pasture exercise and appropriate feeding of a balanced, low-starch, fat-supplemented diet to both the foal and its dam will likely be beneficial in management of affected foals.[822]

Glycogen Branching Enzyme Deficiency

Glycogen branching enzyme deficiency represents an important cause of stillbirth and early neonatal death in the Quarter Horse and Paint breeds.[798,801,822] The syndrome is caused by a mutation in the *Gbe1* gene and results in severe impairment of glucose homeostasis.[800] The clinical presentation is variable, with foals born alive that are weak and hypothermic. Although they often respond positively when assisted to nurse or bottle-feed, intermittent hypoglycemia and seizures may develop unless they nurse regularly.[823] Other clinical signs can include fever, tachypnea, and tachycardia, and because of this very nonspecific spectrum of clinical signs it can be difficult to differentiate these foals from those suffering from neonatal sepsis.[824] Respiratory failure and sudden death can occur, even with only mild to moderate exercise.[823] Clinicopathologic evaluation may reveal leukopenia; intermittent hypoglycemia; and persistent elevations of CK, AST, and GGT activities.[822] Despite supportive care the condition is ultimately fatal, with most foals succumbing by 6 to 8 weeks and no reports of survival beyond 18 weeks of age.[822,823] A genetic test is available for diagnosis of this disease.[801]

Nutritional Myodegeneration (White Muscle Disease)

Nutritional myodegeneration (NMD) is a noninflammatory, degenerative disease primarily seen in foals less than 30 days of age. It affects skeletal as well as cardiac muscle and is associated with low serum selenium and vitamin E concentrations.[825-829] The primary deficiency of vitamin E and selenium appears to be in the mare, and for this reason NMD is most commonly seen in areas with selenium-deficient soils, forages, and grains.[830] These areas include the northeastern, northwestern, mid-Atlantic, and Great Lakes regions of the United States. The clinical presentation of NMD can be acute or subacute. The subacute form is associated with muscular weakness, whereas the acute form is associated with rapidly progressive weakness leading to recumbency and death within a few days.[831] Dysphagia is a common finding in the subacute form and is related to involvement of the muscles involved in prehension, mastication, and swallowing. It may contribute to the development of FTPI and aspiration pneumonia.[828] Severely affected foals typically have involvement of the myocardium and the respiratory musculature, contributing to cardiovascular and respiratory failure and leading to death.[822] Diagnosis of NMD is based on clinical signs in combination with increased muscle enzyme activities (CK and AST), decreased blood selenium, decreased glutathione peroxidase activity, and response to vitamin E and selenium treatment.[828,830] Profound electrolyte abnormalities may be present, including hyperkalemia, hyponatremia, hypochloremia, and hypocalcemia, with hyperkalemia potentially contributing to cardiac arrest in severely affected foals. Myoglobinuria may be present, and pigment nephropathy can lead to the development of acute renal failure. Muscle biopsies may be supportive of NMD, but a more definitive antemortem diagnosis requires assessment of vitamin E and selenium concentration or glutathione peroxidase activity.[828] Postmortem examination consistently reveals bilaterally symmetric myodegeneration with a dry appearance and pale discoloration of affected muscles. Treatment requires supportive care, IV fluid therapy for correction of hypovolemia, electrolyte derangements, metabolic acidosis, and diuresis. Dysphagic foals will require nutritional support, either by indwelling nasogastric feeding tube or parenterally. Vitamin E and selenium supplementation is essential in the treatment of affected foals (Table 20.13). The injectable form of selenium also contains vitamin E but at an insufficient concentration, requiring that foals also receive injectable or

TABLE **20.13 Treatments Drugs Used for Nutritional Myodegeneration**

Drug	Dosage	Route	Frequency (h)
Vitamin E (preferably in the form of DL-alpha-tocopheryl acetate)	2–6 IU/kg	PO	24
Selenium	0.055–0.067 mg/kg	IM (deep)	Once
	1 mg total dose	PO	24

IM, Intramuscularly; *IV,* intravenously; *PO,* orally.

oral vitamin E. Although the initial prognosis is guarded, foals that regain the ability to stand have a more favorable prognosis.[823] Prevention of NMD can be aided by ensuring that mares have adequate dietary vitamin E and selenium intake and by prophylactic parenteral administration of vitamin E and selenium to newborn foals in endemic areas.

FOAL ANTIMICROBIAL THERAPY

The presence of documented focal or systemic bacterial infection, such as septic arthritis, pneumonia, enterocolitis, meningitis, or umbilical remnant infections, represents a clear indication for the use of antimicrobial therapy in the foal. Unfortunately the clinical situation is not always so straightforward. Because of the risk of septicemia in any compromised neonatal foal, it is often better to make the assumption that bacterial infection is present rather than risk allowing the patient to deteriorate further while awaiting confirmation of the diagnosis.[194] In those situations in which bacterial infection is likely or suspected, aggressive therapy that includes antimicrobials is indicated. Although there are some risks associated with antimicrobial therapy, primarily AAD, these risks are greatly outweighed by the risks associated with withholding antimicrobial therapy from a patient with sepsis secondary to bacterial infection. Early appropriate empiric antimicrobial therapy has been shown to reduce mortality in human patients suffering from septic shock,[832] and although published evidence is lacking, clinical experience in neonatal foals supports this conclusion as well.[833]

When implementing antimicrobial therapy one must consider some basic pharmacologic concepts. The first concept is whether the antimicrobial selected is appropriate for the likely target of the therapy. To understand this, one must have a concept of the drug's mechanism of action and how that relates to the different classes of bacteria and their inherent susceptibilities. Second, how is the drug to be delivered, and is that route of delivery likely to achieve therapeutic concentrations of the drug at the affected site? There are key factors that profoundly affect our ability to effectively deliver antimicrobials to some sites of infection, and failure to take these into account will preclude effective treatment. The physical and pharmacologic characteristics of the different antimicrobials and their interactions with various tissues will also have a significant influence on the efficiency and efficacy of the treatment of bacterial infections. Consideration should also be given to the route of administration and frequency of dosing, particularly if treatment is to be administered by lay personnel or owners.

Achieving therapeutic concentrations at the site of infection can be challenging, especially when the drug has to cross an epithelial barrier (CNS, eye, lung, biliary, etc.). Drugs that are highly lipid soluble tend to distribute more fully to the tissues, whereas water-soluble drugs tend to distribute primarily within the extracellular water and penetrate epithelia poorly. The presence of inflammation will allow for increased tissue permeability of epithelial barriers; however, the resolution of inflammation allows for epithelial restitution. This may limit the ability of water-soluble drugs to maintain therapeutic respiratory concentrations as healing progresses, and recurrent infections may result.

The pharmacodynamic characteristics of the different antimicrobials also impact decisions regarding the route and frequency of administration. The two fundamental classes of drugs are the time-dependent and the concentration-dependent antimicrobials. Efficacy of time-dependent antimicrobials, such as the β-lactams, require that the concentration at the site of infection be maintained above the minimum inhibitory concentration (MIC) for as much of the treatment interval as possible. Time-dependent drugs benefit from intramuscular and oral administration because slower absorption yields lower serum concentrations, but therapeutic concentrations are typically maintained for longer periods of time. The use of CRIs for delivery of time-dependent drugs can yield optimal pharmacokinetics and is feasible in the hospital environment using electronic infusion pumps. The efficacy of concentration-dependent drugs requires high peak serum concentrations for maximal efficacy (greater than 10 times MIC for the aminoglycosides) but does not require high concentrations throughout the treatment interval. These compounds benefit from IV or topical administration to achieve high peak concentrations, with prolonged treatment intervals.

It is also important to remember that foals differ from adult horses in a number of ways that may impact the choice of antimicrobial therapy. First, foals have substantially greater total body water content than adult horses, typically requiring that the dosage of water-soluble drugs be increased. For example, doses of aminoglycosides are often increased as much as 100% in foals, compared with dosing in adults, to compensate for this increase in the volume of distribution. Also, neonatal foals do not have complete maturation of their hepatic and renal systems, especially during the first week of life, which may result in impaired elimination of certain drugs metabolized or eliminated by those routes. Different types of toxicities associated with antimicrobial use in foals must also be considered—for example, the risk of arthropathy associated with the administration of fluoroquinolones (because their rapidly growing cartilage tissue).

There are some advantages in designing foal antimicrobial therapy. Most orally administered antimicrobials are more effectively absorbed in foals compared with adults, which allows for wider use of this route. In addition, foals appear to be at reduced risk of AAD, which is likely because they have not yet fully transitioned to hindgut fermentation. Last, some antimicrobials used in in foals are cost-prohibitive in adult horses because of the total dose required; hence, the cost for foals is much less.

Therapeutic Targets

The most common isolates encountered will vary somewhat based on the specific site of infection and the predisposing factors associated with the infection. However, when looking at

retrospective studies of isolates from bacteremic neonatal foals some patterns become apparent. Over the past 30 years the most common bacteria isolated from blood cultures of infected foals have been gram-negative organisms.[25,123,171] Gram-positive organisms isolated from infected foals represented less than 20% of isolates and were typically present in mixed infections with gram-negative organisms.[25,123] Although some of the variance in the patterns of bacteria isolated from foals may result from regional differences, it does appear that more recently an increase in the percentage of gram-positive isolates has occurred.[177] Several studies have reported increased numbers of gram-positive isolates ranging from 30% to 43% of the total isolates.[180,181] This temporal change in patterns of isolates highlights the need to consider the likely pathogens present in the formulation of the initial empiric antimicrobial plan. Based on the most recent reports, *E. coli* remains the most common isolate followed by *Enterococcus* spp., *Actinobacillus* spp., β-hemolytic *Streptococci, Staphylococcus* spp., and *Enterobacter* spp.[180,834] Unfortunately there have also been temporal changes in the patterns of antimicrobial susceptibility observed in the bacteria isolated from bacteremic foals. Although there may be some debate as to the driving force behind these changing patterns of antimicrobial sensitivity, there is no doubt that the phenomenon is real. Some earlier reports mentioned the presence of a few isolates that were resistant to multiple antimicrobials,[120,177] but recent reports have demonstrated substantial numbers of multidrug-resistant (MDR) organisms (up to 38% of isolates).[180,182] Definitions vary somewhat among references, but generally speaking, MDR organisms display resistance to three or more of the core antimicrobials in a sensitivity panel. Recent studies in human medicine have characterized the most common and problematic of the MDR organisms as the ESKAPE group, which includes *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa,* and *Enterobacter* spp.[835] This group of pathogens is responsible for the majority of nosocomial infections in human hospitals, and all routinely "escape" most currently used antimicrobial drugs.[836] The increasing prevalence of MDR organisms will require that antimicrobials are used judiciously and appropriately to limit the further spread of these organisms. The risk associated with these organisms also reinforces the need to perform appropriate culture sampling (blood, synovial fluid, CSF, body cavity effusions, etc.) to be sure of the pathogens involved and tailor antimicrobial therapy appropriately.

Antimicrobials

β-Lactams

β-Lactam antibiotics bind to penicillin binding proteins, interfering with bacterial cell wall synthesis. This leads to the formation of defective cell walls that are osmotically unstable, and cell death usually results from cell lysis. These drugs include the penicillins, synthetic penicillins, cephalosporins, and carbapenems. Modifications of the basic penicillin or cephalosporin molecule confer differences in antimicrobial activity, as seen with the synthetic penicillins and third-generation cephalosporins, which exhibit an increased gram-negative spectrum. Increased stability against β-lactamases may also be achieved, such as seen in the carbapenems. β-Lactam drugs are time-dependent antimicrobials and must be present in the tissues at concentrations greater than the MIC throughout most, preferably all, of the dosage interval to be effective.

Penicillin G is the most commonly used β-lactam antimicrobial in equine medicine, and it exhibits good efficacy against many gram-positive organisms and anaerobes, but it has a limited gram-negative spectrum. Penicillin G exhibits good synergy with aminoglycoside antimicrobials, making it a useful drug in a combination therapy approach. Procaine penicillin is administered intramuscularly, whereas the aqueous solutions of sodium or potassium penicillin are administered intravenously (Table 20.14). Procaine penicillin G is readily available and inexpensive, but the requirement for repeated intramuscular injections makes it less desirable for use in neonatal foals because of their minimal muscle mass. Potassium or sodium penicillins are substantially more expensive than procaine penicillin on a daily cost basis but are commonly used in hospitalized foals with ready venous access. There are reports of administering potassium or sodium penicillin as an IV CRI, which can provide favorable pharmacokinetics with these time-dependent compounds.[833] Toxicity is low for the penicillins and is primarily associated with adverse reactions to the inadvertent IV or intraarterial injection of the intramuscular preparation, procaine penicillin G, which likely represents adverse reactions to procaine rather than penicillin, although anaphylactic reactions have been reported.[837]

Ampicillin and amoxicillin are synthetic penicillins that exhibit better activity against gram-negative bacteria because of improved outer cell wall penetration. They do suffer some loss of efficacy compared with penicillin G regarding susceptible gram-positive bacteria. Ampicillin is widely used as an alternative to penicillin in the treatment of neonatal sepsis, typically in combination with amikacin.[177,194,834,838] Other β-lactam drugs that are occasionally used in foals include the antipseudomonal penicillins and the carbapenems. These drugs exhibit a superior gram-negative spectrum of action and are primarily used in cases where aminoglycosides cannot be administered or in the treatment of pathogens resistant to aminoglycosides. The use of these drugs should be restricted to cases with documented infections involving susceptible MDR organisms. The most commonly used antipseudomonal penicillin is ticarcillin, which is typically combined with clavulanic acid.[839,840] Clavulanic acid causes irreversible time-dependent inactivation of many of the β-lactamases, enhancing the activity of ticarcillin against organisms producing these enzymes. Imipenem, a carbapenem antimicrobial, has been used in foals for the treatment of MDR infections. Imipenem is used in combination with cilastatin, which slows renal elimination of imipenem and allows for a decreased frequency of dosing.[841]

Cephalosporins

Cephalosporins are traditionally grouped into "generations" according to their order of discovery and their spectrum of action. First-generation drugs exhibit a primarily gram-positive spectrum, whereas subsequent generations have an increasing gram-negative spectrum and corresponding decreases in the gram-positive spectrum. Fourth-generation drugs are considered to be truly broad spectrum. The primary cephalosporin administered to horses is ceftiofur, which is a third-generation drug.[842] It exhibits a fairly broad spectrum with an emphasis toward gram-negative coverage. Because of this spectrum of activity ceftiofur has often been used as the sole therapy in the initial treatment of foals. The relative safety of ceftiofur in foals has fostered this approach, because it allows the clinician to avoid using combined therapy including aminoglycosides. Unfortunately some recent studies have documented frequent

TABLE **20.14 Antimicrobial Dosages for Use in Foals**

Drug	Dosage	Route	Frequency (hours)
Acyclovir	16–20 mg/kg	PO	8
Amikacin	25–30 mg/kg (neonates) 20–25 mg/kg (2–4 weeks) 7–14.5 mg/kg (weanlings)	IV	24
Amikacin	8 mg/kg	Aerosol	24
Ampicillin sodium	10–20 mg/kg	IV, IM	8
Amoxicillin trihydrate	10–20 mg/kg 20–30 mg/kg	IM PO	8 6–8
Azithromycin	10 mg/kg	PO	24 h for 5 days, then every 48 h
Cefazolin	25 mg/kg	IM	6–8
Cefepime	11 mg/kg	IV, IM	8
Cefpodoxime proxetil	10 mg/kg	PO	6–12
Ceftiofur sodium	5 mg/kg	IV	12
	2.2 mg/kg	IM	12–24
	1.5 mg/kg/h	IV	CRI
	2.2 mg/kg	Aerosol	24
Ceftiofur crystalline-free acid	6.6 mg/kg	IM	96 (two doses)
Cefotaxime	50–100 mg/kg	IV	6
Cephalexin	30 mg/kg	PO	8
Ceftriaxone	25 mg/kg	IV	12
Chloramphenicol	50 mg/kg	PO	6
Clarithromycin	7.5 mg/kg	PO	12
Doxycycline	10 mg/kg	PO	12
Erythromycin	25 mg/kg	PO	6–8
Fluconazole	8 mg/kg (loading) 4 mg/kg (maintenance)	PO PO	Once 12
Gentamicin	11–13 mg/kg (neonates) 6.6 mg/kg (weanlings)	IV, IM	24
Gentamicin	2.2 mg/kg as a 50-mg/mL solution	Aerosol	24
Imipenem/cilastatin	5–10 mg/kg 10–20 mg/kg	IM IV	12 6
Metronidazole	10 mg/kg (neonates) 15 mg/kg (10–12 day old) 15 mg/kg (over 2 weeks)	PO PO PO	12 12 8
Minocycline	4 mg/kg	PO	12
Penicillin G	20,000 IU	IM (procaine penicillin) IV (K or Na penicillin)	12 (IM) 6 (IV)
Rifampin	5–10 mg/kg	PO	12–24
Sulfadiazine-trimethoprim	30 mg/kg	PO	12
Ticarcillin	44 mg/kg	IV	6
Valacyclovir	27 mg/kg (loading) 18 mg/kg (maintenance)	PO PO	8 12

CRI, Continuous rate infusion; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally.

resistance to ceftiofur in organisms isolated from foals, and there does appear to be a trend toward increasing resistance over time, especially among gram-negative enteric bacteria.[180,834] The use of ceftiofur sodium as a CRI has also been investigated and appears to yield suitable pharmacokinetics.[843] Ceftiofur is also available in a sustained-release form, which contains CCFA. Subcutaneous administration of CCFA yields appropriate pharmacokinetics for highly susceptible bacteria in foals.[844] Self-limiting diarrhea was reported in 66% of the foals treated with CCFA, but this does not appear to be a clinical problem associated with this drug. Repeated subcutaneous dosing of CCFA (13.2 mg/kg) at 48-hour intervals for four doses has been reported to maintain appropriate therapeutic concentrations in foals.[845] Other cephalosporins may have utility in foals, such as cefquinome, ceftriaxone, cefpodoxime proxetil, cefotaxime, ceftazidime, and cefepime. Cefquinome

is a fourth-generation cephalosporin that is labeled in Europe for the treatment of foal septicemia caused by *E. coli,* but it is not available in the United States at this time.[846] Cefquinome is dosed at 1 mg/kg IV or intramuscularly every 12 hours, for very susceptible pathogens, but a higher dose of 4.5 mg/kg IV every 12 hours is indicated when dealing with pathogens with higher MIC values.[847] Cefpodoxime proxetil is a third-generation drug that is administered orally, but unfortunately the expense of this drug renders it of limited utility in most cases.[833] Cefepime is a fourth-generation drug that can be useful in the management of MDR infections.[848]

Aminoglycosides

The aminoglycosides continue to constitute a major component of the equine clinician's armamentarium, despite their well-described potential for nephrotoxicity. The primary reasons for this are that the aminoglycosides are bactericidal, exhibit primarily a gram-negative spectrum, and demonstrate good synergy with β-lactam antimicrobials.[634] The bacterial penetration of aminoglycosides is in part an oxygen-dependent transport process and partially accomplished by passive diffusion. This dependence on oxygen-driven transport renders anaerobes resistant to the aminoglycosides. The role of passive diffusion leads to a dependence on high tissue concentrations of the drug to achieve high intracellular concentrations. Routes of administration and/or dosage schedules associated with high peak concentrations at the site of infection, such as extended-interval dosing, are associated with improved clinical responses.[849] Prolonged treatment intervals decrease the risk of nephrotoxicity while still demonstrating clinical efficacy caused by the prolongation of bacterial killing, even after the aminoglycoside concentration drops below the MIC for the targeted organism. This phenomenon is termed the *postantibiotic effect.* The use of extended interval dosing also has been demonstrated to lessen the development of both acquired and adaptive antimicrobial resistance, which are caused by the high peak concentrations achieved and the period of time during which the drug is below the MIC.[634]

Neonatal foals have reduced rates of drug clearance, which necessitates prolonged treatment intervals, but their clearance increases to adult levels within the first few weeks of life.[634] They also have greater volumes of distribution, compared with adults, which necessitates substantially higher dosages to achieve the desired peak serum concentrations. A recent study examining the pharmacokinetics of gentamicin in foals indicated that gentamicin should be dosed at 12 mg/kg IV every 36 hours in foals less than 2 weeks of age, whereas a lower dose of 6.6 mg/kg IV every 24 hours was estimated to be adequate in foals 2 weeks of age or older.[850] Because of the unpredictability of aminoglycoside pharmacokinetics in sick foals, it is recommended that therapeutic drug monitoring be performed to ensure that both an adequate peak serum concentration is achieved as well as appropriate trough concentrations. Peak serum concentrations are typically monitored at 30 minutes after administration of the IV dose, and trough concentrations are monitored immediately before the subsequent dose. This approach is effective but may lack sensitivity in detecting impaired clearance of the drug. In addition, because of the timing of the sample collection the results of the assay will not be available until after the administration of the next dose, which may delay adjustment of the dosage or interval, if indicated. An alternative approach is to obtain serum samples at 30 minutes and 8 hours after drug administration, which can allow for estimation of drug clearance in a more timely manner, allowing for more rapid adjustment of the therapeutic protocol.[634]

Potentiated Sulfonamides

Potentiated sulfa compounds are very common in equine medicine because of their broad spectrum, oral route of administration, and affordability. These drugs exhibit time-dependent pharmacodynamics, and their effects are considered to be bactericidal. The potentiated sulfas distribute well to the tissues. Toxicity is most commonly associated with disturbance of gastrointestinal flora associated with the development of colitis. Although these drugs are not appropriate for initial therapy of septic foals, when organisms are documented to be susceptible they can be used quite effectively.

Tetracyclines

Tetracyclines are bacteriostatic and broad spectrum, possessing activity against a wide variety of bacteria and protozoa as well as *Mycoplasma* and *Rickettsia.* These compounds are time dependent in nature. The most commonly used compounds are oxytetracycline and minocycline. Toxicity has been reported from the disturbance of gastrointestinal flora in adults, but this appears to be rare in foals. Because the tetracyclines are primarily eliminated via the urinary tract, there is the risk for toxicity in animals with renal insufficiency. Very large dosages of oxytetracycline are administered to foals suffering from tendon contracture, and repeated or injudicious administration has been associated with nephrotoxicity.[629] Rapid IV injection of oxytetracycline has been associated with collapse in horses, perhaps caused by chelation of calcium in the blood. For this reason oxytetracycline is administered at 6 to 8 mg/kg slowly IV twice daily, usually diluted in 0.5 to 1 L of normal saline and administered over 30 minutes. Doxycycline is no longer widely used because of decreased availability and increased expense. Minocycline has come into widespread use in horses because of superior pharmacokinetics compared with doxycycline and a much more reasonable cost of treatment. Although no pharmacokinetic studies have been performed in foals, minocycline is empirically administered at adult dosages.[851]

Macrolides

Macrolides (erythromycin, azithromycin, and clarithromycin) are considered to be bacteriostatic; have a broad spectrum of action; and accumulate in tissues, particularly the lungs.[852] Their primary application is for the treatment of rhodococcal pneumonia in foals. Macrolides are eliminated by hepatic metabolism and can affect the pharmacokinetics of other drugs metabolized by the P450 system. Erythromycin administration in foals with rhodococcal pneumonia has been associated with frequent hyperthermia and diarrhea, and this drug is no longer used for this purpose in most areas of the United States. Azithromycin and clarithromycin are the most commonly used macrolides in foals at this time. Rifampin therapy is typically administered in conjunction with the macrolides in the treatment of rhodococcal pneumonia because of its potential synergistic effects. The combination of clarithromycin-rifampin has been shown to be more effective than erythromycin-rifampin or azithromycin-rifampin in the treatment of rhodococcal pneumonia.[441] Despite decades of clinical experience supporting the efficacy of the combination of macrolides and rifampin, there is recent evidence that coadministration of rifampin with macrolides substantially inhibits

macrolide absorption.[444,445] Current recommendations support the continued use of macrolide-rifampin combinations in the treatment of rhodococcal pneumonia in foals.[349] There has been recent interest in the use of the macrolide gamithromycin in foals because this drug exhibits favorable pharmacokinetics in foals following once-weekly intramuscular injections. It also has been shown to be noninferior to the combination of azithromycin and rifampin in the treatment of rhodococcal pneumonia in foals.[435,443]

Rifamycins

Rifampin is a macrocyclic antibiotic and is used primarily in foals as an adjunct therapy to the macrolides for treatment of rhodococcal pneumonia. It can be combined with other antibiotics for treatment of abscesses, but it should never be used alone because of the risk of rapidly developing antimicrobial resistance. In addition to using rifampin in the treatment of rhodococcal infections, it has been reported to be effective for the treatment of staphylococcal infections.

Chloramphenicol

Chloramphenicol is widely distributed to the tissues and has a wide spectrum of action including both gram-positive and gram-negative bacteria, as well as *Rickettsia, Mycoplasma,* and anaerobes. The half-life of chloramphenicol is short, and it is a time-dependent drug, requiring frequent dosing (6-hour intervals).[853] Human health concerns regarding possible chloramphenicol-associated nondose-dependent fatal aplastic anemia made it illegal to use this drug in food animals over the past 50 to 60 years. As a result of the minimal use of the drug there are low levels of resistance to chloramphenicol in many types of bacteria, which has created a potentially important role for chloramphenicol in the treatment of MDR organisms. Intriguingly, the usage of chloramphenicol has been proposed for human patients infected with MDR organisms, despite the risk of aplastic anemia.[854] Regardless, the potential risk of aplastic anemia to humans handling chloramphenicol necessitates thorough client education when dispensing this drug (avoid contact with aerosolized drug or direct contact with mucous membranes). Animal toxicity appears to be rare and is associated with reversible or irreversible bone marrow suppression. Florfenicol is closely related to chloramphenicol but has not been associated with aplastic anemia in humans and is labeled for use in food animals. Administration of florfenicol to adult horses has been associated with acute colitis and is contraindicated, but this has not been reported in foals. There are anecdotal reports of successful clinical use of florfenicol in foals at 24- to 48-hour dosing intervals; however, a recent pharmacokinetic study suggested that a shorter treatment interval of 10 hours may be appropriate.[833,855]

Fluoroquinolones

Fluoroquinolones have a relatively broad spectrum, with excellent activity against gram-negative organisms but minimal activity against streptococci. They are bactericidal and exhibit excellent tissue penetration. The fluoroquinolones exhibit peak concentration-dependent bactericidal effects and prolonged postantibiotic effects, which is similar to the aminoglycosides. As a result they can be given at relatively high doses at a decreased frequency. Enrofloxacin is the most widely used fluoroquinolone in horses, but its use is contraindicated in foals because of adverse effects on cartilage maturation.[856] Marbofloxacin has been used in foals and appears to be safe, although no controlled studies have been performed to confirm this clinical impression.[833,857]

Metronidazole

Metronidazole is a nitroimidazole antimicrobial that is highly effective against anaerobic organisms. Because of the limited anaerobic spectrum of most other antimicrobials used in foals, metronidazole is commonly used when anaerobic involvement is suspected or confirmed in foals. A recent pharmacokinetic study found that there were age-dependent influences on metronidazole kinetics in foals and suggested a range of dosages over the course of the first 2 weeks of life.[551]

Aerosol Administration

Aerosol administration of antimicrobials has been demonstrated to achieve high concentrations of antimicrobials at the respiratory mucosal surface while minimizing the development of systemic side effects. Other potential advantages to delivering medications to the lower respiratory tract by aerosolization include a decrease in the total dose administered, avoidance of systemic side effects, and a rapid onset of action.[463] The administration of antimicrobials by aerosolization does have limitations, however, including potential problems with drug delivery and pulmonary irritation, as well as the expense of the required equipment and the time required for administration. Several antimicrobials have been investigated for aerosol administration in horses, including gentamicin, ceftiofur, cefquinome, and marbofloxacin. Both gentamicin and ceftiofur are well tolerated and can be administered as aerosols.[459,466]

FLUID THERAPY IN THE FOAL

One of the fundamental dilemmas facing a clinician when evaluating a sick foal is whether or not fluid therapy is indicated. To determine the answer to that question one must consider the variety of indications for fluid therapy. The most common indication is for the correction of volume depletion or dehydration. Other indications for fluid therapy can be the correction of specific electrolyte imbalances, the provision of colloidal support, correction of acid-base disorders, restoration of oxygen-carrying capacity, and provision of immunoglobulins. In many cases more than one of these indications is present, and one must be careful in assessing the patient because changes in clinical status over time may result in one or more new indications for fluid therapy arising, even as others may have been resolved.

The next question regarding fluid therapy is what type of fluid does this patient need. The choice of fluid composition will depend on multiple variables, which include the primary goal of fluid therapy as well as patient-specific, route-specific, and practical considerations. The clinician must then determine the most appropriate route for administration of fluid therapy in the individual patient, and this may also factor into the decision-making process regarding the types of fluids to be administered. The amount of fluid therapy to be administered must also be determined, primarily based on the patient's fluid deficit and need for maintenance and replacement of ongoing losses. The anticipated duration of therapy can be more difficult to assess in the formulation of a treatment plan, but this represents an important factor in deciding how fluids will be administered and the potential costs to the client for fluid therapy. Finally, the clinician must develop a plan for monitoring ongoing fluid therapy and for determining when fluid therapy is no longer required.

Patient Requirement for Fluid Therapy

The first challenge in patient evaluation is the accurate assessment of hydration status. The typical parameters used in assessing clinical hydration during a physical examination are mucous membrane color, capillary refill time, jugular refill time, pulse quality, the temperature of the extremities, mental status, and urine production. Fundamentally these represent indicators of perfusion, rather than hydration, which is an important distinction given that there are situations, such as cardiogenic or vasodilatory shock, in which a well-hydrated patient can present with extremely poor perfusion. The term *dehydration* actually refers to situations in which there is a total body deficit of pure water. The clinical signs most commonly used for the assessment of dehydration are increased skin turgor, tacky mucous membranes, and sunken eyes. Unfortunately skin turgor is difficult to assess in foals, and a recent study in adult horses indicated that it was also not a reliable estimator of clinical hydration status in that population.[858] Further insight into hydration status can be gained by the measurement of urine specific gravity, which in the properly hydrated foal should be in the range of 1.010 to 1.001. Values greater than 1.010 indicate that the foal is retaining water and is likely not adequately hydrated. Urine output is another useful parameter, but it can be hard to gauge in foals that are not continuously monitored. The normal foal should urinate at least once every 2 hours. More accurate assessment of urine output is only possible in foals that have a urinary catheter in place, allowing for urine collection and measurement. Urine output should be greater than approximately two thirds of the total fluid intake including all IV infusions and any enteral fluids or feeding. Hypotension, considered a mean arterial pressure (MAP) less than 60 mm Hg, may be an indication of hypovolemia but can also result from decreased cardiac output or excessive venous capacitance. If the hypotensive patient does not respond to volume replacement then additional therapy in the form of vasopressors and/or inotropes is indicated (see the later section Inotrope and Vasopressor Therapy).

When attempting to determine whether hypovolemia and/or dehydration are present it is helpful to consider how fluid is distributed within the body. Neonatal foals have substantially higher total body water (TBW) content than adult horses, at 75% and 67%, respectively.[859] TBW is present in two primary compartments, the intracellular fluid (ICF) and ECF, with the ECF subdivided into the interstitial fluid and the plasma volume. In neonatal foals the ECF and ICF each represent approximately half of the TBW, and the plasma volume represents approximately one fourth of the ECF.[859] TBW is primarily determined by the total body sodium content, which is closely related to the sodium concentration within the ECF compartment and regulated by the ingestion or elimination of sodium.[860] Decreases in the plasma sodium concentration (hyponatremia) are indicative of a relative excess of free water and/or decreases in total body sodium content. The kidneys will respond by eliminating water while retaining sodium, restoring normal sodium concentration and TBW content. Increases in the plasma sodium concentration represent a loss of free water and will stimulate thirst, leading to water ingestion and correction of the TBW deficit.

Types of Fluids

Having determined that the patient needs fluids, the next challenge is determining the types of fluids that should be administered. There are many choices of fluids, and they fall into three broad categories: crystalloids, colloids, and oxygen-carrying solutions. Crystalloid solutions contain electrolytes and nonelectrolytes (such as dextrose) that are capable of diffusing through the capillary wall into the interstitium, whereas colloid solutions contain larger molecules that do not readily diffuse and tend to remain within the vascular lumen. Oxygen-carrying solutions contain either red blood cells or other substances capable of delivering oxygen from the lungs to the tissues. In the majority of situations the most appropriate fluid will be a crystalloid solution. These solutions are classified based on their tonicity relative to normal plasma and are isotonic, hypertonic, or hypotonic.

Isotonic electrolyte-containing fluids will have little influence on the ICF volume but will expand the ECF volume, expanding the circulating blood volume. Because these fluids contain large amounts of sodium, a substantial amount of the fluid will be retained in the body unless the kidneys excrete the sodium and water together. Sodium overload can result in hypernatremia, which has been associated with increased mortality and severity of illness in human patients.[861] In addition to the substantial sodium content of the isotonic electrolyte solutions, there is typically a substantial chloride content as well. This is most pronounced with isotonic saline (0.9%), which contains 154 mEq/L of both sodium and chloride (Table 20.15). Although the sodium content is only slightly supraphysiologic, the chloride content is dramatically greater than that present normally in the plasma. In some patients renal elimination of chloride is impaired and is not adequate to deal with this high chloride load.[862] Excessive chloride administration is associated with the development of hyperchloremic metabolic acidosis, inflammation, hypotension, and adverse renal outcomes in human patients.[861] More physiologic fluids, such as lactated Ringer's solution (LRS), Plasma-Lyte A, and Normosol-R, contain lower concentrations of chloride more closely mimicking normal serum concentrations. Dextrose 5% in water is an exception to these rules, because it is an isotonic crystalloid fluid that does not contain any electrolytes and is primarily used to replace total body water deficits.

Hypertonic crystalloid fluids have higher electrolyte concentrations than plasma and have fewer indications for their use. The most commonly used hypertonic crystalloid is hypertonic saline, which is primarily used to expand the circulating blood volume. This effect results from the shift of fluid from the interstitial space into the circulation, but it is very transient because of the rapid diffusion of the sodium load from the circulation into the interstitium. The other commonly used hypertonic crystalloid is hypertonic sodium bicarbonate, which is typically administered to correct metabolic acidosis. By providing sodium without any accompanying chloride this solution directly addresses strong ion acidosis, such as hyponatremic metabolic acidosis. It is less useful in addressing other types of metabolic acidosis, such as lactic acidosis, and care must be taken when administering this solution to foals with depressed ventilation because it will increase carbon dioxide production and potentially worsen respiratory acidosis.

Hypotonic crystalloid solutions contain much less sodium and chloride than the isotonic replacement fluids. This can be very helpful, because the lower sodium load decreases the risk of water retention and edema formation, and the lower chloride load decreases the risk of hyperchloremic metabolic acidosis. For these reasons hypotonic crystalloid solutions are most useful for maintenance fluid therapy, in which there is less need for electrolyte replacement and more need for the

TABLE **20.15 Composition of Intravenous Fluid Solutions Commonly Administered to Foals**

	Fluid Types							
Components	Plasma	0.9% Saline	Lactated Ringer's Solution	Plasma-Lyte A/Normosol-R	Plasma-Lyte 56/ Normosol-M with 5% dextrose	5% Dextrose in Water	50% Dextrose in water	7.2% Saline
Na^+ (mEq/L)	140	154	131	140	40	—	—	1232
Cl^- (mEq/L)	104	154	111	98	40	—	—	1232
K^+ (mEq/L)	5	—	5.4	5	13	—	—	—
Mg^{2+} (mEq/L)	1	—	1	3	3	—	—	—
Ca^{2+} (mEq/L)	2.2	—	2	—	—	—	—	—
Dextrose (g/L)	—	—	—	—	50	50	500	—
Bicarbonate (mEq/L)	25	—	—	—	—	—	—	—
Lactate (mEq/L)	1	—	29	—	—	—	—	—
Gluconate (mEq/L)	—	—	—	23	—	—	—	—
Acetate (mEq/L)	—	—	—	27	16	—	—	—
Osmolarity (mOsm/L)	285	309	278	295	363	253	2525	—

provision of water. The use of resuscitation fluids, such as LRS and Normosol-R/Plasma-Lyte A, for maintenance therapy in foals has been associated with the development of hypernatremia and hyperchloremia, which reinforces this concern.[863] Because patients on maintenance fluid therapy often have reduced dietary intake, there is an increased need for potassium supplementation, and maintenance fluids have accordingly higher concentrations of potassium. There are concerns that the administration of hypotonic fluids could cause red blood cell lysis, and for this reason maintenance fluids often have dextrose added to bring the tonicity of the solution into a more appropriate physiologic range. Following administration the dextrose is metabolized and has no impact on fluid shifts within the body. The use of 5% dextrose in water (D5W) represents an alternative to hypotonic crystalloid fluids for maintenance therapy in foals; this solution will not contribute any sodium load because there are no electrolytes. This is problematic because there is an ongoing need for electrolytes caused by renal, gastrointestinal, and insensible losses. For this reason D5W should not be used alone and is typically combined with isotonic polyionic crystalloid solutions to provide for replacement of any electrolyte deficits as well as ongoing losses.

Colloids are fluids containing relatively large molecules less readily able to diffuse across the capillary membrane. This allows them to exert colloid oncotic pressure within the circulation, resulting in fluid shifts from the interstitium into the vasculature and expanding circulating blood volume. Colloids will also aid in retaining fluids that have been administered within the vasculature for a longer period of time than would be possible with crystalloids alone. The most commonly used colloid solution is fresh frozen equine plasma, which contains albumin as the primary colloid. Albumin, while the most physiologic colloid, also has a relatively small size and will diffuse into the interstitial fluid space in which it will then exert a colloidal effect, potentially exacerbating the development of edema. Blood is another natural colloid. In addition to the colloidal effect of the albumin that it contains, blood has the benefit of providing red blood cells to improve oxygen-carrying capacity and tissue oxygen delivery. Another solution with oxygen-carrying capacity is ultrapurified polymerized bovine hemoglobin. This product has colloidal effects, but they are not the primary reason that this product would be used. Polymerized hemoglobin has been used with apparent clinical efficacy in foals and horses at doses of 2 to 5 mL/kg.[750,752] This product is not currently available in the United States, but it is available in Europe (Oxyglobin, Dechra Veterinary Products, Shrewsbury, UK).

Synthetic colloids, such as hetastarch and pentastarch, are shelf-stable and do not require collection or thawing before administration, making them very useful in the critically ill patient. The synthetic colloids are typically less expensive than frozen equine plasma and also may provide a more long-lasting colloidal effect than albumin. There are concerns that synthetic colloids, especially hetastarch, may interfere with coagulation, especially in patients with severe systemic inflammation that may already be suffering from subclinical coagulative dysfunction. New-generation hetastarch preparations have lower molecular weight and lower degrees of molar substitution and may have improved safety profiles.[864] Of even greater concern is the recent evidence from human medicine that resuscitation with hetastarch solutions may be associated with an increased risk of acute kidney injury and mortality.[865] Although there are no studies addressing these concerns, in veterinary patients it is recommended that hetastarch solutions should only be used in patients with a demonstrated need for colloid therapy, and potentially in combination with equine plasma, rather than as the primary resuscitation fluid or the sole colloid. Hetastarch solutions should not be administered in doses of more than 5 to 10 mL/kg, and cumulative dosing should be restricted to no more than 20 mL/kg.

Route of Administration

The next challenge is determining the route by which fluids will be administered to the patient. The most physiologic route is the enteral route, but it can be easy to overlook the utility of this route, especially in hospitalized patients. Generally, if the gut is working it should be used for at least whatever component of the fluid therapy is appropriate. Enteral administration will be limited in both the volume that can be delivered and the rate at which the fluid will be absorbed, rendering it of limited utility in the critically ill patient, but it may be very useful in

delivering maintenance fluid therapy. Enteral therapy may also be less expensive and more practical in the field setting when treating the less severely compromised patient. IV administration will achieve the most rapid results because it allows for the rapid administration of large amounts of fluids and is the most commonly used route of administration in critically ill patients. IV access is associated with some risks, primarily catheter-associated complications such as thrombophlebitis and air embolus aspiration. Neither subcutaneous nor intraperitoneal fluid administration is well tolerated in equine patients, and these routes of administration are rarely used.

Practical considerations related to the ability to administer fluid therapy may impact all of these decisions. IV access can be challenging to establish in the sick neonatal foal, especially in a field setting. Although over-the-stylet catheters are commonly used, they can be difficult to place in hypotensive foals and are susceptible to kinking or displacement caused by foal movement and frequent handling. These catheters are best used for short-term fluid administration in normotensive foals. The most commonly used over-the-stylet catheters are made of Teflon, which can be more irritating to the vein than other materials, but polyurethane over-the-stylet catheters also are available (MILA International, Inc., Erlanger, KY; Arrow, Teleflex Inc., Wayne, PA). Over-the-wire catheters, although slightly more complex regarding placement, are easier to use in hypotensive patients and are easier to maintain for longer periods of time. These catheters are typically made of polyurethane, which is less thrombogenic than Teflon. Silicone over-the-wire catheters are the least thrombogenic and are rarely used in foals. Over-the-wire catheters are also available in longer lengths (20 cm) than over-the-stylet catheters (13 cm), which is helpful in critically ill foals because they can be placed almost as deep as a central venous line, potentially decreasing the risk of vascular irritation associated with delivery of hypertonic solutions or irritating medications. Multiple-lumen over-the-wire catheters are available that can be helpful in critically ill patients because they allow for parenteral nutrition or medications to be delivered through a separate catheter lumen than the one used for IV fluid administration. The downside to these multilumen catheters is primarily their large outer diameter, which can make them more challenging to place and may increase the risk of catheter site or vascular complications.

Enteral administration of fluids can be achieved using a nasogastric tube, but this approach is primarily useful for administration of a few doses of fluids, after which the requirement to repeatedly pass the tube may represent a very stressful intervention. Leaving the nasogastric tube in place is also problematic because of local irritation within the pharynx and interference with voluntary drinking and eating. If repeated enteral administration is anticipated, then serious consideration should be given to the placement of an indwelling enteral feeding tube (14 Fr × 125 cm, MILA International, Inc., Erlanger, KY). The small outer diameter of these tubes allows for ongoing voluntary intake of feed or water. Having one of these tubes in place makes it very simple to administer multiple small boluses of enteral fluids or milk with minimal patient stress. Further discussion of enteral feeding can be found in the section Nutritional Support for the Foal later in this chapter.

Dosage

The clinician must also determine the volume of fluids to be administered and the duration of fluid therapy. The factors that must be considered in determining the amount of fluids to administer are the volume needed for maintenance of normal bodily function, the magnitude of the existing fluid deficit, and the ongoing losses potentially associated with the disease process (diarrhea, reflux) as well as any insensible losses (sweat). When designing the fluid therapy plan it is important to consider the maintenance fluid plan as separate from the replacement fluid plan, which includes both replacement of existing deficits and ongoing losses. The types of fluids used for these purposes are typically different, and inadvertent use of maintenance fluids for replacement, or vice versa, can be deleterious to the patient. The calculation of maintenance fluid requirements in the foal can be approached in two ways. The traditional approach is based on the accepted value of 3 to 5 mL/kg per hour (75–120 mL/kg/day) as the maintenance fluid requirement. The primary problem with this approach is that it represents a very broad range of fluid rates and may result in fluid overload if not closely monitored. A second approach to the determination of maintenance fluid requirements has been proposed, based on the Holliday–Segar formula, which provides a "drier," more conservative rate of fluid administration. The calculation is as follows: for the first 10 kg of body weight, 100 mL/kg per day of fluids are administered, then 50 mL/kg per day for each kilogram from 11 to 20 kg body weight, and then 25 mL/kg per day for each kilogram of body weight >20 kg.[190,866] In a 50-kg foal this calculation yields a maintenance rate of 2250 mL/day, or 94 mL/h, which equates to 1.9 mL/kg per hour.[866] When formulating the fluid plan do not forget to incorporate other fluid sources that may be administered to the foal, which includes any enteral feedings, as well as fluids given as drug infusions or parenteral nutrition. It is easy to overlook these additional sources, yet they may constitute a significant proportion of the daily fluid intake.

The other consideration in the design of the maintenance fluid regimen is the ongoing need for electrolytes, particularly sodium and potassium. If isotonic replacement solutions are administered for maintenance purposes, then hypernatremia and hyperchloremia are likely complications.[863] Those solutions also contain inadequate amounts of potassium for maintenance. The use of hypotonic crystalloid maintenance solutions is, therefore, more appropriate. The recommended daily rate of sodium supplementation in foals is less than 3 mEq/kg, unless they have increased renal sodium losses.[866] Administration of a maintenance solution such as Plasma-Lyte 56 at 1.9 mL/kg per hour will provide approximately 2 mEq/kg per day of sodium. It is important to remember that the foal will likely be receiving other sources of sodium in the form of drug infusions and catheter flushes and in solutions such as parenteral nutrition, plasma, or synthetic colloids. Regarding potassium, the daily maintenance requirements are quite substantial in foals that are not nursing because milk contains high levels of potassium. Supplementation of potassium at 1 to 3 mEq/kg per day is a reasonable starting point. Hypotonic maintenance solutions, such as Plasma-Lyte 56, contain substantially more potassium than replacement solutions (13 mEq/L vs. 5 mEq/L, respectively), but this is still insufficient for the neonatal foal, and supplementation will be required. The addition of potassium chloride at 20 to 40 mEq/L to a hypotonic maintenance solution is a reasonable starting point for supplementation. Care should be taken not to administer a fluid with that amount of potassium supplementation at a high rate, however, because administration of potassium at a rate greater than 0.5 mEq/kg per hour may result in cardiac complications caused by hyperkalemia.

TABLE **20.16** Clinical Assessment of Hydration Status

Degree of Dehydration	Skin Tenting	Capillary Refill Time	Mucous Membranes
<5%	1–3 sec	<2 sec	Slightly tacky
5–10%	3–5 sec	2–3 sec	Tacky
>10%	>5 sec	>3 sec	Dry

TABLE **20.17** Clinical and Physiologic Parameters Useful in the Assessment and Monitoring of Hydration Status

Parameters	Overhydrated	Ideal	Underhydrated
Heart rate	—	80–120	>140
Respiratory rate/effort	Upward trend	<56	—
Hematocrit	20	35–45	>45 (increasing)
Total protein (g/dL)	<3	5–8	>8
Urine output (mL/kg/h)	>2	1–2	<0.5
Urine specific gravity	—	1.005–1.010	>1.012
Plasma lactate (mmol/L)	—	<2	>5 (neonate) >2.5 (over 4 days)
Peripheral edema	Obvious signs	May be seen in some foals	—
Central venous pressure (cm H_2O)	>8–12	3–8	Negative to 5
BUN/creatinine	—	Normal	Increasing

BUN, Blood urea nitrogen.

Using the clinical perfusion indicators mentioned previously (mucous membrane color, capillary refill time, jugular refill time, heart rate, and pulse quality) one can derive a rough estimate of the degree of clinical dehydration (Table 20.16). This approach yields estimates of dehydration ranging from 5% to >10%, and these values can be used when calculating the estimated fluid deficit. For example, a 50-kg foal with a clinical estimate of 5% dehydration will require 2.5 L of fluids (50 kg × 0.05 = 2.5 kg of fluid) to replace their deficit. Clinicopathologic testing can aid in refining the estimate of the fluid deficit, with variables such as packed cell volume, total plasma protein concentration, urine specific gravity, BUN concentration, serum creatinine concentration, and serum lactate concentration all potentially providing useful insight (Table 20.17). The packed cell volume will be increased with hypovolemia but may show less marked elevations with dehydration. Total protein concentration will typically increase with hypovolemia and dehydration as well, but this marker may lack sensitivity in patients with hypoalbuminemia and/or hypoglobulinemia. Urine specific gravity is a fairly sensitive marker of dehydration and is very clinically useful. BUN and creatinine concentrations are indicators of hypovolemia and decreased perfusion rather than dehydration. Both BUN and creatinine are relatively insensitive markers of decreased perfusion, especially BUN, and only begin to increase with substantial decreases in GFR. Serum lactate concentration may be a more sensitive marker of perfusion but can also be elevated in response to impaired tissue oxygen utilization or decreased hepatic lactate clearance. Measurement of central venous pressure (CVP) can be very useful in assessing the foal's fluid status. This technique is somewhat technically challenging but is feasible with limited equipment. If the foal has been catheterized with an over-the-wire 20-cm catheter, then the placement of the catheter tip will be fairly central, and this catheter can be used for the determination of an approximate CVP. With the foal in lateral recumbency all ingoing fluid therapy is stopped while the measurement is taken. A water manometer or electronic pressure transducer can be used, and the zero position on the manometer should be set at approximately the height of the base of the heart. The manometer is primed with sterile heparinized saline and then opened to the IV catheter. Slight fluctuations of pressure should be observed with respirations, and the measurement taken is the approximate mean of this range.

Once a determination of the existing fluid deficit has been made, a deficit fluid replacement plan can be formulated. Use of an isotonic replacement fluid (LRS, Normosol-R, and Plasma-Lyte A) is appropriate for this purpose, as previously discussed; remember that deficit therapy is given in addition to the ongoing maintenance fluid support described earlier. Rather than simply dividing up the calculated fluid deficit and administering it over a set period of time (i.e., 2.5 L over 12 hours), it is more useful to administer boluses of replacement fluids at 20 mL/kg (e.g., 1 L to a 50-kg foal) over 10 to 30 minutes and then reassess the patient's status and determine whether further boluses are required. Some foals may require more than replacement of their calculated deficit, but care should be taken not to exceed a 60-mL/kg total dose unless there are compelling clinical reasons that this is indicated, such as ongoing losses. Excessive administration of bolus fluid therapy has been associated with worsened outcomes in human patients.[867,868] If greater than 60 to 80 mL/kg of fluid replacement is required and the patient remains hypotensive, then they should be considered nonresponsive to fluid therapy, and the initiation of inotrope and/or vasopressor therapy should be seriously considered (see the next section Inotrope and Vasopressor Therapy). Reassessment of the patient's hydration status and response to fluid therapy involves the use of all the parameters discussed earlier, with serial measurements being critical to this process.

Replacement therapy is intended to address the patient's ongoing fluid losses, and determination of the magnitude of these losses is more art than science because they are difficult to measure. In many clinical situations the foal does not have a urinary catheter in place, so assessment of renal losses is entirely empiric based on frequency of urination and perceived volume. The assessment of gastrointestinal losses is similar in nature, whereas the losses caused by sweating are extremely difficult to estimate. The fluids used for replacement of losses should be isotonic balanced replacement solutions, because the fluids lost by these routes will be accompanied by electrolyte losses as well. If foals appear to be urinating and defecating normally and are not obviously sweating, then additional replacement fluids are not indicated. In those foals with increased losses associated with these systems one can add intermittent boluses of 10 to 20 mL/kg of replacement-type fluids to address the estimated loss. Monitoring of ongoing fluid therapy is very important and requires frequent assessment to

ensure that the goals for fluid therapy in the individual patient are being achieved and to avoid the development of adverse outcomes such as fluid overload. Repeated assessment of the clinical indicators of hydration status and perfusion is readily performed and extremely valuable in monitoring fluid therapy because normalization of these parameters is evidence of therapeutic efficacy.

INOTROPE AND VASOPRESSOR THERAPY

Hemodynamic factors, such as volume depletion, low cardiac output, or inappropriate vasodilation, lead to systemic hypotension, which may result in organ hypoperfusion through reductions in perfusion pressure with potentially deleterious consequences for the gastrointestinal and renal systems.[869] Tissue perfusion can be supported by the provision of IV fluids to address hypovolemia and improve venous return to the heart, providing adequate preload to support cardiac output, and fluid repletion is always the first intervention to be used in affected foals. Although many foals suffering from hypotension will respond well to IV fluid administration, a subset of these cases will be nonresponsive to fluids and will require additional blood pressure support. Treatment with inotropes and vasopressors may be indicated in these cases to increase cardiac contractility and afterload, respectively. Administration of these agents requires that the foal be in a hospital environment with close monitoring of hemodynamic function and the availability of electronic infusion pumps that can provide accurate CRIs. Blood pressure monitoring is absolutely essential, and this can be accomplished by direct (arterial catheter) or indirect (oscillometric tail cuff) means. In most situations the indirect approach will be used because the placement and maintenance of arterial catheters in foals can be extremely challenging. Although the data obtained from direct measurement are superior, the technical challenges render this approach impractical. Indirect techniques are not ideal because they can be affected by tail cuff size and placement and can be inaccurate, but they provide acceptable accuracy for clinical use, particularly in the monitoring of trends in MAP over time.[870,871]

It can be challenging to determine the point at which a patient requires additional blood pressure support. In human patients, exceeding the critical lower level for MAP, which is regarded as 60 to 65 mm Hg, is vital to maintain cerebral, coronary, and renal blood flow.[872] A major goal in the management of critically ill foals, therefore, is to maintain the MAP above 60 mm Hg, although this level does not necessarily indicate adequate tissue perfusion.[130,873,874] There is no apparent advantage to achieving higher MAP, and doing so may actually be deleterious because of altered distribution of blood flow resulting in decreased perfusion of some tissues.[718,872] It is critical to use other indicators of tissue perfusion, including heart rate, mentation, central venous oxygen tension, urine output, acid-base status, and trends in blood lactate concentration, because it has been suggested that neonatal foals may have a different physiologic response to hypotension than adult horses.[873] When implementing inotrope or vasopressor therapy it is advised to start at the lowest end of the dosage range (Table 20.18) and to monitor the response to therapy before increasing the dosage because it is impossible to predict the response of an individual patient. The short half-life of these agents means that the response to therapy can be assessed quickly, often in as little as 10 to 15 minutes, reinforcing the need for continual patient reevaluation.

TABLE **20.18 Dosages of Inotrope and Vasopressor Agents**

Agent	Dosage Range
Dopamine	3–20 μg/kg/min
Dobutamine	1–20 μg/kg/min
Norepinephrine	0.1–2 μg/kg/min
Vasopressin	0.1–2 mU/kg/min
Epinephrine	0.2–2 μg/kg/min

Adapted from Palmer J. Update on the management of neonatal sepsis in horses. *Vet Clin North Am Equine Pract*. 2014;30:317-336, vii; Dickey EJ, McKenzie H 3rd, Johnson A, et al. Use of pressor therapy in 34 hypotensive critically ill neonatal foals. *Aust Vet J*. 2010;88:472-477; Tennent-Brown, BS, Seahorn, JL. Inotrope and vasopressor therapy. In: Southwood LL, Wilkins PA, eds. *Equine Emergency and Critical Care Medicine*. Boca Raton, FL: CRC Press; 2015:675-684.

TABLE **20.19 Target Sites of Action of Inotropes and Vasopressors**

Agent	α_1	β_1	β_2	Dopaminergic	Vasopressin-1
Dopamine	+++	++++	++	+++++	0
Dobutamine	+	+++++	+++	0	0
Norepinephrine	+++++	+++	++	0	0
Vasopressin	0	0	0	0	+++++
Epinephrine	+++++	++++	+++	0	0
Phenylephrine	+++++	0	0	0	0

0 = no significant affinity; + through +++++ = minimal to maximal affinity.
Adapted from Pollard S, Edwin SB, Alaniz C. Vasopressor and inotropic management of patients with septic shock. *P T*. 2015;40:438-450.

Dobutamine is a positive inotrope commonly used to treat hypotension in neonatal foals, and it often represents the first-line drug of choice[30,875] (Table 20.19). The β-adrenoceptor agonist increases myocardial contractility, and therefore cardiac output, via its action on β_1-receptors. Concurrent stimulation of β_2-receptors may also produce peripheral and splanchnic vasodilation. This vasodilatory effect may be unproductive because it can result in decreases in systemic vascular resistance and MAP, which means that dobutamine may not be the ideal choice as a single agent in the treatment of fluid-refractory hypotension.[876] For this reason dobutamine is normally used in combination with a vasopressor in human patients.[877] The positive benefit of the vasodilatory effect of dobutamine is that it may improve splanchnic perfusion when used concurrently with vasopressors.[876] By increasing myocardial contractility dobutamine also increases myocardial oxygen demand, which can be problematic in the patient with already impaired oxygen delivery. The other concern with dobutamine is that because of its stimulation of β_1-receptors it can cause tachycardia and arrhythmias, especially at higher doses.[877]

Dopamine was traditionally used as a first-line agent in human and veterinary medicine because it exhibits dose-dependent stimulation of a wide variety of receptors, with dopaminergic activity at low doses, β_1 and β_2 activity at moderate doses, and α_1 activity at high doses. Through the stimulation of dopaminergic receptors low-dose dopamine increases renal and splanchnic perfusion, although this has not

proven to be beneficial in preventing organ failure in human patients.[878] At higher doses dopamine increases cardiac contractility, vasoconstriction, and heart rate, all of which tend to increase MAP.[877] Unfortunately the vasopressor response to dopamine is less pronounced and less consistent than that achieved with norepinephrine.[879] When the inotropic effects of dopamine were compared with dobutamine in hypotensive human neonates, dopamine was less effective in restoring blood flow.[880] At high doses (greater than 20 μg/kg/min) dopamine can cause pulmonary venous vasoconstriction and reduced splanchnic perfusion.[30] For all of these reasons dopamine is now much less commonly used in human or equine critical care.

Norepinephrine is primarily an α-adrenergic receptor agonist, but it also has some limited β_1 and β_2 effects. Norepinephrine induces arterial and venous vasoconstriction, resulting in increases in MAP, effective circulating blood volume, and venous return and preload, with minimal increase of heart rate or stroke volume.[881] Despite historic concerns regarding potential splanchnic hypoperfusion, norepinephrine is now regarded as the first-line pressor agent in hypotensive human patients.[877] Current human guidelines recommended the administration of norepinephrine as a sole agent initially, with dobutamine added if hypoperfusion persists despite adequate MAP.[175] Norepinephrine has been reported to be effective in increasing MAP and urine output in hypotensive foals that were nonresponsive to both fluid administration and dobutamine therapy.[130] Another study compared the effects of norepinephrine alone and the combination of norepinephrine and dobutamine with a control treatment of saline infusion.[882] Both norepinephrine and norepinephrine-dobutamine increased arterial blood pressure and systemic vascular resistance and decreased heart rate and cardiac index compared with saline, but no effect was observed on renal function. Norepinephrine-dobutamine did result in higher arterial pressures than norepinephrine alone. This combination therapy approach is now commonly used for the treatment of foals with refractory hypotension.

In recent years in human medicine, AVP (antidiuretic hormone) has gained popularity in managing vasodilatory shock and cardiac arrest despite concerns regarding potential splanchnic hypoperfusion at higher dosages.[883] This concern regarding splanchnic hypoperfusion deserves consideration because this effect was observed at high doses of vasopressin in a study that examined the effects of dobutamine, norepinephrine, and vasopressin in healthy anesthetized foals with induced hypotension.[875] Although vasopressin has a myriad of effects involving numerous receptors and pathways, it controls blood pressure primarily by vasoconstriction via its actions on the vasopressin-1 receptor.[884] Vasopressin has stronger vasoconstrictive effects on large arterioles than norepinephrine, which may explain its effectiveness even in patients refractory to standard catecholamine therapy.[885] Vasopressin also has been shown to have a positive interaction with hydrocortisone therapy in the treatment of refractory shock in humans.[175] When used as a treatment for vasodilatory shock vasopressin has been shown to decrease heart rate, improve overall hemodynamics, and lead to a reduction in inotrope requirement.[886] A recent human meta-analysis determined that vasopressin therapy in human patients in septic shock was safe, useful in weaning patients off of catecholamines, and associated with decreased mortality.[887] The consensus in human medicine appears to be that vasopressin is a reasonable second-line choice as a vasopressor in patients not exhibiting a positive response to norepinephrine therapy.[877]

There are a few anecdotal reports of the use of vasopressin as a second-line vasopressor in equine critical care, with one reference, by Collins et al., indicating that vasopressin has begun to be used as the first-line therapy for foals with fluid-refractory hypotension.[30,718,888] At this time there is only one published report regarding vasopressin therapy in clinically ill foals.[889] In that report the effects of norepinephrine or vasopressin on cardiovascular responses and fluid balance were compared in a group of 34 foals with hypotension refractory to both fluid therapy and dobutamine. Eighteen foals were treated with vasopressin, whereas 16 foals received norepinephrine. Six of the foals in the vasopressin group had failed to respond to norepinephrine therapy, which was withdrawn before initiation of vasopressin therapy. The severity of illness was pronounced and similar between groups, with a mean lactate of 10.5 ± 4.4 mmol/L in the vasopressin group and 9.6 ± 4.6 mmol/L in the norepinephrine group. The two groups also had similar sepsis scores at admission, with a mean of 15.9 ± 6.1 in the vasopressin group and 16.1 ± 4.5 in the norepinephrine group. Vasopressin administration was associated with a significant increase in MAP and in urine output as well as a significant decrease in heart rate, whereas norepinephrine administration was associated with a significant increase in MAP. The overall survival rate in this study was only 38%, likely reflecting the severe systemic disease present in this population of foals evidenced by their admission sepsis scores and lactate concentrations, and was consistent with a previous report from the same institution, in which the survival rate for foals presenting with lactate concentrations greater than 6 mmol/L was reported to be only 40%.[126] The authors of this report also describe increased use of vasopressin as a first-line therapy for foals with refractory hypotension.[889]

Other pressor agents include epinephrine and phenylephrine, both of which are strong adrenergic receptor agonists and can have negative effects on splanchnic and renal perfusion.[890] Epinephrine is a catecholamine with potent activity at β-adrenergic and α-adrenergic receptors. Epinephrine increases MAP by increasing cardiac output and vascular tone, and in human patients it is regarded as the first alternative to the combination of norepinephrine and dobutamine.[877] However, epinephrine has been associated with hyperglycemia, hypokalemia, lipolysis, tachycardia, decreased splanchnic perfusion, increased lactate concentration, and increased platelet aggregation.[30,877] Phenylephrine has potent α_1 activity but has no cardiac effects, mediating its effects through the constriction of the peripheral arterial vasculature.[877] Phenylephrine is primarily of utility in patients with arrhythmias resulting from dobutamine and/or norepinephrine administration and has little application in equine neonatal critical care.

Although not a vasopressor per se, low-dose hydrocortisone therapy has been shown to improve the response to vasopressors and shorten the duration of vasopressor therapy in human shock patients.[891,892] The mechanisms responsible for this effect are unclear, but do not appear to be associated with primary corticosteroid insufficiency. Rather, it appears that corticosteroid therapy directly results in improved vasopressor responsiveness of peripheral vessels, because hydrocortisone raises blood volume, increases vascular tone, and enhances endothelial reactivity to vasopressors.[893] A thorough discussion of hydrocortisone replacement therapy can be found in the previous section Endocrine Disorders.

ANTIINFLAMMATORY AND ANALGESIC THERAPY

The indications for antiinflammatory therapy in the foal are numerous. Most often these compounds are used to regulate fever and local inflammation, reducing patient discomfort, but there are situations in which they are required for the control of systemic inflammation as well. The primary class of antiinflammatories used in foals is NSAIDs, which consists of drugs inhibiting arachidonic acid synthesis via COX inhibition. These drugs typically exhibit antipyretic, antiinflammatory, and analgesic effects.[894] There are also several drugs in the NSAID group that have effects on pathways other than arachidonic acid metabolism. The second class of antiinflammatory drugs is the corticosteroids (steroidal antiinflammatory drugs [SAIDs]). These drugs have potent dose-dependent antiinflammatory and immunosuppressive effects, but typically have little antipyretic or analgesic activity.[665] In situations where the primary goal is analgesia one can use NSAIDs, but opioid drugs provide analgesia without the concerns regarding gastrointestinal and renal toxicity associated with many NSAIDs. Although not commonly used in very young foals, alternative analgesics such as ketamine and lidocaine may be beneficial in managing older foals with severe, refractory pain.

The NSAIDs include nonspecific COX inhibitors such as phenylbutazone and flunixin meglumine, more selective COX-2 inhibitors such as ketoprofen, and COX-2–specific drugs like meloxicam and firocoxib. Nonspecific COX inhibition can be associated with side effects including gastrointestinal ulceration and renal injury.[895] Phenylbutazone has been associated experimentally and clinically with toxicity in foals[895,896] and appears to have a narrow therapeutic index in this population. In addition, it can be difficult to administer appropriate dosages of phenylbutazone to foals because of their small size and the composition of the forms of phenylbutazone that are available. For all of these reasons phenylbutazone is rarely used in foals. Flunixin meglumine, however, when given parenterally at appropriate dosages, has been demonstrated to be safe in foals, even when administered for several weeks,[897,898] and this is supported by clinical experience. Flunixin meglumine is primarily used in foals with severe systemic inflammation, severe discomfort, or persistent fevers. It is important to note that the metabolism and elimination of NSAIDs can be impaired in neonatal foals, potentially requiring increases in dosing or prolongation of the dosing interval.[899-901] For these reasons it is recommended that the nonspecific COX inhibitors be used with caution in the clinically ill neonatal foal, particularly in foals with severe systemic inflammation, hypovolemia, or the potential for gastric ulceration.

In theory, drugs like ketoprofen and carprofen should be safer for use in foals because they are more COX-2 selective than phenylbutazone and flunixin. Although there is no peer-reviewed evidence to support the claim of reduced toxicity, both of these drugs have been used in foals with apparent safety.[902,903] The pharmacokinetics of ketoprofen has been studied in foals, and the dosage and treatment intervals recommended in that report are both greater than those for adult horses[899] (Table 20.20). Ibuprofen has also been studied in foals and was found to be safe when administered for up to 6 days.[904] There are no published reports of the pharmacokinetics of carprofen in foals.

The mostly highly COX-2–specific NSAIDs that have been studied in horses and foals are meloxicam and firocoxib, with firocoxib demonstrating the greatest degree of COX-2 specificity. Firocoxib has favorable pharmacokinetics and is reported to be safe in foals when administered by the oral or IV routes.[905,906] Firocoxib has been demonstrated to be effective for musculoskeletal and visceral pain in horses,[907,908] but the analgesic efficacy of firocoxib has not been assessed in foals. Anecdotally it seems that firocoxib may be more effective for musculoskeletal pain than for visceral pain, but this has not been scientifically evaluated. Meloxicam is marketed for equine use in Europe but is currently only labeled for small-animal use in the United States. Meloxicam pharmacokinetics and safety have been evaluated in foals,[909] and no evidence of gastrointestinal or renal toxicity was detected. Interestingly, meloxicam was eliminated more rapidly in foals than in adult horses, which is quite different from what has been found with other NSAIDs. For that reason the authors of that study recommended that meloxicam be dosed every 12 hours in foals, rather than 24 hours.[909]

In addition to the COX inhibitors there are several antiinflammatory drugs that have been used in foals and may have some application. Dipyrone (metamizole) has been widely used in horses as an analgesic, antipyretic, and antispasmodic drug and clinically appears to be safe when used as a single dose in foals with abdominal pain. Acetaminophen has been used very little in horses because of concerns about the potential for hepatotoxicity, but recent reports suggest that this drug may be both safe and effective as an analgesic.[910] Although dipyrone and acetaminophen have some COX inhibitory effects, that pathway is not considered to be primarily responsible for the drugs' therapeutic effects.[911,912] The current hypothesis is that these drugs act primarily through other pathways, including the serotonergic, opioid, and cannabinoid systems.[913,914] Dipyrone or acetaminophen are sometimes combined with more traditional NSAIDs to achieve enhanced analgesic effects,[915] but there are limited reports regarding this approach in the horse.[912]

In addition to the NSAIDs there are other drugs that may exhibit antiinflammatory effects, such as pentoxifylline and DMSO. Pentoxifylline is a phosphodiesterase inhibitor that has been shown to have wide-ranging antiinflammatory effects and is frequently used in adult horses suffering from severe systemic inflammation.[916] Although the pharmacokinetics of pentoxifylline are not known in foals, it has been used in foals at adult dosages.[185] DMSO is a free radical scavenger that is widely used in horses and foals suffering from severe localized or systemic inflammation, despite a relative lack of evidence of efficacy.[917] When administered intravenously at an appropriate dilution DMSO appears to be safe and is frequently administered to foals suspected to be suffering from NE.[185] Although not a traditional antiinflammatory, the antimediator polymyxin B is sometimes used in foals with SIRS because it has the capability of binding circulating endotoxin and inhibiting the upregulation of the inflammatory response.[917,918] A recent study performed in healthy foals with experimentally induced endotoxemia found that administration of polymyxin B at 6000 U/kg IV every 8 hours attenuated some of the clinical and clinicopathologic effects of endotoxemia.[919] Polymyxin B is potentially nephrotoxic, however, so caution is indicated when considering the utilization of this therapy in the critically ill, hypovolemic foal.

The administration of SAIDs to foals is not frequently indicated and should be restricted to clinical syndromes in

TABLE **20.20 Dosages of Antiinflammatory and Analgesic Medications Used in Foals**

Drug	Dosage	Route	Frequency (h)
Aspirin	10–100 mg/kg	PO	24
Butorphanol	0.1 mg/kg (up to 8 weeks of age)	IV, IM	PRN
Carprofen	0.7 mg/kg (adults)	PO	24
Dexamethasone	0.01–0.02 mg/kg 0.05–0.2 mg/kg	IM, IV, PO	24–48
Dimethyl sulfoxide	0.5–1.0 mg/kg as a 10% solution over 30–60 min	IV	12–24
Firocoxib	0.1 mg/kg 0.09 mg/kg	PO IV	24
Flunixin	0.25–0.5 mg/kg 1.0 mg/kg	IV, PO	8 12–24
Hydrocortisone	0.17–0.67 mg/kg (total dose 1–4 mg/kg/day)	IV	4–6
Ibuprofen	25 mg/kg	PO	12
Ketamine	0.4–1.2 mg/kg/h	IV	CRI
Ketoprofen	2.2 mg/kg 3.3 mg/kg (<24 h)	IV	24
Lidocaine	1.3 mg/kg loading 0.05 mg/kg/min CRI	IV	CRI
Meloxicam	0.6 mg/kg	PO	12
Methylprednisolone sodium succinate	1 mg/kg	IM, IV (slow)	12–24
Phenylbutazone	1.1–2.2 mg/kg	IV, PO	12–24
Polymyxin B	6000 U/kg in saline	IV	8
Prednisolone sodium succinate	0.25–2.5 mg/kg 0.8–5.0 mg/kg	IV	6, PRN
Prednisolone	1–2.2 mg/kg	PO	12–24
Pentoxifylline	10 mg/kg (adults)	PO	12
Tramadol	3 mg/kg	IV	Not defined

CRI, Continuous rate infusion; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally; *PRN,* as needed.

which overwhelming localized or systemic inflammation must be controlled. In foals with interstitial pneumonia, ALI, or ARDS, SAID therapy is critical in the downregulation of pulmonary inflammation and restoration of pulmonary function and represents the primary pharmacologic therapy for these conditions.[324] This syndrome is discussed in detail in the previous section Respiratory Disorders. Severely ill foals can suffer from CIRCI, which is associated with poor clinical outcomes.[667] This syndrome is discussed in detail in the previous section Immunologic Disorders. Cortisol replacement therapy using small doses of hydrocortisone administered frequently may provide antiinflammatory and physiologic benefits in CIRCI-affected foals and does not appear to interfere with the functioning of the innate immune system.[313,315]

If the primary goal of therapy is analgesia independent of antiinflammatory effects there are a number of alternative therapies available. For short-term analgesia the α_2-adrenergic agonists, such as xylazine and detomidine, are commonly used because they are very effective in controlling severe pain. The limitations of the α_2 drugs are profound sedation and decreases in gastrointestinal motility.[920] Alternatively, one could consider the use of an opioid agonist or agonist/antagonist. Butorphanol, an opioid agonist/antagonist, is the most commonly used drug because it is readily available and safe to administer. The limitations of butorphanol are primarily that it causes substantial sedation and only lasts for a short period of time when given as a bolus. Administering butorphanol as a CRI allows for a much more stable analgesic effect and may lessen the sedative effects. Opioid agonists, such as tramadol and fentanyl, are rarely used in foals but could have utility in managing chronic, severe musculoskeletal pain.[921,922] Lidocaine is a local anesthetic, but when administered systemically as a CRI it can provide effective analgesia, especially for visceral pain. It is not associated with sedative effects but can cause neurologic signs if given at an excessive rate. In a recent study lidocaine administration to foals achieved lower systemic concentrations than in adult horses but appeared to be safe and clinically effective.[923] Ketamine is a dissociative agent most commonly used for induction and/or maintenance of general anesthesia, but it has been reported to have analgesic effects when administered at lower doses as a CRI.[920]

NUTRITIONAL SUPPORT OF THE FOAL

Developing an appropriate nutritional plan when treating a sick foal can be challenging because one must ensure that the foal has adequate energy and nutrients for basal metabolism and immune function and ideally for growth as well. This should be a straightforward process in which the number of calories required by the foal is calculated, followed by a determination of the volume of the appropriate nutrient-containing solution and the administration of this nutritional source by

the appropriate route. Unfortunately the energy requirements for sick foals are not well understood and will vary among patients. Additionally, the ability of the foal to appropriately metabolize the nutrients provided is not guaranteed because both age and degree of illness impact the foal's ability to produce metabolic hormones as well as the ability of the tissues to respond to hormonal stimulation. Another difficulty arises because the energy content of mare's milk cannot be easily determined, and the exact formulation of substitutes such as artificial milk replacer is not always known. Ultimately the burden falls on the clinician to formulate the best plan possible with the information at hand and to ensure that the foal is closely monitored. This will ensure that the goals of the nutritional plan are met while the risk of complications is minimized.

The foal's nutritional requirements and dietary composition change substantially during the transition from neonate to weanling, requiring careful consideration of the foal's stage of growth when formulating a nutritional plan. At birth the foal transitions from a continuous supply of nutrients provided by the dam via the placenta to intermittent absorption of ingested nutrients. At the same time the metabolism of the neonate is no longer able to depend on the maternal glucose concentration to maintain normoglycemia, and the pancreas assumes responsibility for regulating glucose homeostasis. These dramatic alterations in energy metabolism do not always occur smoothly, and the foal possesses limited energy reserves in the form of glycogen and fat. The result is that hypoglycemia occurs frequently in even the normal neonatal foal, and clinically ill foals are at risk of profound hypoglycemia if deprived of energy intake for even a few hours.

The caloric requirements of the normal foal are sizable; they need to support not only their high basal metabolic needs but also maintain a rate of growth of as much as 2.5% of body weight per day in the neonatal period. This means that the neonates caloric requirement is as great as 150 kilocalories per kg body weight per day (kcal/kg/day) but decreases gradually to around 120 kcal/kg per day at 3 weeks of age and then to 80 to 100 kcal/kg per day by 1 to 2 months of age.[924,925] A more recent study has suggested that actual energy requirements of foals from 2 to 6 months of age may be 10% to 20% less than these values.[926] Because these measurements are given in terms of foal body weight, it is important to realize that as the energy requirement per kilogram is decreasing the foal's body weight is increasing; thus, the total caloric requirement increases with age. The initial energy source for the foal is mare's milk, which has substantially greater lactose content than cow's milk, with lower milk fat content. On a dry matter basis, mare's milk averages about 64%, 22%, and 13% sugar, protein, and fat, respectively, compared with 38%, 26%, and 30% sugar, protein, and fat, respectively, for cow's milk. Mare's milk therefore derives most of its energy content from carbohydrates, and an appropriate endogenous production of insulin by the pancreatic β cells is required for the foal to metabolize and utilize these carbohydrates appropriately.

Maturation of pancreatic β-cell function occurs very late in gestation in the fetal foal and is dependent on the normal rise in fetal circulating cortisol concentration, which occurs in the final days of gestation.[927] This preparturient cortisol rise is critical for many aspects of readying the foal for birth, both in terms of endocrine function as well as respiratory and cardiovascular function. Following birth there is a gradual maturation of the endocrine response to ingested carbohydrates. It has been shown that normal newborn pony foals demonstrated impaired glucose clearance following the administration of exogenous glucose on the first day of life, suggesting a degree of insulin resistance.[928] By 10 days of age foals demonstrate increased rates of glucose clearance, but this response remains lower than that seen in normal adult equines. This gradual maturation may be an appropriate response to changes in the composition of mare's milk, because colostrum contains little lactose, and in the volume of milk ingested, which is less on the first day of life than on subsequent days.[924,928]

Starting as early as the second day of life foals will begin ingesting small amounts of hay, grass, and grain while at the same time they are ingesting maternal feces, which likely provides the initial microbial flora required to support digestion of these feeds. It is unlikely that grain and roughage are thoroughly digested until several weeks of age, at which point the foal begins the gradual transition from a milk-based diet to a forage-based diet. The amount of milk produced by the mare peaks at around 2 months of lactation and then begins a steady decline, which continues until the time of weaning, necessitating that the foal begin relying on ingestion of solid food for an increasing proportion of its nutritional requirements. At the same time, the foal's hindgut function is increasing and is likely fully functional by around 3 to 4 months of age. By the age of 6 months the foal is receiving less than 30% of the total nutritional requirement in the form of milk, which allows for a fairly easy dietary transition when weaning occurs. As the foal's hindgut function increases, there is a corollary shift in the primary energy substrate from carbohydrates absorbed in the small intestine to volatile fatty acids absorbed from the large intestine.

When evaluating the sick neonatal foal one must always remember that the disease processes at work in the foal may have had their origins in utero. Maternal illness, maternal malnutrition, maternal toxin exposure, placentitis, and placental insufficiency all have the potential to profoundly influence the development and maturation of fetal metabolism. Studies investigating the role of a "restricted" uterine environment on fetal development have demonstrated lifelong impairment of growth and development in affected foals.[929] Conversely, the provision of a "luxurious" in utero environment can lead to enhanced growth rates out to 3 years of age.[929] The influence of maternal diet is important, because a diet high in soluble carbohydrates fed to the mare in late gestation contributed to a decrease in insulin sensitivity of the foals at 160 days of age.[930] It is clear that there is a potential for lifelong effects on metabolic function secondary to this "prenatal programming" effect, potentially contributing to the development of metabolic disease later in life.[931] This prenatal programming may affect the neonatal foal's ability to appropriately metabolize nutrients in the clinical setting, with foals from a compromised placental environment potentially exhibiting insulin resistance and carbohydrate intolerance.

As previously discussed the late gestation rise in fetal cortisol is critical in the final maturation of energy metabolism, and many foals delivered prematurely fail to undergo this rise in fetal cortisol concentration; therefore, they are unable to respond normally to the changes in metabolism that occur after birth. Hypoglycemia, complicated by decreased endogenous energy reserves and the impairment of nursing caused by concurrent weakness, depression, and/or difficulty standing, is a common problem in these foals. Following the successful delivery of nutrients by the enteral or parenteral routes

these foals are likely to be intolerant of carbohydrates, which is caused by impaired endogenous insulin production, and they may suffer profound hyperglycemia. Foals suffering from systemic inflammation, such as that associated with septicemia, may also exhibit hyperglycemia caused by insulin resistance and carbohydrate intolerance. Management of these foals may require lipid-containing parenteral nutrition solutions and/or the administration of exogenous insulin to achieve adequate caloric input.

Attempting to determine the true caloric needs of the clinically ill foal is one of the greatest challenges in designing a nutritional strategy. Historically it was believed that critical illness created a "hypermetabolic" situation in which the patient had increased energy needs caused by increased tissue energy consumption. The energy requirements of the sick foal do not appear to be as great as once was thought,[932] however, because there is a reduction in the overall metabolic rate from a decrease in activity level in combination with a temporary reduction in growth rate. Indirect calorimetry testing of clinically ill neonatal foals has shown that their resting energy requirement is only 45 to 50 kcal/kg per day, which is one third of the energy requirement for growing, active, normal foals.[933,934] As these foals recover, their energy requirements gradually increase to approximately 65 to 70 kcal/kg per day, which is similar to the energy requirements of age-matched control foals.[934]

When managing the critically ill neonatal foal it may be preferable to pursue a hypocaloric approach in which one endeavors to prevent the foal from entering a severely catabolic state while accepting that all of the nutritional needs of the patient may not be met.[935,936] This approach addresses the fact that aggressive nutritional support can result in overfeeding, the risks of which may easily outweigh the possible benefits of providing nutritional support. Excessive carbohydrate administration will lead to an increased generation of carbon dioxide and can worsen hypercapnia in foals with compromised respiratory function. Excessive carbohydrate delivery will also cause hyperglycemia, which is considered to be a proinflammatory stimulus and has been associated with worsening of outcome in human critical illness.[937,938] Overfeeding of protein will result in increased protein catabolism and can result in the potentiation and/or development of azotemia.[938] The excessive administration of lipids may result in hypertriglyceridemia.[719] In contrast to the risks of overfeeding, there is little evidence in human patients that short-term (several days) hypocaloric nutritional support results in worsened outcomes compared with regimens designed to meet the patient's metabolic needs.[935,936] There is some evidence to suggest that this approach, especially regarding the maintenance of appropriate control of blood glucose levels, is associated with decreased rates of complications and improved outcomes.[937]

The first step in the development of a nutritional plan involves selection of the route of nutrient delivery. Providing nutritional support by the enteral route is generally preferred for two reasons. First, this is the most natural and physiologically sound means of nutrient delivery. Second, the intestinal mucosa is partially dependent on the products of digestion for energy and nutrients. A thorough evaluation of gastrointestinal function is needed before the institution of enteral nutritional support. This will include abdominal auscultation, checking for gastric reflux, and possibly abdominal radiographs and ultrasonographic examination for the evaluation of bowel dimensions and motility. Foals with evidence of gastrointestinal dysfunction, such as gastric reflux, bowel distention, increased bowel wall thickness, and ileus, are unlikely to tolerate enteral feeding. A conservative approach to enteral feeding is also indicated for premature or immature foals in which there may be incomplete development of the gastrointestinal tract. Foals with perinatal asphyxia syndrome may be intolerant of enteral feeding caused by ileus and dysfunction as a result of intestinal ischemic injury.

Mare's milk is the preferred substrate for enteral feeding. It is highly digestible and obviously provides the correct balance of nutrients for normal growth and development. Commercial mare's milk replacers can be used, but it should be recognized that these products are bovine in origin and have lower digestibility compared with mare's milk. This increases the risk of intestinal dysfunction associated with enteral feeding. Semiskimmed (2% fat) cow's milk to which 20 g/L dextrose (equivalent to 40 mL of 50% dextrose solution per liter) has been added can be used if mare's milk or mare's milk replacer is unavailable. Foals that are unable to nurse the mare may be fed through a bottle, bowl, or nasogastric feeding tube. Many sick, recumbent foals have a weak and/or uncoordinated suckle reflex, and therefore, milk should be administered through a feeding tube.

Use of a small-bore, indwelling tube and feeding of small volumes at frequent intervals (e.g., every 20 minutes) is preferred over repeated passage of a nasogastric tube at 1- to 2-hour intervals. Large-bolus feedings may overwhelm digestive capacity, and repeated passage of a stomach tube is an unnecessary stress on the foal. Another advantage of small-bore indwelling tubes is that they do not interfere with voluntary feed and water intake. Therefore the tube may be left in place as the foal is transitioned to feeding from the mare. The feeding tube should be inserted with the foal in sternal recumbency, and correct placement within the esophagus should be confirmed by radiography or endoscopy. The tube may be fastened to the external nares by sutures. At each feeding, it is important to check that the tube is still in place and that there is no reflux. The foal should be in sternal recumbency or standing when it is fed. Milk should be administered by gravity flow followed by a small amount of clean water to flush the tube. The tube should be capped between feedings to prevent aspiration of air. Feeding tubes should be replaced every 1 to 2 days to reduce risk of gastrointestinal tract infection.

A suggested initial rate of milk delivery is 2 to 3 mL/kg body weight per hour, or 100 to 150 mL/h for a 50-kg foal (Table 20.21). This will provide 2.4 to 3.6 L of milk to a 50-kg foal during the first 24 hours of enteral support. Dextrose-containing fluids can be administered IV to provide additional calories during the transition to an adequate level of enteral feeding. The feeding rate can be gradually increased over the next 2 to 3 days (e.g., increase to 4–5 mL/kg/h on day 1 and then to 6–8 mL/kg/h on day 3), which represents a total daily intake of 10% to 15% of body weight. Simultaneously, IV caloric support (dextrose) can be gradually withdrawn. This feeding level will likely meet the resting energy requirements of hospitalized foals. Depending on the rate of clinical improvement and the length of hospitalization, it may be possible to increase the volume of feeding to 20% to 22% body weight per day, which approximates the milk intake of healthy neonatal foals. Clinical monitoring should include frequent assessments of gastrointestinal function, including gastric reflux, intestinal sounds, abdominal distention, and quantity and quality of feces. Gastric reflux, bloating, colic, diarrhea,

TABLE **20.21 Feeding Recommendations for Neonatal and Growing Foals**

Foal Age (Days)	Energy Requirement	Volume of Mare's Milk or Milk Replacer	Percentage of Body Weight Fed
0–1	50–150 kcal/kg/day	2–3 mL/kg/h	5–7%
2–3	100–150 kcal/kg/day	4–5 mL/kg/h	10–12%
4–7	150 kcal/kg/day	6–8 mL/kg/h	14–20%
8–30	120 kcal/kg/day	9–10 mL/kg/h	22%
30 to weaning	80–100 kcal/kg/day	Gradually decreasing and replaced with solid feed	—

or constipation can indicate intolerance to enteral feeding and the need for adjustments to the feeding program. This may involve a decrease in the volume or frequency of enteral feedings. In some situations there may be concerns regarding the ability of the foal's gastrointestinal tract to digest and absorb lactose, as in rotaviral infections during which production of lactase by the enterocytes is likely impaired. In these situations lactase enzyme can be added to the milk or milk replacer before feeding at the rate of 9000 U (one tablet) per feeding. Additional volumes of enteral fluid may be required in foals with diarrhea, and a simple balanced isotonic enteral solution can be formulated by adding 5.6 g of table salt (NaCl), 0.6 g of Lite Salt (50% NaCl, 50% KCl), and 3.4 g of baking soda ($NaHCO_3$) per liter of water.[939]

It is generally preferred to support foals via the enteral route,[940,941] both because this is the most natural and physiologically desirable route and because the epithelial cells lining the intestine are partially dependent on the products of digestion for energy and nutrients. Unfortunately there are a variety of situations in which a foal may be unable to receive enteral nutrition or is unable to tolerate the volume of enteral nutrition required to support basal metabolism and growth. These range from the critically ill neonate with gastrointestinal complications to the suckling foal with severe enterocolitis. The rapid institution of parenteral nutrition can aid in preventing the development of protein/calorie malnutrition and substantial energy deficits. The limitations of parenteral nutritional support are primarily caused by the expense of this therapy and the risk of secondary complications. These complications may include hyperglycemia, hypertriglyceridemia, thrombophlebitis, and an increased risk of bloodstream infections.

The primary goal of parenteral nutrition, as with any type of nutritional support, is to ensure that the patient is supplied with adequate calories to support basal metabolism at a minimum and ideally to provide additional support to allow for ongoing growth. A reasonable initial goal for parenteral nutrition administration in the foal is 30 to 40 kcal/kg per day. Although this level of caloric support does not fully meet the theoretic energy requirements of the healthy neonate, it comes close to meeting the resting energy requirement in hospitalized foals.[924,933] In this situation parenteral nutrition is used purely as a temporary support to prevent the foal from entering into a severely catabolic state, in which protein catabolism would increase and use amino acids for energy production.[720,924,942] Failure to provide adequate nutritional support may also have a substantial negative influence on the immune response.[942-944] Short-term parenteral supplementation (less than 24 hours) may consist of IV carbohydrate solutions and does not require the patient to receive a balanced nutritional source consisting of carbohydrates, amino acids, and lipids, but if parenteral nutrition is expected to be administered for a longer period then a more complete formula should be used.

Carbohydrate-containing solutions represent the simplest means of providing IV caloric support to foals. A solution containing 5% dextrose can be used, and there are several options available including D5W, LRS with 5% dextrose, 0.45% saline with 5% dextrose, Normosol-M with 5% dextrose (Hospira, Lake Forest, IL), and Plasma-Lyte 56 with 5% dextrose (Baxter Healthcare Corp., Deerfield, IL). Fluids containing dextrose should not be used for initial fluid resuscitation because this will almost certainly result in the delivery of excessive amounts of dextrose to a foal with any degree of dehydration, resulting in profound hyperglycemia. Following initial fluid resuscitation, solutions containing electrolytes as well as dextrose (0.45% saline with 5% dextrose, Normosol-M with 5% dextrose, and Plasma-Lyte 56 with 5% dextrose) may be used as the primary fluids for maintenance therapy in foals with minimal ongoing fluid losses. D5W is not an ideal choice as a maintenance solution because of the absence of electrolytes and is primarily useful in providing free water to patients suffering from hyperosmolar conditions. The caloric content of a 5% dextrose solution is 0.17 kcal/mL, so an infusion rate of 10 mL/kg per hour would be required to deliver approximately 40 kcal/kg per day (0.17 kcal/kg/h × 24 h/day = 41 kcal/kg/day). This rate of infusion is over twice that considered to be a maintenance rate for a neonatal foal. In addition, care must always be taken when adjusting the infusion rates of 5% dextrose-containing solutions in response to changes in the patient's fluid status to ensure that excessive amounts of dextrose are not infused, especially in premature or very sick foals that are likely to be poorly tolerant of dextrose infusions.

Alternatively, a 50% dextrose solution can be delivered without further dilution using an infusion pump, as long as additional isotonic fluids are being administered concurrently to provide dilution and avoid endothelial injury caused by the hypertonic nature of this solution. Use of 50% dextrose solution should be avoided if an infusion pump is not available because it is very easy to inadvertently administer an excessive amount of dextrose, leading to hyperglycemia. The caloric content of 50% dextrose solution is 1.7 kcal/mL, so an infusion rate of 1 mL/kg per hour of this solution will deliver approximately 40 kcal/kg per day (1.7 kcal/kg/h × 24 h/day = 41 kcal/kg/day). This low rate of infusion means that the primary fluid needs of the patient can be met with a dextrose-free isotonic electrolyte-containing fluid, the infusion rate of which can be altered in response to changes in patient fluid status without concerns related to the requirements of the nutritional plan. At the end of the first 24 hours of treatment the fluid therapy plan and nutritional plan should be revisited to determine whether the patient can begin to rely on enteral fluid and nutritional intake or if continued parenteral therapy is required. Because dextrose-containing fluids are a very incomplete nutritional source, they should not be used as the primary nutritional source for more than 24 hours. Continued

parenteral nutritional support will require the formulation of a more complete solution that provides amino acids and possibly lipids.

One important aspect of providing longer term (over 24 hours) parenteral nutrition to foals is the inclusion of a protein source. The metabolic response to injury and sepsis is to increase protein degradation in muscle tissue. This catabolic response can be reduced by supplying a source of nitrogen or by increasing energy intake. The recommended ratio for nonprotein calories to nitrogen is 100 to 200 nonprotein calories per gram of nitrogen.[945] The inclusion of lipids in the parenteral nutrition formulation allows for the provision of a larger number of calories per unit volume compared with solutions containing only dextrose. Another advantage of lipid emulsions is that they are isotonic, so they moderate the hypertonicity of the parenteral nutrition formulation and potentially decrease the risk of thrombophlebitis. Unfortunately, formulating parenteral nutrition solutions with lipids increases the cost of the solution and may increase the risk of complications.[946] Hyperlipidemia can occur in association with lipid administration to foals but does not appear to result in adverse effects.[719,946] Lipid emulsions are prone to contamination and promote bacterial growth. Because of these risks the IV lines through which lipid-containing solutions are administered should be changed daily, substantially increasing client costs. In a recent report the use of lipid-containing parenteral nutrition solutions allowed for the provision of 40 to 92 kcal/kg per day (mean = 63 kcal/kg/day) to foals, as opposed to only 25 to 66 kcal/kg per day (mean = 41 kcal/kg/day) with a dextrose-based solution.[719]

There are two basic approaches to the formulation of parenteral nutrition to foals. The first approach involves the exact determination of the anticipated metabolic needs of the patient, followed by the development of a formulation that will meet all of these needs in a fairly precise manner, using a mixture of dextrose, amino acids, and lipids. This approach is fairly complex and is best performed using a computerized spreadsheet to aid in performing the various calculations. The second approach is more practical and consists of using two basic parenteral nutrition formulas (Table 20.22). One of these solutions is intended for short-term use and consists only of 50% dextrose and 8.5% amino acid solutions (Solution I). The second solution incorporates a lipid energy source and is preferred for long-term administration or for administration to foals that are poorly tolerant of infused dextrose (Solution II). Solution I is formulated using 2000 mL of 50% dextrose (Dextrose 50%, Baxter Healthcare Corp., Clintec Nutrition Division, Deerfield, IL) and 2000 mL of 8.5% amino acids (Travasol 8.5%, Baxter Healthcare Corp., Clintec Nutrition Division, Deerfield, IL), whereas Solution II is formulated with 1500 mL of 50% dextrose, 500 mL of 20% lipids (Intralipid 20%, Baxter Healthcare Corp., Clintec Nutrition Division, Deerfield, IL), and 2000 mL of 8.5% amino acids.[719] The caloric density of these solutions is 1.02 kcal/mL for Solution I and 1.08 kcal/mL for Solution II. The ratio of nonprotein calories to nitrogen is 125 nonprotein calories per gram of nitrogen (NPC/gN) for Solution I and 131 NPC/gN for Solution II. An easy-to-use, shelf-stable multichamber bag preparation identical to Solution I is manufactured for human use, and it is cost-effective and practical for use in foals (Clinimix 4.25/25 sulfite-free [4.25% amino acid in 25% dextrose] injection, Baxter Healthcare Corp., Clintec Nutrition Division, Deerfield, IL).

TABLE **20.22 Formulation of Parenteral Nutrition Solutions**

Formula	Composition	Caloric Density (kcal/mL)	Nonprotein Calories/gN
1	1500 mL 50% dextrose, 1500 mL 8.5% amino acids	1.02	125
2	1500 mL 50% dextrose, 500 mL 20% lipids, 2000 mL 8.5% amino acids	1.08	131

An electronic infusion pump should always be used when administering parenteral nutrition solutions, because the rate must be tightly controlled and adjustments to the infusion rate must be made easily and accurately. Excessive rates of administration can easily induce profound hyperglycemia, which has been shown in other species to be associated with severe complications and increased risk of death.[947] The solutions used for parenteral nutrition are all hypertonic and can cause injury to the vascular endothelium, increasing the risk of thrombophlebitis. For this reason it is recommended that parenteral nutrition solutions be administered through a 20-cm-long polyurethane long-term catheter placed in the jugular vein, because this provides a "central" line in most foals. The use of a multiple-lumen catheter allows for one lumen to be dedicated to infusion of the parenteral nutrition solution, minimizing the risks of contamination. Catheter management is extremely important when foals are receiving parenteral nutrition, and the catheter site and vein should be monitored at least twice daily for heat, swelling, or exudation. Increased resistance to fluid flow in the catheter may be an indication of thrombosis deeper within the vasculature and will often necessitate the placement of a catheter in an alternative site, such as the opposite jugular vein, a cephalic vein, or a lateral thoracic vein.

All components of parenteral nutrition solutions must be mixed in a sterile manner before administration. The bag containing the final parenteral nutrition composition should be covered with a brown plastic bag during administration to protect it from light, which can degrade the amino acids within the solution. The rate of infusion (in mL/h) is calculated based on the desired kcal/kg per day to be administered. A reasonable initial goal is 40 to 60 kcal/kg per day. The initial infusion rate of parenteral nutrition solutions should be 25% of the calculated final rate, and the rate should be gradually increased every 1 to 3 hours following monitoring of the blood glucose concentration to ensure that hyperglycemia (blood glucose >150 mg/dL) is not present. If the patient tolerates parenteral nutrition well and maintains blood glucose concentrations at or near normal levels, then consideration can be given to increasing the parenteral nutrition administration rate to a maximum of 50 to 60 kcal/kg per day.[948] When parenteral nutrition is to be discontinued it is recommended that the infusion rate gradually be reduced, decreasing the infusion rate in 25% to 50% increments every 4 to 6 hours while gradually introducing enteral feeding. It is important that blood glucose monitoring is continued during this weaning process to detect or prevent the development of hypoglycemia.

The foal must be frequently monitored, especially during the initial phase of parenteral nutrition therapy. This monitoring should include a general physical examination, with close

attention to neurologic status and respiratory function. Rectal temperature should also be closely monitored because fever is a common early manifestation of systemic infection. Blood glucose concentrations should be frequently monitored, initially on an hourly basis until the patient has stabilized with the appropriate rate of parenteral nutrition infusion, followed by monitoring every 3 to 6 hours for the first day of therapy. The frequency of blood glucose monitoring is dependent on the stability of the patient and may need to be more frequent in the critically ill, but it may not need to be monitored beyond every 12 hours in the stable patient. Monitoring of urine output and urine glucose concentration may aid in the detection of hyperglycemia. Although the actual renal threshold for glucose is not well described in foals, glucosuria and diuresis are typically seen when blood glucose levels exceed 180 mg/dL. Additional clinicopathologic monitoring should consist of daily complete blood counts and serum chemistry profiles in the critical case, whereas these can be performed every 48 to 72 hours in more stable patients. Serum electrolytes should be monitored at least twice daily. Particular attention should be paid to serum potassium concentrations because they can decrease rapidly, especially in foals receiving insulin therapy. Urine output should be monitored continuously, in combination with intermittent monitoring of urine glucose concentration, because of the risk of hyperglycemia-induced diuresis and glucosuria. Ideally body weight should be assessed on a daily basis to ensure that the foal is at least maintaining its body weight while on parenteral nutrition. Foals receiving parenteral nutrition solutions containing lipids should be monitored for the development of hypertriglyceridemia.[719,949]

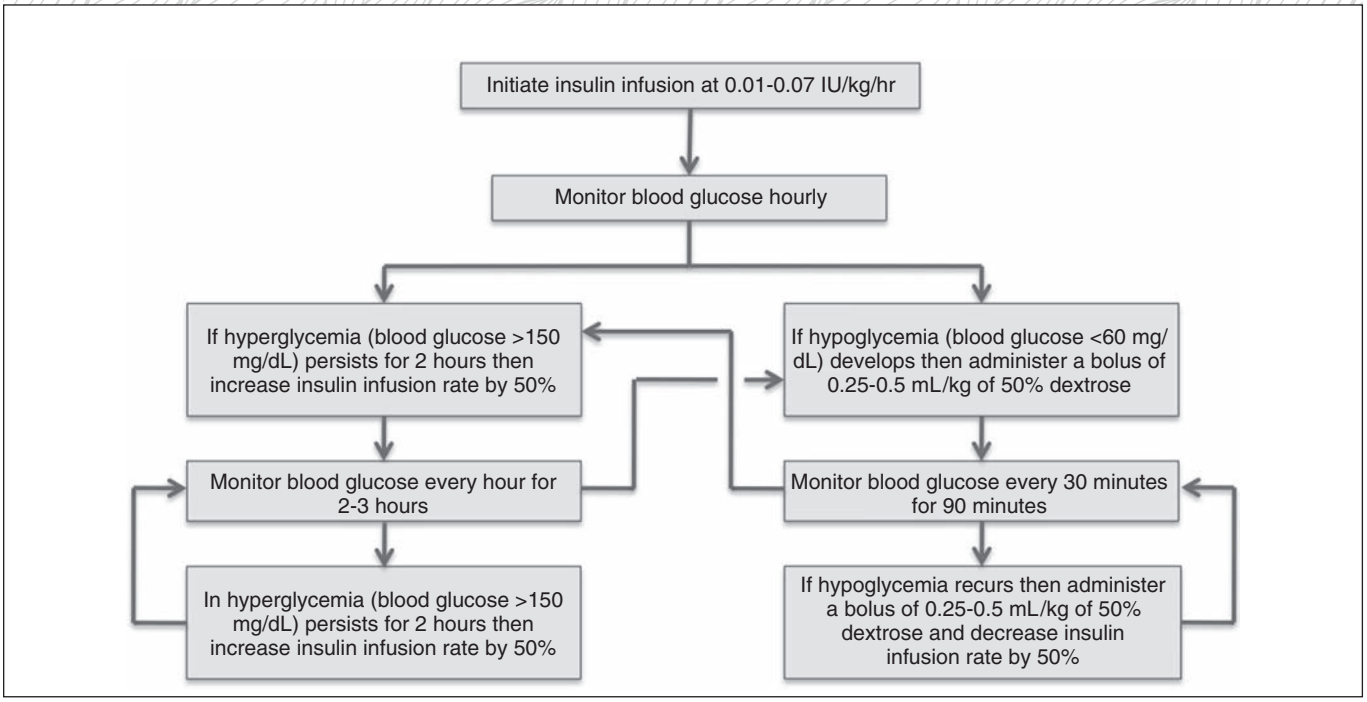
Insulin Therapy

The critically ill foal will often demonstrate carbohydrate intolerance, and this can make it very difficult to achieve even a conservative rate of administration of IV nutrition. This situation can be addressed by the use of a lipid-containing parenteral nutrition solution, but if this is ineffective then the only alternative is administration of exogenous insulin. The administration of insulin to the neonatal foal is not to be undertaken lightly because this therapy places additional demands on both the clinician and nursing staff to ensure that profound hypoglycemia does not occur. Intermittent dosing of subcutaneous insulin may offer some advantages in terms of simplicity of administration, expense, and moderation of effects, but this route of administration does not allow for changes in dosage over the short term. One recommended dosage for subcutaneous insulin in foals is 0.1 to 0.5 IU of regular insulin every 12 hours.[950] A retrospective report of foal parenteral nutrition described subcutaneous insulin dosage rates 0.02 to 0.1 IU/kg given every 6 to 24 hours.[949] This approach is not recommended because the risks of hypoglycemia and hyperglycemia are greater than with CRIs, and it can be much more challenging to achieve homeostasis in terms of blood glucose concentrations when using intermittent bolus insulin therapy.

The use of CRI for the administration of insulin allows for a fairly rapid onset of action while providing a simple and timely means of adjustment of the dosage. Because of the gradual saturation of the cellular insulin receptors, the maximal effect of CRI insulin is not typically seen until roughly 90 minutes after initiation of the infusion. The response to the alteration of the rate of infusion occurs over a similar time frame, so one should take care to avoid altering the rate of infusion of parenteral nutrition solutions too soon after changing the rate of insulin infusion. An initial insulin infusion rate of 0.07 IU/kg per hour of regular insulin has been reported to be well tolerated and may represent a reasonable starting point in foals intolerant of parenteral nutrition.[720,951] This dosage was derived from a retrospective study of foals treated with parenteral nutrition, which reported initial insulin doses ranging from 0.014 to 0.2 IU/kg per hour, with a mean of 0.065 IU/kg per hour.[719] Interestingly, in that study the final insulin dose ranges remained very similar, from 0.015 to 0.2 IU/kg per hour, with a mean of 0.07 IU/kg per hour. Some advocate starting at lower dosages in foals, such as 0.01 IU/kg per hour.[952] This conservative approach is very safe, with less risk of hypoglycemia than the higher dosage rate, but may require a longer period of time before the dose is titrated to a high enough level to control hyperglycemia. Even lower dosage rates of insulin have been reported, with a recent retrospective report describing insulin infusions at dosages of 0.0016 to 0.018 IU/kg per hour.[949]

Therefore an initial insulin infusion rate of 0.01 to 0.07 IU/kg per hour represents a reasonable starting point. When "fine-tuning" insulin therapy it is best to avoid simultaneous alterations in both the insulin infusion rate and the parenteral nutrition infusion rate, because this can lead to a "roller-coaster ride" in which the blood glucose concentration rises and falls wildly because of the delay in the body's response to these changes[720] (Box 20.6). Blood glucose monitoring should be performed at least hourly for the first 2 to 3 hours after initiation of the insulin CRI, and if hyperglycemia (blood glucose >150 mg/dL) is persistent beyond the first 2 hours of insulin therapy, then the insulin infusion rate may be increased by 50%, followed by hourly blood glucose monitoring for a further 2 to 3 hours. This procedure for increasing the insulin infusion rate may be repeated if hyperglycemia persists. Conversely, if hypoglycemia (blood glucose <60 mg/dL) is noted then a bolus of 0.25 to 0.5 mL/kg of 50% dextrose solution should be administered intravenously over 3 to 5 minutes. The blood glucose level should then be reassessed every 30 minutes for at least 90 minutes ensure that hypoglycemia does not recur. If hypoglycemia does recur, then a second bolus of dextrose is administered and the insulin infusion rate is decreased by 50%. Close monitoring will then be required for a further 60 to 90 minutes to ensure that hypoglycemia does not recur and that hyperglycemia does not develop. Further changes to the insulin infusion rate are not usually necessary once a steady state has been achieved in which the blood glucose level is stable and the desired rate of parenteral nutrition administration has been achieved. Patient reassessment is indicated if one finds that the foal has become even more insulin resistant (requiring additional insulin administration to avoid hyperglycemia) as there may be an overall deterioration in the patient's condition accompanied by increasing systemic inflammation. When insulin therapy is to be discontinued the insulin administration rate should be gradually titrated downward in parallel with the parenteral nutrition rate, but there can be a substantial lag between changes in the insulin infusion rate and the patient's response to this change. Some time should be allowed to account for this lag. It is critical that foals being weaned from insulin infusions receive some form of enteral nutrition during this time period. It may be wise to wean them from parenteral nutrition and insulin over longer periods of time (24–36 hours) than would be required for a foal receiving parenteral nutrition alone to prevent glucose derangements.

BOX 20.6 Protocol for the Monitoring and Regulation of Insulin When Administered as a Continuous Rate Infusion to Foals



Adapted from McKenzie HC 3rd, Geor RJ. Feeding management of sick neonatal foals. *Vet Clin North Am Equine Pract*. 2009;25:109-119, vii.

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